# MIDAZOLAM

# AS AN

# ANAESTHETIC AGENT

# IN CHILDREN

by

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# ABSTRACT

A relatively high dose of midazolam has to be administered orally to achieve the favourable effects of premedication in children and this could be associated with arterial oxygen desaturation. Pethidine has been commonly administered as a premedicant to children for many years, however its association with oximetric desaturation has not previously been investigated. In this thesis the incidence, duration and severity of oximetric desaturation episodes was determined following premedication in children with midazolam and pethidine. To facilitate this research, Satmaster™, a computer programme which permits storage, retrieval, signal evaluation and data compilation, was developedin conjunction with the software authors and subjected to artefact template analysis to reduce the inclusion of spurious oximetric data in the determination of the incidence of desaturation. It was found that neither pethidine nor midazolam premedication increased the incidence of episodic desaturation when compared to that occurring during normal sleep. If analgesia is not a premedication requirement, oral midazolam confers the advantage over pethidine of avoiding the pain of an intramuscular injection, without compromising oxygen saturation.

The availability of flumazenil permits specific reversal of the unconsciousness and reflex depression associated with the hypnotic effect of midazolam administration. The combined pharmacokinetics and pharmacodynamics of midazolam and flumazenil in children have not previously been reported. Midazolam pharmacokinetics were shown to compare favourably with those of propofol in a

similar patient population and it was found that midazolam antagonism with flumazenil produced similar clinical awakening rates to those achieved after propofol induction. Blood pressure changes on induction were measured using a standard intermittent noninvasive technique and these were compared with continuous pressure measurements using a Finapres, modified for paediatric use and computerised data acquisition. Propofol induction was associated with hypotension of a significantly greater degree and duration compared to midazolam and thiopentone.

Postoperative recovery after anaesthesia is particularly important for ambulatory surgery. The effect of midazolam on psychomotor performance, residual sedation and mood was shown to be related to plasma concentration. These indices were also used to assess recovery after anaesthetic induction with either midazolam, thiopentone or propofol. A post-box toy completion ratio (PBTR) was developed for assessment of psychomotor performance in children and compared with a standard component of the Wechsler intelligence scale (WISC-R). The PBTR was found to be as sensitive as the WISC-R in this assessment, but also has the advantage of ease of administration. The quality and rate of recovery following unantagonised midazolam induction in the immediate postoperative period is inferior to propofol and thiopentone but within one hour of awakening there is no difference in recovery characteristics between the agents. Recovery of orientation, co-operation and comprehension after flumazenil administration would appear to be as rapid as propofol and superior to thiopentone.

Midazolam (0.5 mg $kg^{-1}$) administered orally is a suitable premedicant for children. The drug's bitter taste can be disguised, it is rapidly absorbed, producing peak sedative effects at 60 min, and has residual anxiolytic effects 120 min after administration. Premedication was not associated with episodic oximetric desaturation and the children entered the operating suite without overt distress, appearing calm and co-operative. Intravenous midazolam (0.5 mg $kg^{-1}$) compares favourably to propofol and thiopentone as an induction agent in some respects, providing a intermediate onset of action, intraoperative amnesia, excellent operating conditions and when reversed with flumazenil, it has a short recovery period without unwanted residual effects. However propofol and thiopentone are both easier to administer because their onset of action occurs in one arm-brain circulation time and they demonstrate a definite end-point. Following anaesthetic induction with midazolam, psychomotor performance returned to preoperative unmedicated levels (recorded the previous evening), without flumazenil administration, within 4 hr of eye opening. There were no adverse side effects associated with the administration of midazolam. Midazolam therefore seems to be a very suitable agent for use in elective surgery in children.

# PREFACE

## STATEMENT OF WORK

## ACKNOWLEDGEMENTS

## STATEMENT OF WORK

This thesis contains no material which has been accepted for the award of any other degree or diploma in any tertiary institution and that, to the best of my knowledge and belief, the thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis. This thesis is exclusively my own work but assistance was given by the following colleagues with data recording and patient care during anaesthesia: Drs. Andrew Lawson, Lorna Andrew, Sue Gunawardene, Catherine Roulson, Alan Brown, Douglas Smith, Anil Visram, John Kornberg, Michael Irwin and George Mya. Dr. Kelvin Chan and Dr. Maureen Chan provided facilities and guidance for the pharmacokinetic assays and analysis; Dr. John Bacon-Shone gave statistical advice; Dr. Nirmala Rao advised on paediatric psychomotor testing; Mr. Stephen Chan designed the computer software for continuous haemodynamic data acquisition; Raymond Lai, Andy Lai, Shirley Tsang and June Ho provided technical assistance; Betty Chan provided secretarial support. The discussion and conclusions drawn in this thesis are my own personal opinion.

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# DEDICATION

I would like to dedicate this work

***to my wife Alice,***

as recognition of her love, advice and encouragement,

during all aspects of preparation of this thesis,

and

***to my loving parents***

for providing me the opportunity to pursue my chosen career.

# CONTENTS

# *CHAPTER I*

# INTRODUCTION

# THESIS OBJECTIVES

Midazolam has been widely used in adult anaesthetic practice as a premedicant and for sedation during minor surgical and invasive diagnostic procedures. The favourable physiochemical properties and the availability of the specific reversal agent, flumazenil, would seem to confer advantages to midazolam as an anaesthetic agent in children. The relationship between premedicant effect in children and midazolam serum levels has not previously been investigated. Induction pharmacodynamics of midazolam have not been compared with propofol and thiopentone, nor has the pharmacokinetic disposition, cardiorespiratory effects and clinical effectiveness of flumazenil administration in children been previously determined.

The objectives of this thesis are, firstly to investigate the effect of midazolam premedication on psychomotor performance, sedative level, mood, memory and oximetric desaturation incidence in children. Secondly, to compare the induction pharmacodynamics of thiopentone and propofol with midazolam, and thirdly to compare the quality and rate of recovery after anaesthetic induction between midazolam (with and without flumazenil antagonism), propofol and thiopentone.

It is hypothesised that midazolam is both a suitable premedicant and induction agent for elective paediatric anaesthetic practice.

# PROPERTIES OF THE IDEAL ANAESTHETIC AGENT

General anaesthesia is a drug induced state combining unconsciousness, analgesia, amnesia, reflex depression and muscle relaxation. The ideal anaesthetic agent should provide all aspects of anaesthesia, permitting rapid reversal and return to the preanaesthetic state, without unwanted effects. However, such an agent is not available, nor likely to be in the future and desired anaesthetic requirements are presently met only by a combination of vastly differing groups of drugs.

To a large extent, tradition has determined the clinical use of premedication. Previously, anaesthetic induction was a slow, unpleasant process accomplished using pungent inhaled agents and accompanied by unwanted reflex stimulation. Premedication was employed to attenuate these responses and shorten induction time (Shearer, 1960). Today, intravenous induction produces a rapid, smooth transition to the second stage of anaesthesia and it could be argued that premedication is no longer necessary (Lindahl, 1990). Now, the most common reason given for administering premedication is to allay patient anxiety and induce patient quiescence (Sigurdsson et al, 1983, Walsh et al, 1987). The ideal premedication should be safe, easy to administer, anxiolytic, allow a smooth anaesthetic induction and have no undesirable effects.

The ideal anaesthetic induction agent should combine desirable physical, pharmacokinetic and pharmacodynamic properties and there should be available a competitive, specific antagonist (Jones, 1989). The drug should be water soluble,

non-irritating to the tissues, stable in aqueous solution, have a long shelf life and be inexpensive to synthesise. The ideal induction agent should produce a rapid and smooth onset of hypnosis, without the unwanted effects of pain, myoclonus or cardio-respiratory depression. The agent should possess analgesic and amnesic properties and recovery of consciousness should be rapid and smooth.

Midazolam, prepared as a water soluble salt, is a powerful anxiolytic with a high clinical therapeutic index and can be administered by a wide variety of routes. It causes only slight ventilatory depression when the clinically recommended dosage is administered and can be specifically antagonised with flumazenil (Cook, 1992). Intravenous administration of midazolam does not seem to possess intrinsic analgesic activity but intrathecally deposited midazolam has been recently shown to possess analgesic properties (Goodchild and Noble, 1987). Use of midazolam as the sole agent to achieve satisfactory anaesthesia would induce a large number of unwanted and potentially lethal effects.

Midazolam seems to be one of the few drugs that can be employed in clinical practice as both a premedicant and for induction of general anaesthesia (Fragen, 1988). A clinical therapeutic index states how selective a drug is in producing a desired effect but is an inappropriate basis for comparison of anaesthetic agents because death resulting from respiratory depression may not be related to the *clinical* safety margin of induction agent administration. A comparison of the properties of midazolam with the characteristics of the ideal premedicant and induction agent will usefully illustrate the potential for use of this drug in general anaesthesia.

# CURRENTLY AVAILABLE PREMEDICANTS AND INDUCTION AGENTS

Premedication regimens have included a wide variety of sedative-hypnotic, narcotic and antisialagogue drug combinations and routes of administration. Often these drugs were administered intramuscularly by injection. Pethidine, morphine, and fentanyl are the most popular narcotics used for premedication. Unfortunately the primary effects of these drugs do not match the desired effects of premedication, viz. sedation and anxiolysis. Moreover, narcotic administration can be associated with dose-dependent side effects, such as skin reactions, postoperative nausea, dysphoria and respiratory depression. Attainment of an adequate level of sedation often requires concurrent administration of another agent such as trimeprazine or droperidol, increasing the likelihood of unwanted effects. Comparative adult studies have indicated that benzodiazepines are more effective in producing anxiolysis and amnesia and have also been shown to be superior hypnotics to barbiturates when administered on the evening prior to surgery (White, 1989).

Recent changes in philosophy and clinical practice have resulted in a rationalisation of premedication. The emphasis on ambulatory surgery and a holistic approach to the preoperative preparation of the child have resulted in increasing use of the oral and nasal routes of administration in children (Feld et al, 1990). Oral administration is an important prerequisite for the ideal premedicant in children and water soluble drugs are well absorbed when given via this route (Nicolson et al, 1989). Premedication with oral and intranasal ketamine provides satisfactory sedation

but this is also associated with dose related undesirable effects which include increased oral secretions and random limb movement (Gutstein et al, 1992). Other premedicant agents may be specifically indicated in certain circumstances such as for prevention of postoperative emesis, vagolysis and prophylaxis against acid aspiration, but these drugs do not have specific sedative and anxiolytic effects (Manchikanti et al 1984, O'Sullivan et al 1985).

Inhalational induction is the most commonly used technique in paediatric anaesthesia, however intravenous induction is the method of choice in most older children (Hannallah, 1992) and propofol has been shown to provide a decreased incidence of airway obstruction compared to inhalational induction in children aged 1 to 7 years (Martin et al, 1992). Sedative-hypnotic, opioid analgesic and sedative-amnesic agents are used for intravenous induction of anaesthesia in children. They represent a wide variety of pharmacological compounds, of which the most popular sedative-hypnotic agents are thiopentone, etomidate, midazolam, ketamine and propofol (White, 1988). Propofol and etomidate are not water soluble and both are associated with pain on intravenous injection. Ketamine induction may be associated with excitatory phenomena and can cause cardiovascular stimulation (Moretti et al, 1984). Induction is rapid with propofol and thiopentone but is associated with cardiovascular depression in adults. Induction doses of thiopentone, midazolam and propofol are associated with respiratory depression but this is not so with ketamine, nor etomidate. Midazolam is the only induction agent which provides significant amnesia (White, 1988). Emergence after etomidate and propofol is rapid whilst that following thiopentone, midazolam and ketamine is intermediate. Unwanted

effects of induction agents include drowsiness, nausea and vomiting, psychomimetic phenomena and dizziness (Marshall and Longnecker, 1991). Although midazolam also causes postoperative drowsiness, this can be antagonised by flumazenil (Hunkeler et al, 1981). Thiopentone produces rapid and smooth loss of consciousness, but is associated with marked cardiorespiratory changes, lacks analgesic properties and recovery is slowed by drowsiness and sedation (Reves 1986, Sebel and Lowdon 1989).

Obviously many of the desirable properties of the ideal induction agent have not been achieved with the currently available drugs. Thiopentone remains the most widely used intravenous induction agent despite its limitations and although it was introduced more than 50 years ago, it remains the induction agent against which more recent drugs must be compared (Dundee, 1984).

# SPECIFIC REQUIREMENTS OF PAEDIATRIC ANAESTHESIA

Children are excellent candidates for outpatient surgery (Hannallah, 1992). Frequently the paediatric surgical patient has no concomitant systemic disease and the proposed surgical procedure is relatively minor. Day surgery minimises both parental separation and exposure to hospital acquired infection for the child. It may appear that general anaesthesia in the child above the age of three years differs little when compared to adults, however there are some special considerations applicable to the child undergoing ambulatory anaesthesia.

The narrowest part of the child's airway is at the cricoid cartilage and the tracheal mucosa in this area is easily damaged by a tracheal tube that is too large (Sumner and Facer, 1986). Small reductions in the internal diameter of the child's trachea cause relatively large increases in airways resistance and work of breathing (Brown and Fisk, 1979). In children under the age of 6 years, peripheral airways contribute about 50% of total airways resistance and therefore minor respiratory disease is likely to cause more substantial problems in these children when compared to adults (Hogg et al, 1970). Children have a runny nose for a significant part of the year and often present for minor surgery with prodromal or recovery symptoms of an upper respiratory tract infection (Hannallah, 1992). The smaller the child, the less is the respiratory reserve, and the higher the risk of postoperative respiratory depression.

Tiret and colleagues reported a prospective survey of anaesthesia-related morbidity and mortality following 40,240 anaesthetics in infants and children (Tiret et al, 1988). They found that circulatory failure was as frequent as respiratory failure in children and that complications were observed almost equally during induction, maintenance and recovery. The fact that the only death within the child age-group occurred during recovery, emphasises that this period is particularly critical (Tiret et al, 1986).

Liver metabolism matures in infancy. The degree of protein binding of thiopentone and the steady state volume of distribution in children, are similar to adult values (Sorbo et al, 1984). Shorter recovery times are expected for children compared to adults because of the faster clearance of induction agents, which is in turn attributable to the relatively larger hepatic mass (Udkow, 1978). In general children seem to require a larger dose of drug on a mg $kg^{-1}$ basis for the induction of anaesthesia, either because they exhibit a decreased central nervous system sensitivity or there is a more rapid distribution from the central to the peripheral compartments (Gepts and Camu, 1991). Furthermore, the volumes of tissues belonging to the vessel-rich group are proportionally larger, accepting a larger fraction of the cardiac output, while muscle and fatty tissues represent a lesser percentage of total body volume compared to adults (Eger et al, 1971).

In view of these anatomical, physiological and pharmacological characteristics in paediatrics, a drug which is both well absorbed following oral administration, and which when given as an anaesthetic induction agent has a high therapeutic index,

non-cumulative metabolism and has available a specific antagonist, would seem the most appropriate choice in children.

# WHY CHOOSE MIDAZOLAM?

The benzodiazepines have advantages over other sedative-hypnotics because they reliably induce sedation and anxiolysis, have an extremely wide therapeutic range and their administration is not associated with histamine release or adrenocortical secretion suppression. However most are unsuitable as anaesthetic induction agents, because of their unpredictable onset of action and the production of active metabolites with longer terminal half-lives than the parent drug, resulting in prolonged postoperative sedation. Furthermore, their lipophilicity and insolubility in aqueous solutions have resulted in propylene glycol formulations which cause pain on injection, venous irritation and thrombophlebitis.

Midazolam (Ro 21-3981) was synthesised in 1974 by Fryer and Walser and is an imidazobenzodiazepine derivative (Walser et al, 1978) (Figure **I.1**). It was released for general use world-wide in 1986 with indications for use as a premedicant, intravenous sedative and for induction of general anaesthesia. Midazolam has a molecular weight of 362, a $pK_a$ of 6.15 and the parental solution is buffered to an acidic *p*H of 3.5. The drug has a fused imidazole ring that accounts for its basicity, stability in aqueous solution and rapid metabolism (Gerecke, 1983). Midazolam is different from other benzodiazepines because in acidic aqueous media it is water soluble, but at physiological *p*H an intramolecular rearrangement occurs and midazolam becomes highly lipophilic. This characteristic of midazolam permits a water soluble parenteral solution which causes minimal local irritation after either intramuscular or intravenous administration, and the high lipophilicity allows rapid

absorption from the gastrointestinal tract and entry into brain tissue. Midazolam is rapidly and extensively metabolised by hepatic microsomal enzymes, resulting in a short elimination half-life of 2-4 hours. The principle metabolite is 1-hydroxymethylmidazolam but small amounts of 4-hydroxymidazolam and 1,4-dihydroxymidazolam are formed in parallel which are then excreted in the urine as glucuronide conjugates (Arendt et al, 1984).

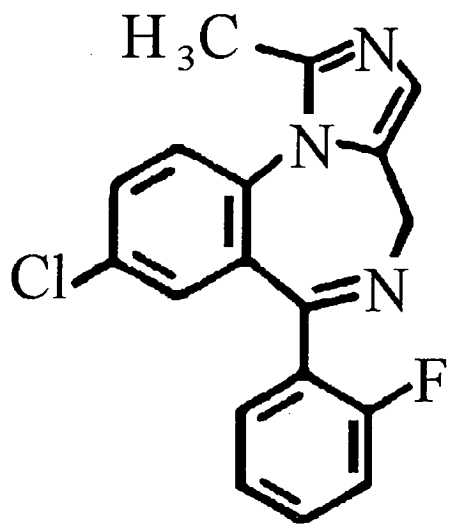


**FIGURE I.1:** Structural formula of midazolam.

In contrast to diazepam, the hydroxylated metabolites of midazolam have minimal central nervous system activity (Ziegler et al, 1983). Midazolam produces amnesia, anxiolysis, sedative/hypnotic, anticonvulsant and muscle relaxant effects, typical of the general actions of the benzodiazepine group of drugs on the central nervous system (Pieri, 1983). The ideal benzodiazepine for anaesthesia should possess a predominant sedative/hypnotic effect, short duration of activity, no active metabolites, be stable and well tolerated and there should be available a pure

competitive antagonist to interrupt transiently or permanently the actions of the agent when the anaesthetist so desires (Amrein et al, 1988). Midazolam very nearly satisfies all these 'ideal' prerequisites and the discovery of flumazenil in 1979 (Hunkeler et al, 1981) makes midazolam a very suitable anaesthetic agent, particularly for use in children.

Flumazenil (Ro 15-1788) is a benzodiazepine antagonist with a molecular weight of 303 and a $pK_a$ of 1.7, which can reverse all the behavioural, neurological and electrophysiological effects of all the benzodiazepine agonists (Hunkeler et al, 1981). Flumazenil is similar in structure to midazolam except that chloride and the phenyl group in midazolam is replaced by fluoride and a carbonyl group, respectively, in flumazenil (Figure **I.2**). Flumazenil is less lipophilic and less water soluble than midazolam but can still be administered as an injectable aqueous solution.

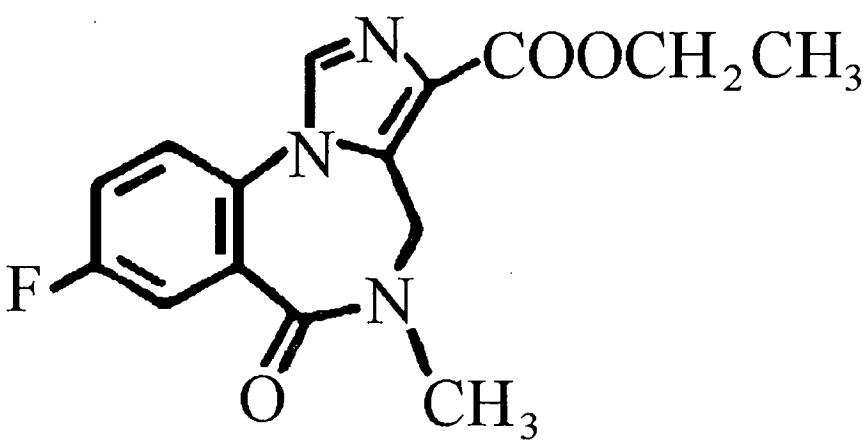


**FIGURE I.2**: Structural formula of flumazenil.

Flumazenil has a high affinity for the benzodiazepine receptor but with an apparent complete lack of pharmacological activity (Ritter et al, 1988). It has a distribution half-life of less than 5 minutes, an elimination half-life of 0.7-1.3 hours in adults and the drug achieves a relatively high plasma concentration compared to midazolam, because it is only 50% bound to plasma proteins (Roncari et al, 1986). The clinical applications of flumazenil require further evaluation but its ability to antagonise benzodiazepines could be advantageous where residual sedation exists beyond anaesthetic needs, accidental or iatrogenic oversedation occurs, following unexpected reactions to benzodiazepines and in the treatment of intentional benzodiazepine intoxication (Geller and Halpern, 1991).

The powerful amnesic and anxiolytic properties of midazolam and use of the parenteral formulation orally, resulted in it rapidly becoming established as a suitable premedicant in children, despite the need to disguise the drug's bitter taste (Feld et al, 1990). There are now numerous studies detailing pharmacokinetic, pharmacodynamic and clinical acceptance of various midazolam premedicant regimens in paediatric patients (Payne et al, 1989). A feature of benzodiazepines is the relationship between drug concentration and effect (Reves, 1984). Pharmacokinetic-pharmacodynamic modelling has recently been re-evaluated in an attempt to explain inter-individual differences in dose response relationships (Henthorn and Avram, 1991). The relationship between serum midazolam levels, mood, level of sedation and psychometric performance following premedication with midazolam has not previously been investigated in children.

At the time when Salonen and colleagues initially investigated the place of midazolam in paediatric anaesthetic practice, neither the usefulness nor pharmacokinetics of the drug had been thoroughly described in children (Salonen et al, 1987). Indeed, there were only 4 original articles reporting the use of midazolam as an induction agent in children prior to 1989, before the work on this thesis commenced. There were no controlled trials of flumazenil administration to reverse postoperative hypnosis associated with midazolam induction of anaesthesia in children and only one case report of its use following benzodiazepine poisoning in children (Wood et al, 1987). The place of midazolam as a premedicant and induction agent in paediatric outpatient anaesthesia is controversial but the introduction of flumazenil permits reversal of any prolonged sedation and may therefore extend its use to this rapidly developing area of patient care (Westhorpe, 1990). However neither midazolam nor flumazenil have yet been licensed for use in paediatric patients. This is not unusual as few drugs are initially licensed for use in patient subgroups. Therefore the safety and efficacy of these drugs must be determined by clinical investigation to determine their place in this specialised field of anaesthesia. The simultaneous clinical pharmacokinetics of flumazenil and midazolam have not been studied in children and there are very few comparable studies in adults (Lauven et al, 1985). The quality of recovery after anaesthesia is related to the incidence of complications (Patel & Rice, 1991) and a controlled comparative study with midazolam of recovery following the administration of common induction agents used in children, has not been undertaken.

The situation described above is that which existed at the commencement of

the work on this thesis in 1989. The literature has expanded considerably over the past five years and the publications which have resulted from this research are listed in *Appendix A*. The following chapters present my research and a review of the use of midazolam as a premedicant and an induction agent for elective surgery in children.

# *CHAPTER II*

# METHODS

# PATIENT SELECTION AND ANAESTHESIA

The selection criteria and standardised components of the anaesthetic technique are described below, with any differences in management being presented in the relevant chapters.

**Table II.1**: Drug studies reported from this thesis

| Number of children | Study description |
|---|---|
| 12 | The pharmacokinetics of propofol (Diprivan) |
| 40 | Antagonism of the hypnotic effect of midazolam |
| 12 | The pharmacokinetics of flumazenil and midazolam |
| 20 | The effect of premedication on oxygen saturation |
| 30 | Premedication with oral midazolam - psychomotor function, anxiolysis, sedation and pharmacokinetics |
| 30 | A comparison of three induction agents - cardiovascular effects and recovery |

In total, 144 children aged 1-12 years were studied (Table **II.1**). All children were ASA grade I (Dripps et al, 1961)(Table **II.2**) and all children, except those participating in the oximetric study, underwent circumcision for the treatment of phimosis. The studies were all approved by the Faculty of Medicine Ethics Committee (The University of Hong Kong) and written informed consent was obtained from the parents (*Appendix A*). Children were excluded from the study if there was a history of asthma or allergies, previous adverse anaesthetic experience, halothane anaesthesia within the previous one month, hepatic, renal, respiratory, cardiac or haematological disease or developmental disability. Children undergoing psychomotor assessment were excluded if aged less than 4 years.

**Table II.2:** American Society of Anesthesiologists (ASA) Physical Status Categories *(modified from Dripps et al, 1961).*

| Category | Description |
|---|---|
| I | Healthy patient |
| II | Mild systemic disease - no functional limitations |
| III | Severe systemic disease * - definite functional limitation |
| IV | Severe systemic disease * that is a constant threat to life |
| V | Moribund patient not expected to survive 24 hours with or without operation |
| E | Emergency |

* Whether or not the system disease is the disease for which the patient is undergoing surgery.

All patients were premedicated with midazolam 0.5 mg $kg^{-1}$ (maximum dose 15 mg) and atropine 0.02 mg $kg^{-1}$ given by mouth 2 hours before operation, except when midazolam premedication was compared with a group of children receiving intramuscular pethidine 1 mg $kg^{-1}$ and when propofol disposition pharmacokinetics were investigated. In this latter group, oral trimeprazine was used because the ethics committee would not authorise two drugs (midazolam and propofol), neither of which at that time were approved for use in children, to be administered to the same patient. To facilitate painless intravenous cannulation, EMLA emulsion cream 2 g (lignocaine 25 mg $g^{-1}$ and prilocaine 25 mg $g^{-1}$) was applied to either the dorsum of the hand or to skin overlying the basilic vein in the cubital fossa. In the operating

suite a 24 or 23-gauge cannula was inserted into the vein underlying the EMLA-pretreated areas.

Induction of anaesthesia was accomplished with either midazolam 0.5 mg $kg^{-1}$, propofol 2.5 mg $kg^{-1}$ or thiopentone 4 mg $kg^{-1}$ injected intravenously over 30 seconds following midazolam premedication. Patients induced with propofol were pre-treated with procaine hydrochloride 1 mg $kg^{-1}$ intravenously 15 seconds before induction of anaesthesia. Children participating in the determination of the pharmacokinetic disposition of flumazenil and midazolam were given alfentanil 5 μg $kg^{-1}$ intravenously, followed 60 seconds later by midazolam, then atracurium 0.5 mg $kg^{-1}$ and the trachea intubated and the child ventilated. Anaesthesia was maintained with 67% nitrous oxide and 0.5% isoflurane in oxygen via a Mapleson F breathing system with hand ventilation to an end-tidal carbon dioxide partial pressure of 5 kPa. Patients breathing spontaneously were given 67% nitrous oxide and 1-3% halothane in oxygen via a Mapleson F (<25 kg) or Mapleson A (>25 kg) breathing system as maintenance anaesthesia. A caudal injection of 0.25% bupivacaine 0.5 ml $kg^{-1}$ was administered to all children undergoing circumcision, 6 min after induction agent administration. Effectiveness of caudal anaesthesia was tested in the recovery room during emergence. Any child demonstrating a response to pain during gentle compression of the neck of the penis was discarded from the study. A composite system of routine monitoring devices included an electrocardiograph, non-invasive arterial pressure recorder, pulse oximeter, capnograph and inspired oxygen concentration (Cardiocap CM-104, Datex Instrumentarium Corp., Helsinki, Finland). At the end of surgery, if a muscle relaxant had been administered, neuromuscular

block was antagonised with neostigmine and atropine, the trachea extubated and ventilation assisted with 100% oxygen by mask and a Mapleson F breathing system, until spontaneous ventilation resumed. Patients breathing spontaneously were given oxygen 28-34% via a Multi-Vent air entrainment mask (Hudson, Temecula, California, USA) until awake.

For all studies, except the oxygen saturation and pharmacokinetic disposition of propofol, a test of recall was performed to evaluate the effect of medications on memory. This test was performed in the following manner. After premedication and just before transfer to the operating suite, the child was shown a simple picture of a school scene for 30 seconds and asked to name and remember five of the depicted objects. Four hours after the operation, the child's ability to recall these objects was tested and he was scored according to his degree of success (Williams, 1968). On arrival in the operating suite, the child was assessed as agitated or crying, aware and apparently anxiety free, drowsy, or asleep but responsive to command (Jones et al, 1990). Induction was graded as good (absence of side effects), adequate (side effects present but not interfering with induction) and poor (side effects severe and protracted). The duration of anaesthesia and cardio-respiratory data during surgery and recovery were recorded. The time to spontaneous eye opening and self-identification were recorded, as was the child's mood using a structured observation score (Krane et al, 1987) (Table **II.3**). The child's level of sedation was also recorded using the modified Steward coma scale (Robertson et al, 1977)(Table **II.4**).

**Table II.3:** Structured observation scale after Krane et al, 1987.

| MOOD | Score |
|---|---|
| laughing, euphoric | 1 |
| happy, playful | 2 |
| calm, drowsy, sleepy | 3 |
| irritable but calmed by mother | 4 |
| screaming, inconsolable | 5 |

**Table II.4:** Modified Steward coma scale (Robertson et al, 1977)

| Airway | | Consciousness | | Activity | |
|---|---|---|---|---|---|
| opening mouth or coughing on command | 3 | fully awake, eyes open, conversing | 4 | raising one arm on command | 2 |
| no voluntary cough, clear airway without support | 2 | lightly asleep, eyes opening intermittently | 3 | non-purposeful movement | 1 |
| obstruction on neck flexion, airway clear without support on extension | 1 | eyes open on command or in response to name | 2 | not moving | 0 |
| airway obstructed without support | 0 | responding to ear pinching | 1 | | |
| | | not responding | 0 | | |
| Add scores for **Airway**, **Consciousness** and **Activity**: | | | | **TOTAL SCORE :** | |

Any side effects of drug administration were noted and when flumazenil was administered, the child's behaviour and the speed of antagonism of midazolam were considered together by an independent observer in the recovery room and were graded as excellent, good, moderate or poor. Raw data are tabulated in *Appendix C.*

# PSYCHOMOTOR ASSESSMENT

Dundee and colleagues noted the need for a comprehensive assessment of the preoperative effects of drugs given prior to anaesthesia and sequelae attributed to their use to permit valid comparisons of the efficacy of premedicant regimens (Dundee et al, 1962). Tests of motor skills and co-ordination are used to assess the effects of anaesthetic agents and the speed of recovery in adults (Cashman and Power, 1989). Medicated children are difficult to study and the use of adult tests of psychomotor skill and cognitive function are inappropriate. Craig and colleagues used a post-box toy to assess recovery after anaesthesia in adult gynaecological patients (Craig et al, 1982). In this thesis, the post-box test was modified so that the child became his own control and thereby reduced the effect of interpatient variability and limited the practice effect, associated with this form of assessment.

The day before surgery, each child was familiarised with a post-box toy (Figure **II.1**) and the completion time of his best performance on seven attempts recorded. After seven attempts the child's learning curve flattened and further attempts resulted in a decline in performance and boredom with the toy. On the day of operation, after midazolam premedication, the child was offered the post-box toy at different times after premedication and his fastest completion time at a single attempt recorded. A ratio of his best preoperative, unmedicated, practised performance, to his post-medication completion times at each assessment was computed as the toy completion ratio (PBTR) for **premedication** assessment. Similary, a postoperative PBTR was computed for **recovery** assessment:

immediately the child became co-operative post-operatively he was again encouraged to complete the post-box toy and his fastest completion time at a single attempt recorded. This was repeated hourly with each subsequent assessment of recovery, for 4 hours. The data were then related to his best unmedicated performance, and a postoperative PBTR computed for each recovery assessment.

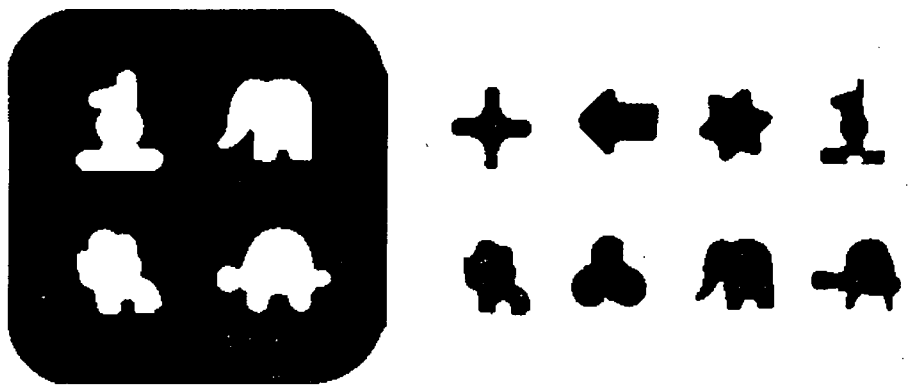

**FIGURE II.1:** The post-box toy used for psychomotor assessment.

Recovery from anaesthesia can also be assessed by a variety of intelligence tests which have been validated for assessment of pre- and postoperative cognitive function over a broad range of abilities in adults and children (Chung et al, 1989). The Wechsler intelligence scale (WISC), which can be matched for the child's age and race (WISC-R), measures verbal and motor performance (WISC-R, 1981). The scale has been used to assess the effects of premedication, as well as the recovery from anaesthesia in adults (Anderson et al, 1985, Rollason et al, 1971). The coding

test component of the WISC-R was performed by children participating in the comparative induction agent study, following each completed post-box assessment. Two coding worksheets were used, one for children aged 5 to 6 years and another for children aged 7 to 15 years (Figure **II.2**).

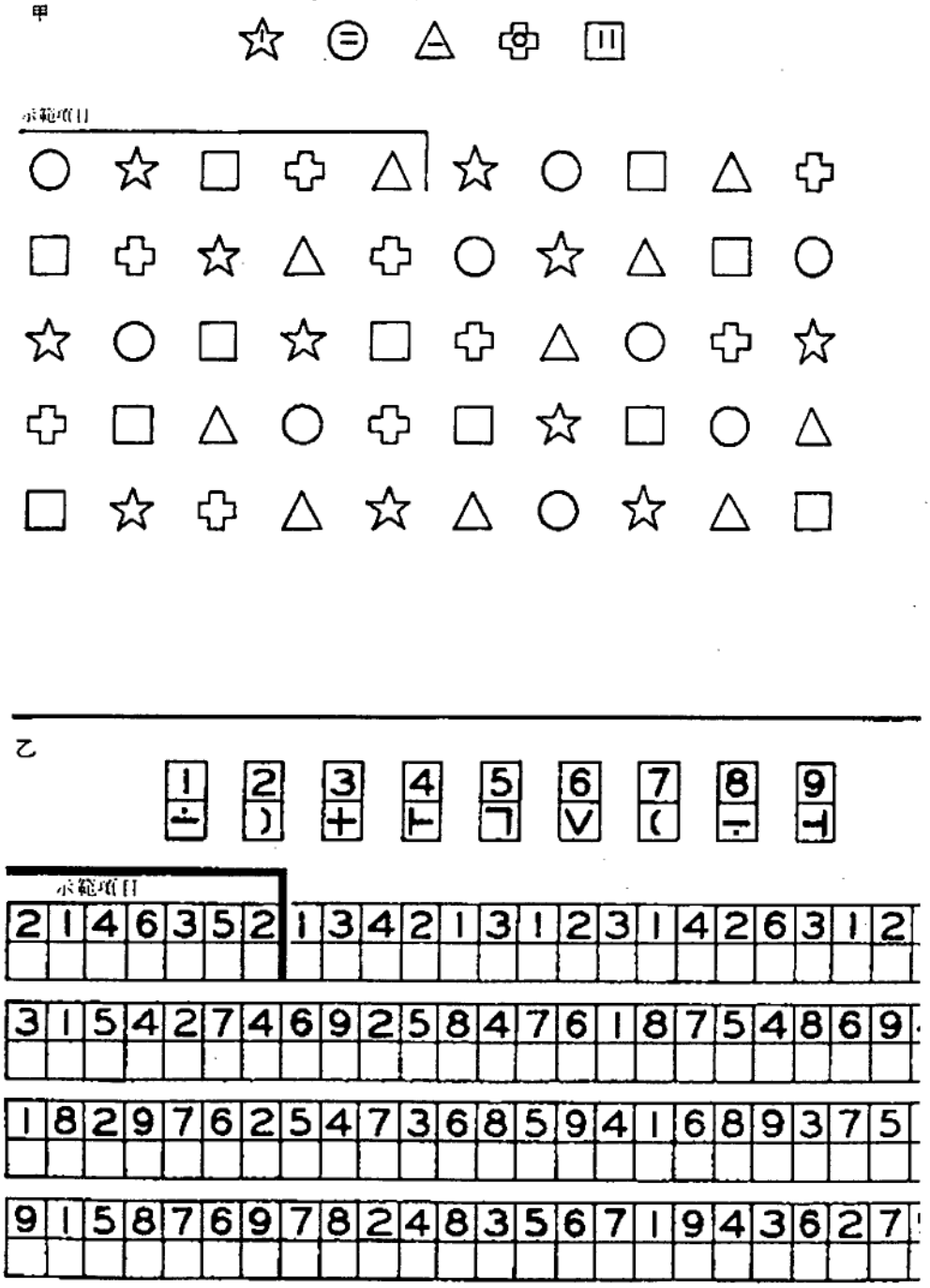

**FIGURE II.2**: WISC-R coding test for children aged 5 and 6 years (upper) and 7-15 years (lower).

The evening before surgery, each child is taught, within the strict guidelines of the test, how to complete the coding worksheet. After successful completion of the practice items in the sample area (5 items for the younger and 7 for the older children), the child is encouraged to complete as many items, in order, without omission, within 120 seconds. The child's performance is then scored with a bonus awarded for a perfect completion within the allotted time viz. 111 - 120" score 45, 101 - 110" score 46, 91 - 100" score 47, 81 - 90" score 48, 71 - 80" score 49, and 70" or less 50. The best completion score after 7 attempts was recorded for later comparison with the child's medicated performance. A figure is scored as correct if it is clearly identifiable as the keyed figure, even if drawn imperfectly or if, after realising his mistake, the child draws the correct figure next to the incorrect one. A maximum raw score of 50 points is possible for the younger child and 93 points for the older child (including any time bonus).

# OXIMETRIC DATA ACQUISITION

The respiratory effects of anaesthetic medications have previously been based on intermittent observations of ventilatory rate or arterial blood gas tensions (Jones et al, 1990). Pulse oximetry has enabled continuous monitoring of arterial oxygen saturation, but data derived from pulse oximetry has inherent limitations, one of which is artefactual desaturation caused by patient movement (Langton and Hanning, 1990).

The same pulse oximeter (Nellcor N-200E, Nellcor Inc., California, USA) was used for all the patients during the study and connected to a Nellcor D-20/250 Oxisensor™ probe, attached to the great toe of each child. Proper function of the oximeter was checked by activating the oximeter's 'self-check' routine and attachment of the instrument to one of the investigators prior to commencement of the study. The serial communication port of the oximeter was connected to a 386SX laptop computer (ALT386SX, Amstrad Plc., Essex, UK). Oximetric, pulse rate and signal amplitude data were sampled 60 times a minute and displayed in real time by Satmaster™ (EMG Scientific, California, USA) on the computer screen. On completion of the study the data were then stored using Satmaster, a software package which allows the retrospective evaluation of desaturation episodes, signal amplitude and pulse rate together with various displays of their incidence and duration.

Data associated with a zero amplitude signal were automatically discarded by the Satmaster software. However, further evaluation was necessary to identify and remove the spurious decreases in arterial oxygen saturation ($S_pO_2$) produced by motion artefact, which were not associated with zero amplitude. Observation of the patient and Satmaster display revealed that characteristic large variations in signal amplitude occurred consistently during probe movement and that these heralded false reductions in $S_pO_2$ (Figure **II.3**).

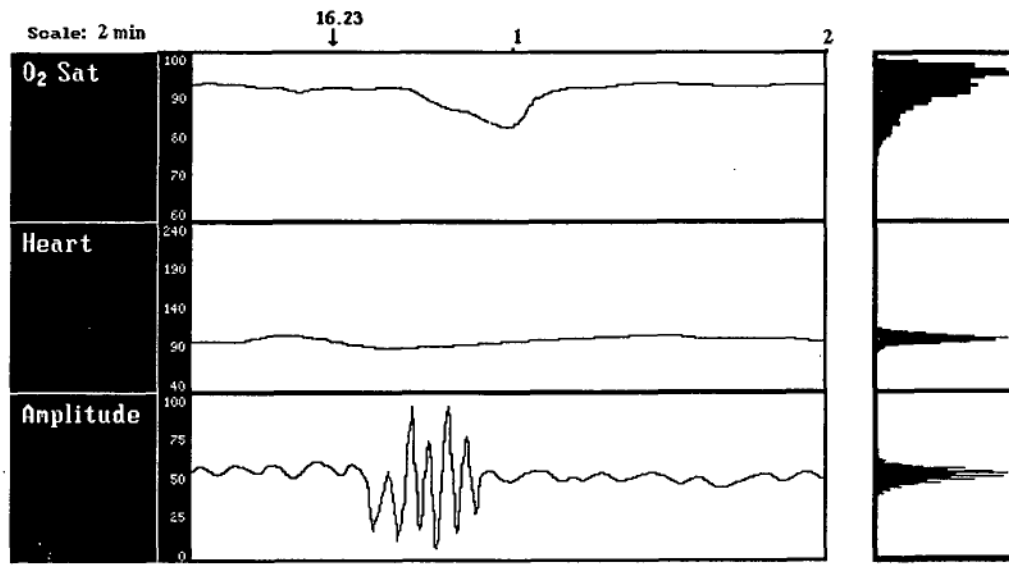


**FIGURE II.3**: The $S_pO_2$ tracing in the upper box illustrates an apparent desaturation to 83%. The amplitude tracing in the lower box demonstrates violent spiking (from 25 to 100 units) due to signal interference associated with patient movement. The time scale for the displayed tracing is two minutes.

This pattern was confirmed to be different from the display produced by true desaturations (Figure **II.4**).

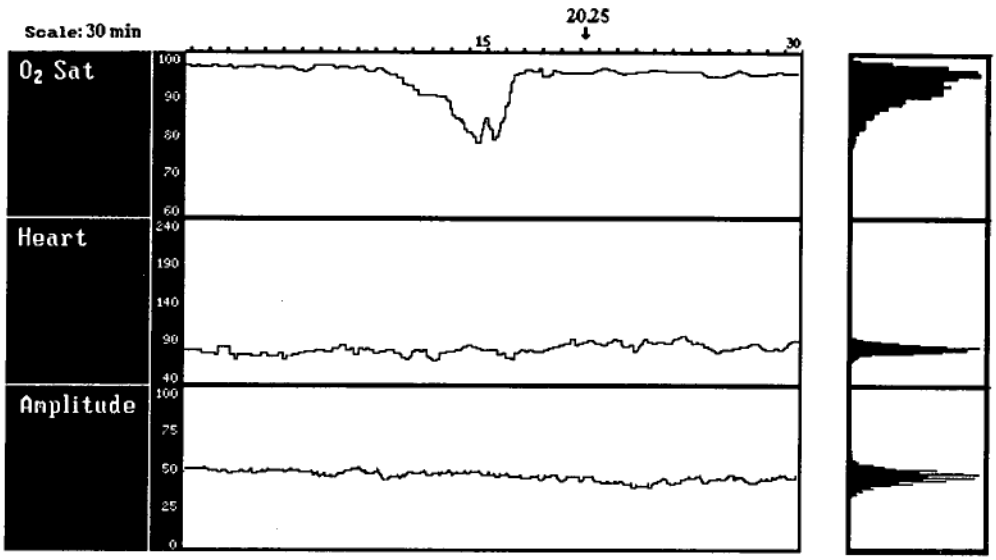


**FIGURE II.4**: Illustrates a valid desaturation episode to 80% with concurrent rise in pulse rate (middle box), while the signal amplitude (when zoomed-in) remains relatively stable. The time scale for the displayed tracing is 30 minutes.

A template was then constructed which was used to retrospectively identify and invalidate the periods of artefactual desaturation due to movement present in the patient data (Figure **II.5**) (Jones at al, 1992).

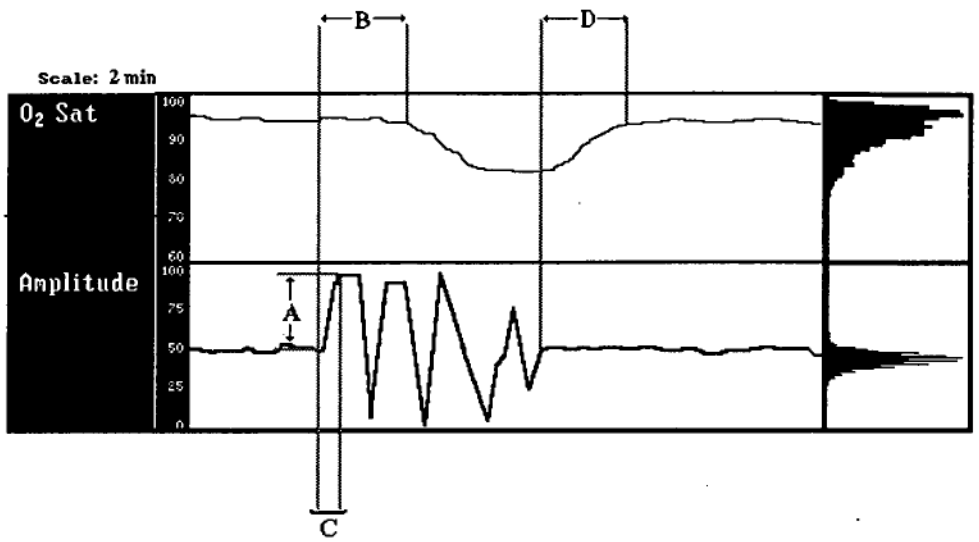


**FIGURE II.5**: The template used to identify artefactual desaturation data due to patient or probe movement

Reductions in $S_pO_2$ were considered false if:

1. there were changes in signal amplitude strength of ± two standard deviations (**A**) from the previous 60 second mean within 10 seconds prior to the fall in $S_pO_2$ (**B**) and
2. the maximum rate of change of signal amplitude occurred within 2 seconds of commencement of signal artefact (**C**) and
3. the saturation signal stabilised to pre-artefact $S_pO_2$ levels within 10 seconds of cessation of signal artefact (**D**).

Each oximetric profile was examined. The recording could be viewed as a whole or magnified so that a recorded segment of two minutes was displayed on the computer screen. Each period of desaturation was evaluated against its concomitant signal amplitude recording. Episodes of desaturation which conformed to the template criteria were discarded and the post-evaluation data compiled and analysed. Oxygen saturation and signal amplitude data recorded from the toe were very similar to that measured with finger probe placement (Reynolds et al, 1993). Furthermore, the temporal lag in desaturation seen in adults appears to be shorter in children because they are smaller, have a faster circulation and normal peripheral vascular perfusion. In another adult study performed contemporaneously with the work for this thesis, the template was shown to have a sensitivity of 96%, a positive predictive power of 98% and a specificity of 60% (Visram et al, 1993). Nearly one-third of all evaluated desaturations had a concurrent change in signal amplitude pattern that suggested both oximeter probes were affected by movement and for the determination of template specificity, these data were discarded. Postoperative oxygen therapy resulted in a small genuine desaturation sample size and this may have distorted the determination of specificity. A larger pool of genuine desaturations may have increased the ratio of true positives to false negatives and therefore increased specificity. An attempt was made to improve specificity of the template by altering the requirements for artefact recognition. Unfortunately, modifications of the template producing a useful increase in specificity were associated with a considerable decline in sensitivity.

# HAEMODYNAMIC DATA ACQUISITION

Continuous monitoring of arterial blood pressure is often desirable (Prys-Roberts, 1981) and is widely practised during anaesthesia. Arterial cannulation has associated morbidity (Slogoff et al, 1983) and a non-invasive alternative may be more appropriate, particularly in children.

Haemodynamic data (pulse rate and non-invasive blood pressure) were recorded by transcription from a Cardiocap screen (Cardiocap CM-104, Datex Instrumentarium Corp., Helsinki, Finland) to data sheets every minute or at 5 minute intervals as appropriate, during the early midazolam and flumazenil studies (*Appendix D*). More recently, direct data acquisition was accomplished for haemodynamic data recording during the comparative investigation of the induction agents propofol, midazolam and thiopentone. The Cardiocap was interfaced with a Sigma PC/XT (Sigma Designs Inc., Fremont, California USA) via an 8-port 232c multi-serial card (Decision Computers International, Taipei, Taiwan). Systolic, mean and diastolic blood pressure, pulse rate and time data were stored to disc in ASCII format at 1 minute intervals in real time using data acquisition software written for this system (Chan, 1991).

The peak haemodynamic changes which occur during intravenous induction of anaesthesia in children may be missed with a sampling rate of once per minute. The Finapres™ (model 2300e; Ohmeda, Denver, Colorado, USA) however permitted non-invasive measurement of the blood pressure, pulse rate and time data with

simultaneous data storage to disc in ASCII format at 10 second intervals, before and during induction of anaesthesia. The Finapres non-invasive continuous blood pressure monitor became available in 1989. It employs the technique of Penaz to continuously servocontrol the pressure in a finger cuff to equal the blood pressure in the digit (Pace and East, 1991). Initial uncontrolled studies in the clinical environment were favourable (Van Egmond et al, 1985) but recent performance has been criticised because of drift, poor agreement between the Finapres and arterial line mean/diastolic pressures (Stokes et al, 1991 and Aitken et al, 1991), and unpredictable variability between the arterial line and the Finapres (Gibbs et al, 1991 and Pace et al, 1991). Previous studies also demonstrate the Finapres to be as accurate as currently employed oscillometric techniques (Gorback et al, 1991). A second generation Finapres (2300e) with improved software was released and shown to be consistently more accurate than an intermittent non-invasive blood pressure monitor (Colin Compact Multi-monitor BP-408 Mark II, Nippon Colin Co., Ltd., Komaki City, Aichi, Japan) in adolescents and the earlier software version (Jones et al, 1992b). This alternative device should meet equivalent standards of reliability before recommendation as a substitute for invasive blood pressure monitoring or other current intermittent non-invasive blood pressure monitors (American National Standards Inc.). In the haemodynamic study described in this thesis, a prototype paediatric Finapres cuff was applied to the middle phalanx of the middle finger strictly according to the manufacturer's instructions, and the output from the Finapres 2300e was interfaced to the computer (Jones et al, 1993a). The data files were imported into Lotus 123W ver 1.0 (Lotus Development Corporation, Cambridge, Massachusetts, USA) for display and basic statistical computation.

To further illustrate the limitation of intermittent non invasive blood pressure measurement, haemodynamic data were recorded using both the Cardiocap and the Finapres simultaneously during the comparative investigation of midazolam, propofol and thiopentone induction of anaesthesia.

# DRUG ASSAYS AND PHARMACOKINETIC ANALYSIS

The concentrations of midazolam, flumazenil (Jones et al, 1993) and thiopentone (Stanski et al, 1983) in serum, and propofol in whole blood (Plummer, 1987), were determined by high performance liquid chromatography (HPLC). HPLC is a separation technique used to identify and measure the concentration of compounds in solution. Separation is achieved by passing the solute through a column which selectively slows down the velocity of the various compounds. The solute and solvent are then passed through a detecting device for the measurement of compound concentration.

The components of the HPLC system for the assay of propofol were the delivery system (Waters M501 pump, Millipore Corporation, Milford, Massachusetts, USA), automatic gradient controller (Waters 680), injector (Waters WISP712 autosampler), a $C_{18}$ reversed phase column (Resolve $C_{18}$, Waters) linked to a $C_{18}$ pre-column (Hibar, E. Merck, Darmstadt, Germany), a fluorimetric detector (Waters M470 scanning fluorescence detector) with excitation and emission wavelengths set at 276 nm and 310 nm respectively and an integrator/recorder (Waters746 data module).

The components of the HPLC system for the assay of midazolam, flumazenil and thiopentone included a delivery system (Waters M501 pump), an injector (Waters WISP712 autosampler), a $C_{18}$ reverse phase cartridge column (Nova-pak, Waters) linked to a $C_{18}$ pre-column and the eluate was measured with a programmable multiwavelength UV detector (Waters M490E) set at 220 nm for midazolam and

flumazenil, and 290 nm and 254 nm for thiopentone, with the integrator/recorder replaced by the Waters MAX810 HPLC system workstation.

All chemicals were of analytical grade. Thymol and sodium dihydrogen phosphate were supplied by British Drug House, Poole, England; cyclohexane, acetonitrile (HPLC grade), glacial acetic acid, dichloromethane (HPLC grade) and methanol were supplied by Mallinckrodt Inc, Paris, Kentucky, USA; triethylamine and diethyl ether were supplied by E. Merck, Darmstadt, Federal Republic of Germany, and tetramethylammonium hydroxide by the Sigma Chemical Company, St. Louis, USA.

## Propofol assay

The propofol assay for the pharmacokinetic and induction studies were performed at different times and in different laboratories. The assay methodology for the induction study is described below and the pharmacokinetic assay method is described in *Chapter IV*. The technique described by Plummer was modified to accommodate small volume blood samples appropriate for children (Plummer, 1987). Samples were collected for measurement of whole blood concentration of propofol and mixed thoroughly in tubes containing lithium-heparin (LH/5, Sarstedt, Numbrecht, West Germany) and stored at +4°C until assayed. Prior stability tests showed that propofol in whole blood samples was stable for a period of three months (Gin et al, 1990). The average recovery of propofol from whole blood was 91% (ranging from 90 - 96%) at 500 ng $ml^{-1}$. Propofol in 0.5 ml whole blood samples and

internal standard thymol (120 ng), buffered with (1 ml) 0.1M sodium dihydrogen phosphate (pH 4.6), were extracted into cyclohexane (5 ml). After 15 minutes mixing, the samples were centrifuged at 20°C for 15 minutes at 3000 rpm. The organic layer was alkalinised with tetramethylammonium hydroxide (50 µl) and evaporated to dryness at 40°C under nitrogen. The residue was redissolved in methanol (100 µl) and the concentrate (20 µl) was analysed by HPLC. The mobile phase consisted of 60% (v/v) acetonitrile in distilled water containing 0.3% (v/v) glacial acetic acid, with a flow rate set at 0.7 ml $min^{-1}$. An external standard (whole blood with a known concentration of propofol) was used at the beginning and end of each run of approximately 30 samples. Each sample run took 15 minutes with the internal standard appearing at 3.8 minutes and propofol at 5.1 minutes.

Calibration graphs were used for each batch and constructed from the mean of three trials at seven concentrations of propofol. The calibration graphs were linear over the propofol concentration range 10 to 1000 ng $ml^{-1}$ with coefficients of variation ranging from 0.1 - 12.6%. The between-batch coefficient of variance was 1.7% at 10 ng $ml^{-1}$ and 4.1% at 500 ng $ml^{-1}$, with the limit of detection being approximately 10 ng $ml^{-1}$ (Figure **II.6**). Complete methodology data are shown in *Appendix E.*

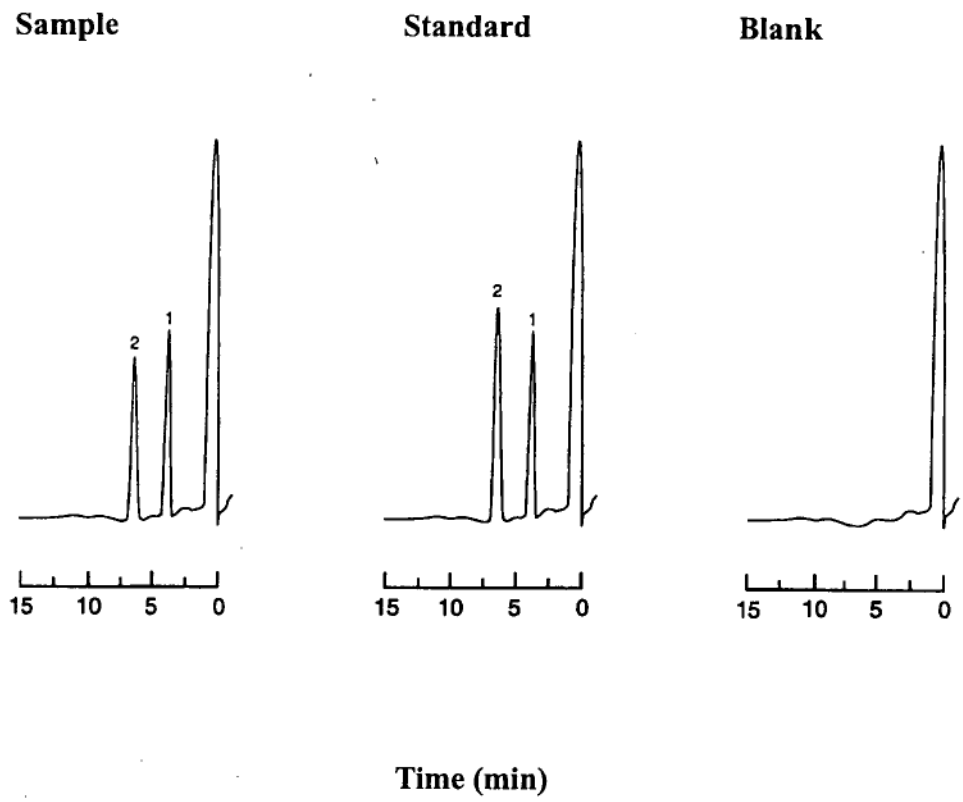


**FIGURE II.6**: Typical chromatogram of propofol in whole blood (sample), external standard and blank, 1 = thymol and 2 = propofol.

## Thiopentone assay

Thiopentone concentration in plasma samples was determined using an HPLC technique with a programmable multiwavelength UV detector set at 290 nm and 254 nm (Waters 490E) based on the technique described by Stanski et al (1983). Thiopentone in plasma (0.2 ml) and internal standard methohexitone (20 μg) were precipitated with 300 μl of acetonitrile. The solution was allowed to mix and stand for

5 minutes and then centrifuged for 20 minutes at 5000 rpm, and approximately 40 µl injected into the HPLC system. The mobile phase consisted of 60% (v/v) 10 mM phosphate buffer (pH 7.0) and 40% (v/v) acetonitrile, with a flow rate set at 1.8 ml $min^{-1}$ (Figure **II.7**).

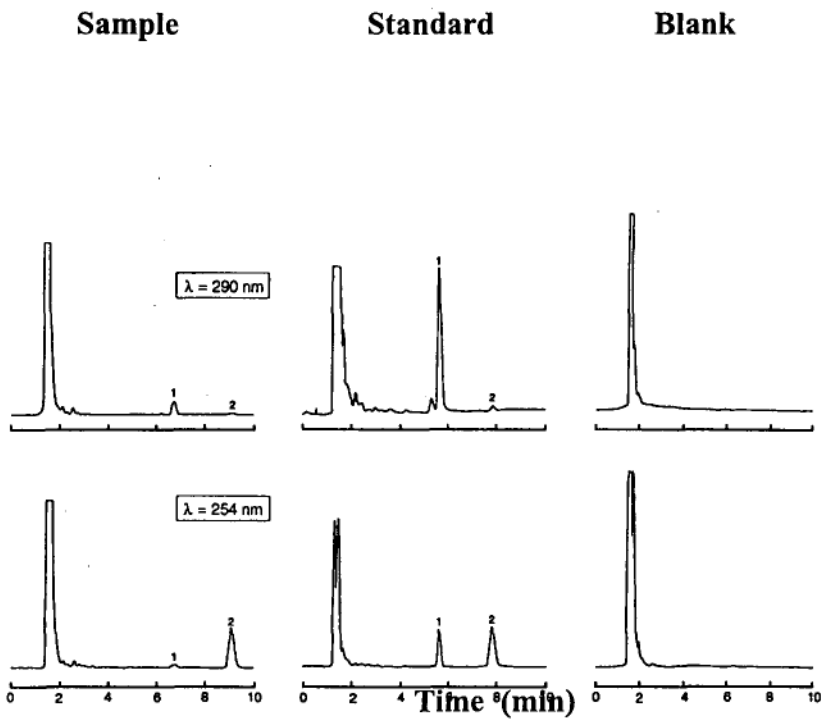


**FIGURE II.7**: Typical chromatograms of thiopentone in plasma, standard and blank (λ=290 nm) and internal standard methohexitone in plasma, standard and blank (λ=254 nm), 1 = thiopentone and 2 = methohexitone.

A range of external standards (serum with a known concentrations of thiopentone and methohexitone) was measured at the beginning and end of each run of 25 samples. Each sample run took 15 minutes with thiopentone appearing at 6.0

minutes and the internal standard at 9.0 minutes. The five calibration graphs were linear over the range 0.05 to 10 $\mu g\ ml^{-1}$ with coefficients of variation ranging from 0.2 to 10.6%. The between batch coefficients of variance for the thiopentone assay were 9.0% and 6.9% at 0.05 $\mu g\ ml^{-1}$ and 5 $\mu g\ ml^{-1}$, respectively, and the limit for detection for thiopentone was 0.05 $\mu g\ ml^{-1}$. Complete methodology data for thiopentone are shown in *Appendix E.*

## Midazolam assay

Midazolam concentration in plasma samples, obtained during the induction agent study, were determined employing an HPLC technique with UV detection set at 220 nm using a programmable multiwavelength detector (Waters 490E) based on the assay technique described by Vletter et al (1990). Midazolam in plasma and internal standard flurazepam (200 ng) buffered with sodium dihydrogen phosphate (0.1M) at pH 9, were extracted into 5 ml organic solvent mixture (diethyl ether and dichloromethane in the ratio 60:40 v/v). The solution was allowed to mix for 15 minutes and then the samples were centrifuged at 20°C for 15 minutes at 3000 rpm. The organic extract was evaporated to dryness under nitrogen and the residue was re-dissolved in methanol (80 µl) and approximately 30 µl of the methanolic concentration was injected into the HPLC system. The mobile phase consisted of 32% acetonitrile in 0.04M sodium dihydrogen phosphate buffer (containing 0.1% triethylamine) at pH 7.0. The flow rate was set at 1.5 ml $min^{-1}$. A range of external standards (serum with a known concentration of midazolam) was measured at the beginning and end of each run of approximately 30 samples. Each sample run took 40

minutes with the internal standard appearing at 20.7 minutes and midazolam at 35.3 minutes. Four calibration graphs were produced for each batch, which were linear over the range 40 to 2000 ng $ml^{-1}$ with coefficients of variation ranging from 1.5 to 11.8%. The between-batch coefficient of variance at 40 ng $ml^{-1}$ was 4.8% and 1.5% at 500 ng $ml^{-1}$, with the limit of detection for midazolam was 10 ng $ml^{-1}$. Complete methodology data for midazolam are shown in *Appendix E*.

## Midazolam and flumazenil assay

The midazolam assay for the simultaneous determination of midazolam, flumazenil and metabolites and the assay used in the induction study were performed at different times and in different laboratories. The following is a general description of the simultaneous midazolam and flumazenil assay. Blood samples (1.0 ml) were collected into tubes containing lithium heparin (LH/5, Sarstedt, Numbrecht, West Germany). Urine samples (1.0 ml) from a bulked 24 hour urine collection were placed into plain tubes for simultaneous determination of midazolam and flumazenil with HPLC and UV detection at 220 nm using a programmable photodiode array detector (Waters 994). Plasma was obtained from blood after centrifugation for 15 minutes at 3000 rpm. Flumazenil and midazolam in plasma or urine sample (0.5 ml) and internal standard flurazepam buffered with 0.1M sodium dihydrogen phosphate (pH 9) were extracted into 5 ml of organic solvent mixture (diethyl ether and dichloromethane 60:40 v/v). The organic extract was evaporated to dryness under nitrogen and the residue was re-dissolved in methanol 80 µl and approximately 30 µl of the methanolic

concentration was injected into the HPLC system. The mobile phase consisted of 32% acetonitrile in sodium dihydrogen phosphate buffer 0.04M (containing 0.1% triethylamine) at pH 7.2. The flow rate was set at 1.5 ml $min^{-1}$. A $C_{18}$ reversed-phase cartridge column (Nova-pak, Waters) linked to a $C_8$ pre-column (Nova-pak, Waters) was used and the eluate was measured by a UV detector set at 220 nm. An external standard (serum with a known concentration of flurazepam, flumazenil, midazolam and metabolites) was run at the beginning and end of each run of 20 samples. Each sample run took 40 minutes with flumazenil appearing at 4.4 minutes, 4-hydroxymidazolam at 11.7 minutes, 1-hydroxymidazolam at 14.6 minutes, the internal standard flurazepam at 20.7 minutes and midazolam at 35.3 minutes (Figure **II.8a & II.8b**).

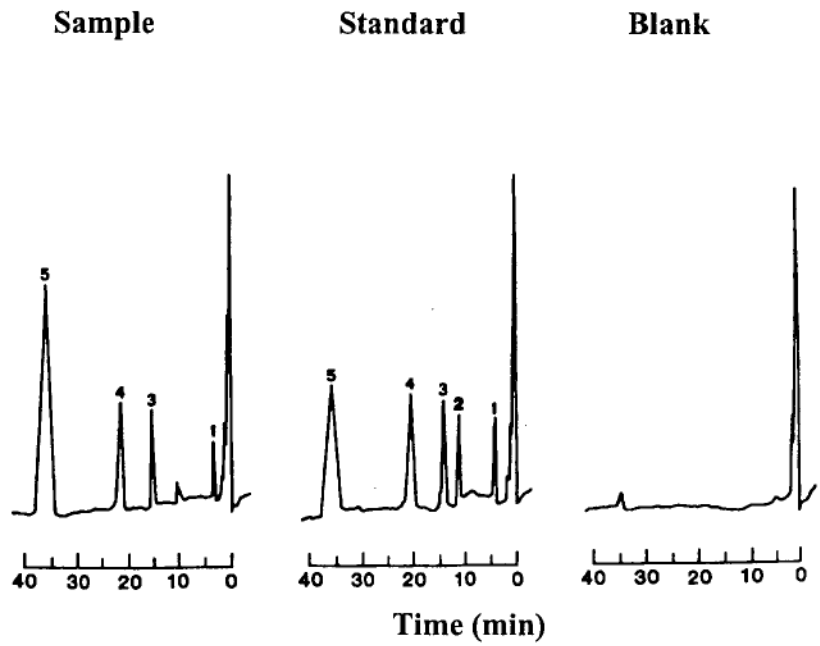


**FIGURE II.8a**: Typical chromatograms from the analysis of plasma for flumazenil (1), 4-hydroxmidazolam (2), 1-hydroxymidazolam (3), flurazepam - internal standard (4) and midazolam (5)

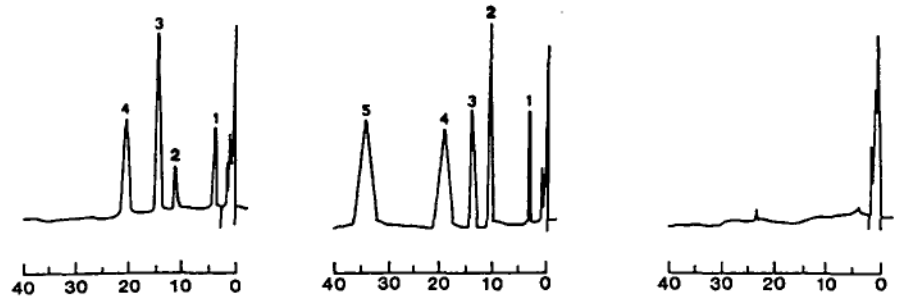


**FIGURE II.8b**: Typical chromatograms from the analysis of urine extract for flumazenil (1), 4-hydroxymidazolam (2), 1-hydroxymidazolam (3), flurazepam -internal standard (4) and midazolam (5)

The calibration graphs were linear over the ranges 4 to 200 ng $ml^{-1}$ for flumazenil, 20 to 1000 ng $ml^{-1}$ for midazolam and 10 to 500 ng $ml^{-1}$ for both 1-hydroxymidazolam and 4-hydroxymidazolam. The between-batch coefficients of variance for flumazenil 10 ng $ml^{-1}$, midazolam 50 ng $ml^{-1}$, 1-hydroxymidazolam 25 ng $ml^{-1}$ and 4-hydroxymidazolam 25 ng $ml^{-1}$ were 4.8%, 5.6%, 4.3% and 4.0%, respectively. The limit for detection for flumazenil was 4 ng $ml^{-1}$ and for midazolam and its metabolites, 10 ng $ml^{-1}$. Urine samples were analysed for unchanged drug and metabolites, and for their glucuronides after β-glucuronidase treatment for 18 hours at 37 °C. The HPLC assay was found to be specific and selective. During development of the assay procedure, it was established that flumazenil, its carboxylic and demethylated metabolites did not interact with each other under the conditions stated.

## Pharmacokinetic analysis

Flumazenil profiles were analysed using the statistical moment theory to obtain pharmacokinetic parameters (Gibaldi and Perrier, 1982a). Terminal elimination half-life ($t_{½}$), areas under plasma concentration-time curves (AUC), and apparent total body clearance (Cl) were calculated. Using the trapezoidal rule, the $AUC_{120}$ was calculated from zero to 120 min; the resident area (t = 120 min to ∞) was calculated as the ratio, $C_{120}$ : elimination rate constant. Plasma clearance was calculated from :

$$Cl_p = \frac{Dose}{AUC_0^{\infty}} \qquad (1)$$

where $Cl_p$ is the plasma clearance and $AUC_0^{\infty}$ is the area under the plasma concentration against time curve. The first order rate constants for the decline of plasma concentration after administration were obtained by linear squares regression of the logarithm of the plasma concentration against time. The steady state volume of distribution was calculated from equation :

$$V_{ss} = Cl_p \times MRT \qquad (2)$$

where $V_{ss}$ is the steady state volume of distribution and MRT is the mean residence time.

Plasma concentration time profiles of midazolam were analysed by the BITRI computer program (Chan et al, 1987, Jones et al, 1990a) which utilises the method of

residuals, whereby each curve is fitted with experimental data in terms of a bi-exponential or tri-exponential function. BITRI chooses the best fit such that the logarithms of squared deviation between exponential and computer values are minimised (Boxenbaum et al, 1974). Distribution and elimination half-lives ($T_{½}^{\alpha}$, $T_{½}^{\beta}$, $T_{½}^{\gamma}$), apparent central volume of distribution (V), apparent volume of distribution at steady state ($V^{ss}$), apparent volume of distribution in the elimination phase ($V^{\gamma}$) and total body clearance (Cl) were calculated using standard formulae (Gibaldi and Perrier, 1982b).

# STATISTICAL METHODS

Data sheets for each trial are shown in *Appendix H* and the raw data for all studies are included in *Appendices C, D, E, F* and *G*. Data in the text, tables and figures are displayed as mean (SD) and [range] and a statistical method of analysis was chosen as appropriate to the type of data to be analysed. In general, data were analysed according to their scale of measurement and the type of study being carried out. Interval scale data compared between two treatment groups of different individuals underwent analysis using an unpaired *t* test; comparison before and after a single treatment in the same individuals used a paired *t* test; if three treatment groups consisted of different individuals, an analysis of variance with Newman-Keuls post hoc analysis was used and multiple treatments in the same individuals used repeated-measures analysis of variance. For significance of association between two variables, Pearson product-moment correlation was used when both variables were continuous and normally distributed.

If it was considered that the data did not represent a normal distribution, the observations were ranked and statistical methods appropriate for data measured on an ordinal scale were employed. Comparison of ordinal scale data between two treatment groups consisting of different individuals used the Mann-Whitney U rank-sum test; before and after treatment comparison in the same individuals was performed with the Wilcoxon signed-rank test; comparison of three treatment groups consisting of different individuals used the Kruskal-Wallis analysis of variance and multiple treatments in the same individuals used the Friedman statistic. Statistical significance

for the degree of association between two variables representing ordinal scale data was determined using the Spearman rank correlation.

Nominal scale data were analysed using chi-square analysis-of-contingency table with Yates correction, except for 2x2 tables which were analysed using Fisher's exact test. Data considered suitable for parametric testing were age, weight, blood pressure, heart rate, respiratory rate, oximetric saturation values, eye opening and self identification times, anaesthetic duration, toy completion and WISC-R completion times. Data analysed using non-parametric procedures were sex, operative procedure, coma scale, sedation score, drug antagonism, incidence of side effects, time within a saturation range and desaturation incidence per hour within a saturation range.

Use of the Finapres 2300e for haemodynamic studies in children required a prior clinical comparison of its performance with other methods of blood pressure measurement (Jones et al, 1992). The strength of agreement between the noninvasive devices and the arterial line, employed a statistical method described by Bland and Altman (1983), which analysed the differences between contemporaneous arterial line measurements and the blood pressure readings from the Finapres and an oscillometric device.

Statistical analysis was executed on a 33MHz Comtech 486 personal computer using the computer interactive statistics programs Minitab™ ver 7.2 (Minitab Inc., State College, Pennsylvania, USA) and CSS:Statistica™ ver 3.1 (Statsoft Inc., Tulsa, Oklahoma, USA).

A $p$ value of 0.05 was chosen as the Type I or $\alpha$ error for all studies. The methods used are described in full in the manuals accompanying the statistics software (Ryan et al, 1985; Minitab reference manual, 1989; CSS:Statistica Vol I-III, 1991) and for general statistical guidance Glantz (1989) and Swinscow (1983) were used.

# *CHAPTER III*

# MIDAZOLAM

# AS A

# PREMEDICANT

# EFFECT OF PREMEDICATION ON OXYGEN SATURATION

The pulse oximeter has become a vital instrument in the detection of perioperative hypoxaemia (Severinghaus and Kelleher, 1992). Previous studies of the effect of premedication on arterial oxygenation using intermittent blood gas sampling have reported conflicting results (Jones et al, 1990; Pierce and Carofalo, 1965; Kopman and Ramirez-Inawat, 1980) and few workers have employed continuous pulse oximetry to examine the preoperative period (de Santos et al, 1991; Roelofse and de-V-Joubert, 1990). Continuous oximetric data acquisition should overcome the limitations of intermittent data sampling and permit a more accurate comparison of the effect on blood oxygenation of premedicant drug regimens. However, to ensure accurate inferences are drawn from the saturation data, retrospective evaluation of perioperative desaturation data, employing the computer programme Satmaster™ (Einstein et al, 1992), is necessary (Jones et al 1992).

To be an effective oral premedicant, midazolam has to be given in a relatively large dose per body weight to children because of the first-pass effect through the liver (Feld et al, 1990). Intramuscular pethidine and atropine has been used as a standard premedication in children for many years because it supposedly causes less respiratory depression than morphine (Feychting, 1985). The aim of this study was to compare the effect of these two premedication regimens on arterial oxygen saturation in the post premedication period and the influence, if any, of premedication on the episodic desaturation incidence during the first postoperative 8 hour period, employing evaluated, continuous pulse oximetry in children undergoing minor surgery.

# MATERIALS AND METHODS

Twenty ASA grade I, Chinese children aged 1-8 years undergoing elective orthopaedic or a minor general surgical procedure were investigated. Subjects were selected according to the criteria set out in the chapter II. In this particular study children were excluded if the predicted operation time was less than half or greater than two hours.

Oximetry data were recorded continuously during four time periods: whilst asleep, on the night before surgery; the period after the premedicant was administered and before transfer to the operating suite; postoperatively in the recovery room; and for a further 8 hours after the child had returned to the general ward (Figure **III.1**).

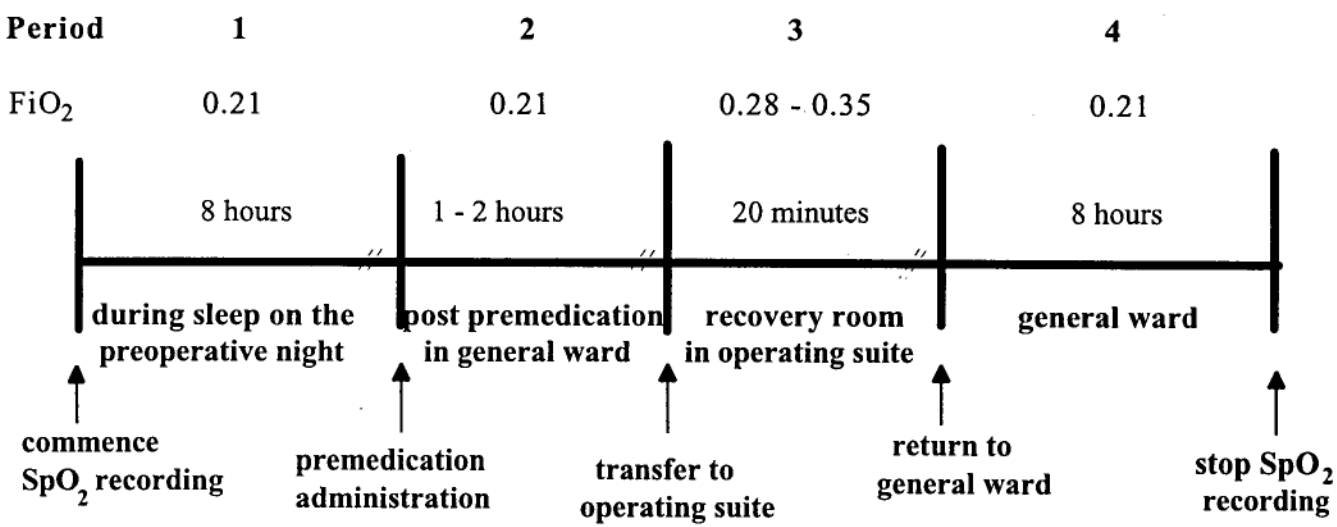


**FIGURE III.1**: Periods of data collection showing approximate duration of saturation data acquisition, concurrent $Fi_1O_2$ administered and patient location

A Nellcor D-20/250 Oxisensor™ probe was attached to the great toe of each child and the same Nellcor N-200E oximeter was connected to each patient throughout the study. Proper function of the oximeter was checked by activating the oximeter's 'self-check' routine and prior attachment of the instrument to one of the investigators. The serial communication port of the oximeter was connected to an Amstrad 386DX laptop computer. Oximetry, pulse rate and signal amplitude data were sampled 60 times a minute and displayed by Satmaster™ (EMG Scientific) on the computer screen. On completion of the study the data were downloaded to disk for subsequent analysis. Satmaster was programmed to invalidate zero signal strength data occurring with probe disconnection. Each oximetry profile was examined by one of the investigators and artefactual desaturation episodes attributed to probe movement were discarded before compilation of the data (Jones et al, 1992). An acute desaturation episode for the purpose of this study was defined as a decrease in oxygen saturation of more than 2% to less than 95% for more than 15 sec duration.

Patients were randomly allocated to receive either pethidine 1 mg $kg^{-1}$ and atropine 0.02 mg $kg^{-1}$ intramuscularly one and a half hour before surgery (n=10), or midazolam 0.5 mg $kg^{-1}$ and atropine 0.02 mg $kg^{-1}$ orally, two hours before surgery (n=10). EMLA emulsion cream 2 g (lignocaine 25 mg $g^{-1}$ and prilocaine 25 mg $g^{-1}$) was also applied to the dorsum of the hand with premedication administration to facilitate painless i.v. cannula insertion in the operating suite. In the operating suite a standard anaesthetic technique was administered to both groups of patients. Induction was with fentanyl 1μg $kg^{-1}$ and propofol 2 mg $kg^{-1}$, the patient was paralysed with atracurium 0.5 mg $kg^{-1}$, the trachea intubated and the lungs ventilated to normocapnia.

A subjective assessment of tonsillar size and a graded view of glottal exposure were noted during direct laryngoscopy (Cormack and Lehane, 1984). Thereafter anaesthesia was maintained with 67% nitrous oxide and 1.0-1.5% isoflurane in oxygen, with additional increments of fentanyl 1 $\mu g\ kg^{-1}hr^{-1}$ and atracurium 0.2 $mg\ kg^{-1}$ every 30 min, administered as required. At the completion of surgery neuromuscular blockade was antagonised with neostigmine 0.05 $mg\ kg^{-1}$ and atropine 0.04 $mg\ kg^{-1}$, extubated 'awake' observing the usual clinical criteria for adequate neuromuscular function (Viby Mogensen, 1982), transferred to the recovery room and given oxygen ($F_IO_2$ 0.28-35) via a Hudson mask until discharge to the ward, thereafter breathing air.

Statistical significance ($p < 0.05$) was determined for age, weight and anaesthetic time data by unpaired t-test; sex and operative procedure data by the Fisher exact probability test, comparison of oxygen saturation data between treatment groups were analysed by the Mann-Whitney rank-sum test and the Wilcoxon signed-rank test was employed for before and after premedication comparison of data in the same patient.

## RESULTS

Both groups were comparable for age, weight, sex, anaesthetic time, operative procedure and no child had a history of previous respiratory disease (Table **III.1**). At direct laryngoscopy all children were found to be Cormack and Lehane grade 1 (Cormack and Lehane, 1984) and no child had tonsillar tissue projecting beyond the palatopharyngeal and palatoglossal arches into the oropharynx.

**TABLE III.1** Demographic data. *Interval scale data are mean (SD) and were analysed using the unpaired t test. Nominal scale data were analysed using the Fisher exact probability test.*

| **Patient data** | **Pethidine group** (n = 10) | **Midazolam group** (n = 10) | ***p* value** |
|---|---|---|---|
| **Age** (yr) | 3.8 (1.8) | 4.6 (2.6) | 0.44 |
| **Weight** (kg) | 16.3 (5.7) | 16.3 (2.3) | 1 |
| **Anaesthetic time** (min) | 63.5 (39.9) | 58.0 (21.4) | 0.71 |
| **Sex** (male) | 9 | 6 | 0.15 |
| **Operative procedure:** | | | |
| orthopaedic | 4 | 6 | |
| general surgical | 6 | 4 | 0.32 |

A total of 335 hours of oximetric data was collected from 20 children. The total raw data time recorded with a saturation less than 95% in all children was 951.5 min, which after evaluation with the template, resulted in a total of 228 minutes of valid desaturation time during the four study periods ($p<0.001$). The raw desaturation time in the period after premedication before operation was 132.5 min which after evaluation resulted in 33.5 min of valid desaturation time ($p< 0.03$). There was no difference in mean oxygen saturation between the two groups during the four periods under investigation, nor the mean percentage of time the oxygen saturation was less than 95% (Table **III.2**).

**TABLE III.2** Saturation data during the four study periods . *Data are mean (SD)*

| Data collection period | Duration of data collection period per patient (hr) | | Mean $S_pO_2$ (%) | | *p* value (*t*-test) | Mean percentage of time with an $S_pO_2 < 95\%$ | | *p* value (Mann Whitney *U*-test) |
|---|---|---|---|---|---|---|---|---|
| **Groups** | **Pethidine** | **Midazolam** | **Pethidine** | **Midazolam** | | **Pethidine** | **Midazolam** | |
| **Preoperative night** | 11.04 (1.22) | 9.63 (0.84) | 98.9 (0.57) | 98.7 (0.67) | 0.48 | 0.2 (0.63) | 1.1 (1.85) | 0.08 |
| **After premedication** | 1.29 (0.34) | 1.80 (0.31) | 98.6 (0.84) | 98.7 (0.94) | 0.81 | 1.6 (2.90) | 2.8 (5.00) | 0.49 |
| **Recovery area** | 0.26 (0.13) | 0.35 (0.19) | 99.4 (0.70) | 99.1 (1.20) | 0.50 | 0.6 (1.30) | 5.7 (12.10) | 0.35 |
| **General ward** | 7.05 (1.05) | 6.52 (1.96) | 98.5 (0.70) | 98.4 (0.84) | 0.78 | 0.8 (1.30) | 1.1 (1.40) | 0.60 |

Within group comparison of the percentage of time recorded with an oxygen saturation < 95% during the preoperative night and during the period after premedication, prior to transfer to the operating suite, revealed no significant difference (Table **III.3**).

**TABLE III.3** A comparison of saturation data before and after premedication. D*ata are mean (SD).*

| **Groups** | **Pethidine group n = 10** | | **Midazolam group n = 10** | |
|---|---|---|---|---|
| **Data collection periods** | ***Mean % of time with an*** $S_pO_2 < 95\%$ | ***Desaturation episodes*** $hr^{-1}$ ***with an*** $S_pO_2 < 95\%$ ***for > 15 sec*** | ***Mean % of time with an*** $S_pO_2 < 95\%$ | ***Desaturation episodes*** $hr^{-1}$ ***with an*** $S_pO_2 < 95\%$ ***for > 15 sec*** |
| **Preoperative night** | 0.2 (0.63) | 0.36 (0.62) | 1.1 (1.85) | 0.65 (0.73) |
| **After premedication** | 1.6 (2.90) | 1.48 (2.60) | 2.8 (5.00) | 1.82 (3.47) |
| ***p* value (Wilcoxon)** | 0.11 | 0.37 | 0.34 | 0.51 |

Furthermore, a between group comparison in the post premedication period of the incidence of desaturation episodes per hour below 95% and of greater than 15 seconds duration, revealed no significant difference ($p$=0.8), nor was the patient's post-premedication incidence of desaturation episodes significantly different from the preoperative incidence (Table **III.3**). Twenty four (65%) of the 37 valid post premedication desaturation episodes occurred 45 to 105 minutes after premedication administration.

Following premedication, only two patients (one from each group) recorded 5 or more desaturation episodes per hour with an $S_pO_2$ < 95% and >15 sec duration, and a genuine desaturation less than 80% for longer than 15 seconds was not recorded in any patients, at any time during the study. The minimum $S_pO_2$ recorded after premedication in either group was 85% and the longest duration of a particular episode was 75 seconds to a lowest saturation of 91%.

# DISCUSSION

This study demonstrates that in otherwise healthy children, the use of two common premedication regimens employing either pethidine or midazolam, does not significantly depress oxygen saturation. These findings are at variance with previous studies in healthy children, one of which showed that both intramuscular and intranasal midazolam (0.2 mg $kg^{-1}$) caused a significant decrease in arterial oxygen saturation from baseline values (de Santos et al, 1991). However Rose and colleagues, using intranasal midazolam demonstrated no change in oxygen saturation levels 15 minutes after administration (Rose et al, 1990). In another study, premedication with rectal midazolam (0.35-0.45 mg $kg^{-1}$) lowered oxygen saturation thirty minutes after administration when compared with a placebo (Roelofse and de-V-Joubert, 1990).

These apparently conflicting results can be explained by our ability to exclude movement-induced artefactual desaturation data before determining the incidence of genuine desaturation episodes (Langton and Hanning, 1990). Patient movement resulted in an overestimation of desaturation time by 75% in this study, confirming similar findings in patients following spinal surgery (Jones et al, 1992). Oxygen desaturation which induces a motor response will not result in rejection by application of the template because the desaturation pattern will not be preceded by a concomitant change in signal amplitude. However genuine oxygen desaturation and probe movement could occur together and these data would be rejected by the template. The route of administration of midazolam in children significantly alters bioavailability and the time to peak serum concentration, making comparison with other studies

difficult. Bioequivalence should be present between a 0.2 mg $kg^{-1}$ intramuscular and 0.5 mg $kg^{-1}$ oral dose of midazolam (Payne et al, 1989). Atropine was administered intramuscularly to the pethidine group and orally to the midazolam group. A differential effect on anatomical dead space resulting from different atropine concentration profiles is a possibility (Olsson et al, 1983), however anatomical dead space reportedly increased by only 12% following intravenous atropine in adults (Nunn et al, 1964) and therefore it is unlikely that the different route of administration of atropine significantly influenced oxygen saturation in this study. Peak serum concentration of midazolam occurs 15 minutes after intramuscular and nasal administration, and 45 to 120 minutes after oral administration. Peak serum concentrations should coincide with the onset of sedation and any decrease in arterial oxygen saturation should be most obvious at this time (de Santos et al, 1991). Other investigators have demonstrated that slow intravenous administration of midazolam to healthy volunteers provides no independent protection from respiratory depression, and respiratory complications are more closely related to the total dose of midazolam (Alexander et al, 1992, Dahan and Ward, 1991). The peak incidence of the recorded minor desaturation episodes in our study occurred 45 to 105 minutes after administration of both pethidine and midazolam. It is possible that our premedication regimen was not as sedative as those used in the Spanish study and did not depress respiration to the same degree, therefore resulting in a lower incidence of recorded desaturation episodes. Also, this study population may not match those in the other series, but a pharmacokinetic explanation of our oximetry findings is difficult to establish. The small lean body mass of Chinese children should result in a smaller central volume of distribution, higher peak serum concentration of midazolam, a more

intense level of sedation of shorter duration, and consequently a higher incidence of episodic desaturation (Greenblatt et al, 1984). This was not the case, and in separate work, it was shown that the serum concentration of midazolam 2 hours after oral administration in Chinese children was similar to the serum concentration reported by other workers using a similar dosing regimen in Caucasian children (Jones et al, 1993). Furthermore, none of the children in this study had any predisposition to upper airway obstruction or arterial oxygen desaturation and all were ASA class I. There are no published desaturation studies following pethidine premedication but a low clinically relevant incidence would be expected because the drug has been used for many years and significant data would have been previously reported. Peak respiratory depression in adults is observed within an hour of receiving intramuscular pethidine and there is a return towards baseline values commencing at about 2 hours (Edwards et al, 1982). Pethidine premedication did not depress ventilation in the children in this study to a degree where significant arterial oxygen desaturation occurred, nor to a level that was clinically or statistically significantly different from each child's own sleep $S_pO_2$.

This study showed that neither oral midazolam 0.5 mg $kg^{-1}$, nor intramuscular pethidine 1.0 mg $kg^{-1}$ given as premedicants, significantly depressed $S_pO_2$ in otherwise healthy children presenting for minor surgical procedures. These findings have recently been endorsed by the work of Tyler and colleagues (Tyler et al, 1995). Furthermore, raw oximetry data requires careful evaluation and elimination of movement artefact before conclusions regarding the incidence of desaturation can be drawn. If analgesia is not a premedication requirement, then oral midazolam confers

the advantage over pethidine of avoiding the pain of an intramuscular injection, without compromising oxygen saturation.

Having established that midazolam 0.5 mg $kg^{-1}$ is an effective premedication regimen in children and that no dangerous effects were detected during the study, the next chapter investigates its sedative and anxiolytic properties. The association between these effects and serum midazolam concentrations was also determined.

# EFFECT OF MIDAZOLAM PREMEDICATION ON PREOPERATIVE PSYCHOMOTOR PERFORMANCE, MOOD AND SEDATION

Anaesthesia for paediatric ambulatory surgery aims to rapidly return the child to a "home-readiness" state and agents with suitable pharmacokinetics are now applied in the outpatient setting (White, 1986). Pharmacological attenuation of the normal response to fear presents a child who is co-operative and calm when separated from his parents and during induction of anaesthesia, and this controlled behaviour also helps allay parental anxiety immediately prior to surgery (Westhorpe, 1990). Circumcision is a suitable surgical procedure for paediatric ambulatory surgery because of the reduction in displacement anxiety for the child, decreased exposure to nosocomial infection, short operative duration, low incidence of complications, and the ease and reliability of providing effective postoperative pain relief (Hannallah and Epstein, 1991). Oral, sweetened midazolam is considered a suitable agent for inducing anxiolysis but some anaesthetists hold the view that preoperative midazolam administration delays recovery and that proper psychological preparation makes premedicant drug administration to a child unnecessary (White, 1985).

The aim of this study was to evaluate the premedicant effect of midazolam on sedation, mood and psychomotor performance in children undergoing circumcision.

# MATERIALS AND METHODS

Thirty ASA grade I Chinese children, aged 4-12 yr, undergoing circumcision for treatment of phimosis were investigated. Children were excluded from the study if there was a history of asthma or allergies; previous adverse anaesthetic experience; halothane anaesthesia within the previous 1 month; hepatic, renal, respiratory, cardiac or haematological disease; developmental disability or age less than 4 yr. The day prior to surgery, each child was familiarised with a post-box toy and the completion time of his best seven attempts recorded. The children also underwent a Wechsler intelligence scale (WISC-R) coding performance assessment, matched for race (HK-WISC Manual, 1981). These assessments were performed by the same investigator at all assessment times, for all patients in the study.

On the day of surgery, EMLA emulsion cream 2 g (lignocaine 25 mg $g^{-1}$ and prilocaine 25 mg $g^{-1}$) was applied to the cubital fossa of the non-dominant arm 2 hr before premedication with midazolam 0.5 mg $kg^{-1}$ (maximum dose 15 mg) and atropine 0.02 mg $kg^{-1}$ by mouth. On administration of the premedicant, a 23-gauge cannula was inserted into a vein underlying the EMLA-pretreated area. Blood samples (1.0 ml) were collected into tubes containing lithium-heparin (Sarstedt LH/5) for measurement of the plasma concentration of midazolam at 30, 60, 90 and 120 min after oral premedication administration. At each of the blood collection times the child was offered the post-box toy and his fastest completion time at a single attempt recorded. The child was also asked to complete the WISC-R coding test within 2 min and scored according to his performance. The raw WISC-R data was then scaled to

produce score equivalents adjusted for the child's age. The child's best, preoperative, unmedicated performance was divided by the child's postmedication performance at each assessment point for both the PBT and WISC-R, and the data expressed as the post box toy completion ratio (PBTR) and WISC-R scale ratio.

The child's co-operation and mood level were recorded using a structured observation score (Krane et al, 1987)(Table **III.4**).

**TABLE III.4**: Structured observation score *(modified from Krane et al, 1987)*

| MOOD | Score |
|---|---|
| laughing, euphoric | 1 |
| happy, playful | 2 |
| calm, drowsy, sleepy | 3 |
| irritable but calmed by mother | 4 |
| screaming, inconsolable | 5 |

Level of sedation was assessed using the modified Steward coma scale (Robertson et al, 1977)(Table **III.5**).

**TABLE III.5**: Modified Steward coma scale (Robertson et al, 1977)

| **Airway** | | **Consciousness** | | **Activity** | |
|---|---|---|---|---|---|
| opening mouth or coughing on command | **3** | fully awake, eyes open, conversing | **4** | raising one arm on command | **2** |
| no voluntary cough, clear airway without support | **2** | lightly asleep, eyes opening intermittently | **3** | non-purposeful movement | **1** |
| obstruction on neck flexion, airway clear without support on extension | **1** | eyes open on command or in response to name | **2** | not moving | **0** |
| airway obstructed without support | **0** | responding to ear pinching | **1** | | |
| | | not responding | **0** | | |

Add scores for **Airway, Consciousness** and **Activity**: **TOTAL SCORE :**

On arrival in the operating suite, all children were assessed by the same anaesthetist as agitated or crying, aware and apparently anxiety free, drowsy, or asleep but responsive to command (Jones et al, 1990). The awake children were then asked if they felt frightened and if so, to specify the cause of their anxiety.

Plasma samples were obtained from blood after centrifugation for 15 min at 3000 r.p.m. and stored at -20°C before assay for midazolam employing an HPLC technique with UV detection at 220 nm using a programmable multiwavelength detector (Waters 490E). Midazolam in plasma and internal standard flurazepam

buffered with sodium dihydrogen phosphate (0.1M) at pH 9, were extracted into 5 ml organic solvent mixture (diethyl ether and dichloromethane in the ratio 60:40 v/v). The organic extract was evaporated to dryness under nitrogen and the residue was re-dissolved in methanol (80 µl) and approximately 30 µl of the methanolic concentration was injected into the HPLC system. The mobile phase consisted of 32% acetonitrile in 0.04 M sodium dihydrogen phosphate buffer (containing 0.1% triethylamine) at pH 7.0. The flow rate was set at 1.5 ml $min^{-1}$. A $C_{18}$ reverse phase cartridge column (Nova-pak, Waters) linked to a $C_{18}$ pre-column was used and the eluate was measured by a UV detector set at 220 nm. The calibration graphs were linear over the range 40 to 2000 ng $ml^{-1}$ with coefficients of variation ranging from 1.5 to 11.8%. The between-batch coefficient of variance at 40 ng $ml^{-1}$ was 4.8% and 1.5% at 500 ng $ml^{-1}$. The limit for detection for midazolam was 10 ng $ml^{-1}$. The HPLC assay was found to be specific and selective.

Correlation between the post box toy and WISC-R raw data was determined using Pearson product-moment correlation. To test any association between serum midazolam concentrations and the psychomotor performance ratios, Spearman rank correlation was employed using the computer interactive statistical program CSS:Statistica™.

# RESULTS

The 30 children had a mean age of 7.1(2.3)[4-12] yr and a mean body weight of 20.6(8.7)[15-37] kg. On arrival in the operating suite only one child was asleep and no child was crying or appeared distressed. On specific questioning, 20 children endorsed their objective appearance, stating that they were not frightened. The remaining children were frightened of either pain and needles, going to sleep and dying, strangers, or being separated from their mother Table **III.6**.

**TABLE III.6** Preoperative mood following oral midazolam (0.5 mg $kg^{-1}$) premedication (n = 30).

| Objective preoperative premedication assessment (n) | | Subjective preoperative premedication assessment (n) | |
|---|---|---|---|
| asleep/drowsy | 1 | not frightened | 20 |
| awake | 29 | pain/needles | 10 |
| crying | 0 | dying/sleeping | 9 |
| | | leaving mummy | 5 |
| | | strangers | 3 |

The mean fastest preoperative post box toy completion time for the 30 children was 18.1(5.9)[11-37] sec and the mean highest preoperative WISC-R scale performance was 17.1(2.4)[11-19]. The preoperative PBTR and WISC-R ratio at different times after premedication are shown in Table **III.7**. The relationship between

midazolam concentrations, PBTR and WISC-R scale ratio are shown in Figure **III.2**. Raw preoperative serum midazolam concentration data for the 30 children are tabulated in *Appendix G*.

**TABLE III.7** Preoperative PBTR and WISC-R ratio at different times after premedication. *Data are mean (SD)[range].*

| Time after premedication (min) | PBTR | WISC-R ratio |
|---|---|---|
| **30** | 0.67(0.18)[0.30-0.97] | 0.84(0.23)[0.33-1.17] |
| **60** | 0.69(0.16)[0.36-0.94] | 0.79(0.21)[0.21-1.06] |
| **90** | 0.74(0.16)[0.43-1.10] | 0.88(0.20)[0.38-1.20] |
| **120** | 0.75(0.15)[0.48-1.10] | 0.91(0.25)[0.16-1.55] |

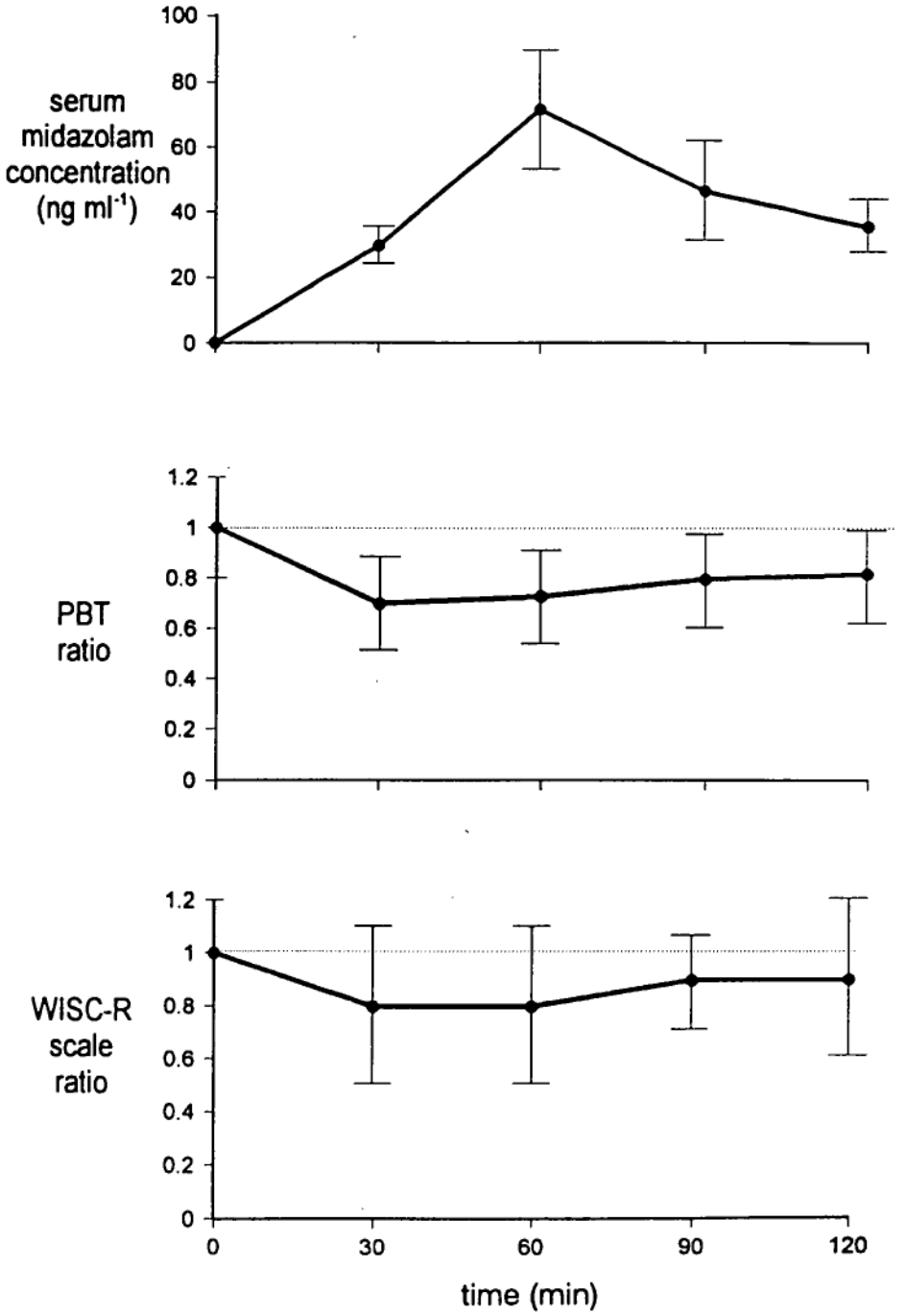


**FIGURE III.2** Preoperative serum midazolam concentration, post box toy ratio (PBTR) and WISC-R scale ratio (n = 30).

There was a significant decline from preoperative unmedicated, fastest performance for both PBT and WISC-R, 30 minutes after midazolam administration ($p$ <0.001, 0.003 respectively), however there was improvement over the following 90 min with WISC-R performance almost returning to unpremedicated levels. Midazolam concentrations peaked to 72.2(18.7) ng $ml^{-1}$ at the 60 minute sample point and declined to a mean preoperative level of 35.7(7.9) ng $ml^{-1}$ at 2 hr. Plotting the log of the PBTR and the WISC-R scale ratio data for all the preoperative assessments demonstrated poor correlation (r=0.3) (Figure **III.3**). Correlation between serum midazolam concentration and the WISC-R assessment was also poor (r = 0.01) and with PBTR, only slightly better (r = 0.2) (Figure **III.4 & .5**).

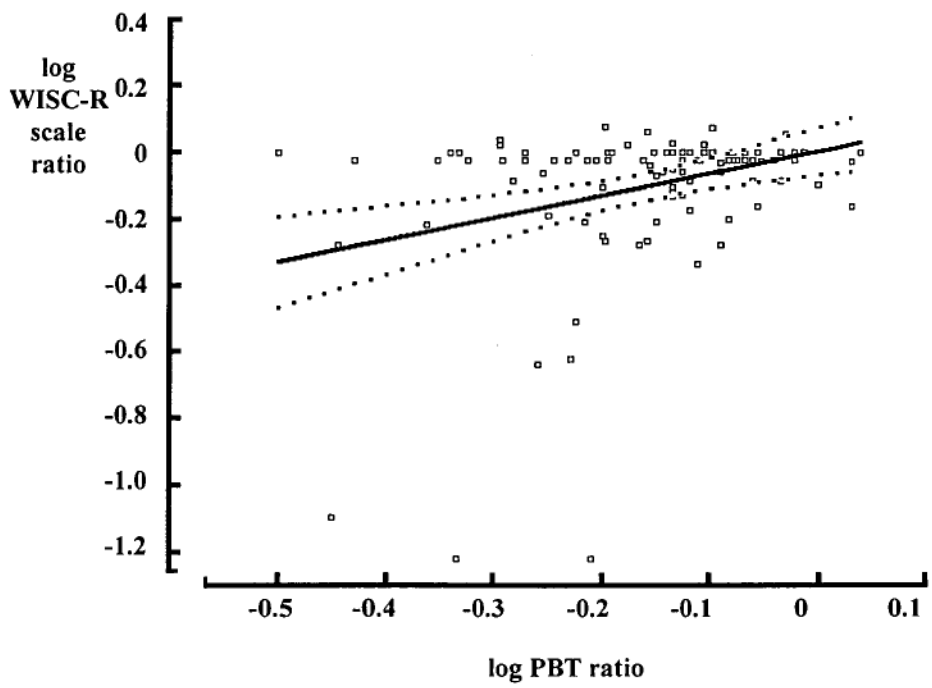


**FIGURE III.3** Preoperative logarithmic data plot of WISC-R scale ratio and PBT ratio (n = 30). Dotted lines represent 95% confidence intervals.

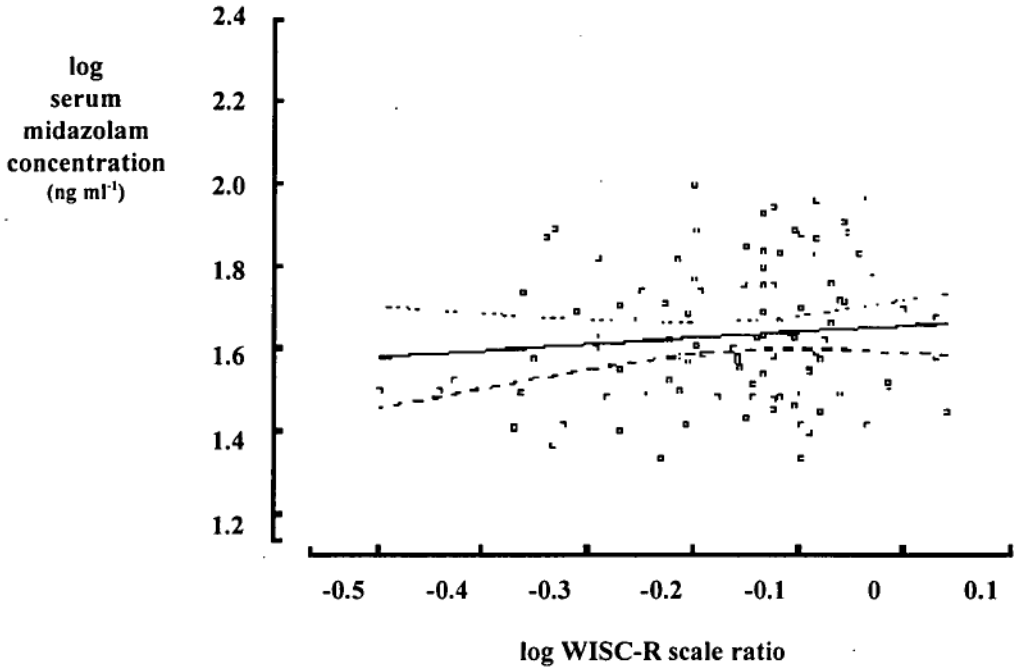


**FIGURE III.4** Preoperative logarithmic data plot of serum midazolam concentration (ng $ml^{-1}$) and WISC-R scale ratio (n = 30). Dotted lines represent 95% confidence intervals.

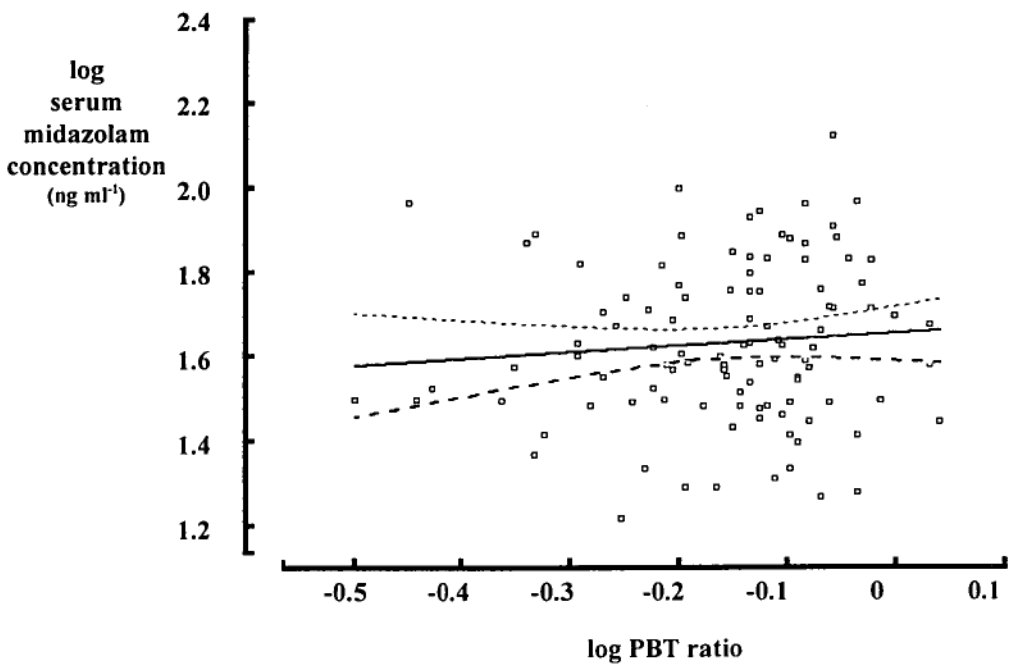


**FIGURE III.5** Preoperative logarithmic data plot of serum midazolam concentration (ng ml-1) and post box toy (PBT) ratio (n = 30). Dotted lines represent 95% confidence intervals.

Only one child refused assessment on two occasions when presented with the psychomotor tests after premedication. The two youngest children in the study were classified as irritable on a further 3 occasions but were calmed by mother and performed the assessment. All other children were either happy and playful or sleepy. Nine children went to sleep following administration of midazolam with the incidence being evenly distributed throughout the two hour study period (Table **III.8**).

**TABLE III.8** Sedative effect and mood of the children at the times of assessment following midazolam premedication.

| | Incidence of | | | |
|---|---|---|---|---|
| **Time after midazolam premedication (min)** | **children asleep (n = 9)** | **unhappy children (n = 2)** | **PBT refusal (n = 1)** | **happy / playful (n = 28)** |
| **30** | 3 | 2 | 1 | 28 |
| **60** | 4 | 0 | 1 | 29 |
| **90** | 4 | 1 | 0 | 28 |
| **120** | 4 | 2 | 0 | 28 |

**n** = the total number of children asleep, unhappy or unco-operative, happy and co-operative.

# DISCUSSION

The aim oral premedication is to obtain a co-operative patient prior to induction of anaesthesia who will accept the face mask or insertion of a venous cannula without distress. The place of midazolam 0.5 mg $kg^{-1}$ as an oral premedicant in children appears now to be established as effective (McMillan et al, 1992) and the results of this study endorse this view. The incidence of sleep at each preoperative assessment point was equally distributed over the two hour period and appeared unrelated to serum midazolam levels. Midazolam is extensively bound to plasma proteins (94-98%) and small changes in binding may cause large alterations in clinical response (Amrein et al,1988). There are no published data describing the variation between children in midazolam binding, and although the unbound fraction of midazolam may show a correlation with sedation. Sleep incidence data in this study may have been confounded by other factors, such as, the age of the child, the time of day when surgery was conducted and the position of the child on the operating list. Furthermore, the relatively frequent psychomotor assessments and blood sampling combined to produce a relatively stressful preoperative environment for the child which was not conducive to sleep. Weldon and colleagues found the sedative effect of midazolam to be maximal 30 min after oral administration (Weldon et al, 1992). Although most of the children in this study were not asleep at the 30 min sample point, 56% of them scored their poorest psychomotor performance at this time.

Patient co-operation lowers anxiety levels during induction of anaesthesia and this improves performance of the staff delivering care. The pre-induction serum

midazolam levels in this study were in the adult anxiolytic range of 20-50 $\mu g\ ml^{-1}$ (Lauven and Kulka, 1990; Nilsson, 1991). All children arrived in the operating room appearing quiet and calm and specific fears were difficult to elicit. Even with explicit questioning of the older children, 66% denied feeling frightened. The mean preinduction midazolam concentration was 35.7 $\mu g\ ml^{-1}$ and children who expressed their fears did not demonstrate low serum midazolam concentrations. Younger children who admitted fear demonstrated a non-specific anxiety, usually responding in the affirmative to all questions. Weldon and colleagues showed that 95% of the children separated from their parents within 45 min of premedication had satisfactory separation scores, compared to only 66% of those separated after 45 min (Weldon et al, 1992). Parnis and colleagues found that patients who received midazolam 0.5 mg $kg^{-1}$ were more likely to be asleep or awake and calm than those receiving a placebo, diazepam or midazolam 0.25 mg $kg^{-1}$ (Parnis et al, 1992). Fifty two subjects investigated in studies described in Chapter IV were also premedicated with midazolam 0.5 mg $kg^{-1}$ and atropine administered orally 2 hr preoperatively and were assessed preinduction. Ninety percent were awake and apparently anxiety free, two patients were asleep and three children were visibly distressed when presenting for induction of anaesthesia. Vetter compared children receiving midazolam, diazepam or placebo and concluded that even without premedication, a majority of the children did not react negatively to an impending anaesthetic (Vetter, 1993). However Vetter found midazolam to be superior to the placebo in facilitating the initial acceptance of the anaesthetic induction mask. The results of our premedication assessments are more in line with the findings of McMillan and colleagues (McMillan et al, 1992) than those of Feld et al (Feld et al, 1990) who reported a relatively low incidence of

"excellent" anxiolysis following midazolam premedication. There are many differences between each of the studies referred to. The age range of the patients, differing times of evaluation and crude method of mood assessment, all limit the usefulness of "separation anxiety" comparisons (Hindmarch and Bhatti, 1987). Coma score was recorded but computed data provided no relevant clinical information, as even children who fell asleep were easily awakened.

This study confirms the work of Payne and co-workers who measured peak serum concentrations at 60 minutes following oral administration of midazolam 0.5 mg $kg^{-1}$ (Payne et al, 1989). The mean peak midazolam concentration measured during this study at 60 min was 72.2 $\mu g\ ml^{-1}$, which falls within the sedative range and well below hypnotic levels. The occurrence of sleep at 60 min was randomly observed and no relationship between serum midazolam concentrations and sleep incidence was demonstrated. Furthermore, peak serum levels did not correlate closely with the maximum decline in psychomotor performance, which occurred 30 minutes after drug administration in this study. The early maximum decline in performance may have been due to lack of practice rather than drug effect; the latter being masked by subsequent performance improvement despite the increasing serum midazolam concentration. The degree of performance impairment was the same for both tests but correlation between the WISC-R and PBTR data was weak. This may be explained by the relative weighting of the cognitive and physical components of each test (Sanders, 1991). The WISC-R required sophisticated matching of symbols and shapes but was not physically demanding, requiring only legible writing in a designated space. The PBT required recognition of simple shapes but placement in the matching holes

required small muscle control and co-ordination. An observed postoperative improvement in correlation between the WISC-R and PBTR may be attributed to a reduction in effect of this cognitive and physical difference, due to the residual influence of general anaesthesia. Although the PBTR lacks discriminant efficiency, better methods of assessment such as critical flicker fusion threshold or choice reaction time, are very difficult to assess in children (Hindmarch and Bhatti, 1987). Most studies in children have simply used clinical parameters such as awakening or eye opening, to assess recovery (Weldon et al, 1992). However, children seem to enjoy post box toy completion assessment and the test is relatively easy to perform, and as such provides a useful assessment of "street-readiness" for discharge and a measurement of the gross effect of premedication on psychomotor performance.

This study suggests that the optimal timing for oral administration of the premedicant midazolam 0.5 mg $kg^{-1}$ is one hour prior to tranfer to the operating room so that serum drug concentrations will be maximal and anxiolytic at the time of induction. However, maximal serum drug concentrations and desired effect do not always correlate. The lowest post box toy performance occurred at 30 minutes, endorsing the parental separation and face mask acceptance data of Weldon and colleagues, who recommend timing of premedication 30 to 60 minutes prior to induction of anaesthesia (Weldon et al, 1992). The sedative and anxiolytic effects of the drug help to provide a quiet environment for a smooth induction of anaesthesia, particularly on those occasions when it is impossible to avoid parental separation.

# *CHAPTER IV*

# MIDAZOLAM

# AS AN

# INDUCTION AGENT

# PHARMACOKINETICS OF

# MIDAZOLAM AND FLUMAZENIL

The previous chapters have endorsed the findings of other workers and demonstrated that midazolam is a suitable premedicant for use in paediatric patients (Tolia et al, 1991; Feld et al, 1990). Flumazenil has been shown to provide rapid, effective and safe antagonism of the hypnotic effects of midazolam (Sanders et al, 1991). The disposition of midazolam in children has been studied by a number of workers (Salonen et al, 1987; Payne et al, 1989; Rey et al, 1991) but the contemporaneous disposition of flumazenil in children has not previously been reported.

This present study was undertaken to measure simultaneous midazolam and flumazenil pharmacokinetics and their relationship to psychomotor performance in children in the early postoperative period.

## MATERIALS AND METHODS

Twelve ASA grade I Chinese children, aged 5-9 yr, undergoing circumcision for the treatment of phimosis were studied. Children were excluded from the study if there was a history of asthma or allergies; previous adverse anaesthetic experience; anaesthesia within the previous month; hepatic, renal, respiratory, cardiac or haematological disease; developmental disability or age less than 4 years.

The day prior to surgery, each child was familiarised with a post-box toy and the completion time of his best performance on seven attempts recorded. On the day of surgery, the patient was premedicated with midazolam 0.5 mg $kg^{-1}$ (maximum dose 15 mg) and atropine 0.02 mg $kg^{-1}$ by mouth 2 h before operation. EMLA emulsion cream 2 g (lignocaine 25 mg $g^{-1}$ and prilocaine 25 mg $g^{-1}$ ) was applied to the dorsum of the hand and the contralateral cubital fossa. On arrival in the operating suite, all children were assessed by the same anaesthetist and recorded as agitated or crying, aware and apparently anxiety free, drowsy, or asleep but responsive to command (Jones et al, 1990). A 23-gauge cannula was inserted into a vein underlying each EMLA-pretreated area. Anaesthesia was induced with alfentanil 5 $\mu$ $kg^{-1}$ i.v. followed 60 sec later by midazolam 0.5 mg $kg^{-1}$ administered over 30 seconds (Salonen et al, 1987). Time zero was taken at completion of the midazolam injection. The child was given atracurium 0.5 mg $kg^{-1}$, intubated and thereafter, anaesthesia was maintained with 67% nitrous oxide and 0.5% isoflurane in oxygen via a Mapleson F breathing system with hand ventilation to an end-tidal carbon dioxide tension of 5 kPa. A caudal injection of 0.25% bupivacaine 0.5 ml $kg^{-1}$ was administered to all patients. Routine

monitoring devices included an electrocardiograph, non-invasive arterial pressure recorder, pulse oximeter, capnograph and inspired oxygen concentration (Datex, Cardiocap). At the end of surgery, muscle relaxation was reversed with neostigmine and atropine, the patient extubated and ventilation assisted with 100% oxygen by mask and Mapleson F circuit until spontaneous respiration had resumed. Six minutes after the administration of neostigmine, a 10 $\mu g\ kg^{-1}$ flumazenil bolus was given followed 60 seconds later by commencement of a 5 $\mu g\ kg^{-1}\ min^{-1}$ flumazenil infusion which was continued until the child could positively identify himself.

The duration of anaesthesia and cardio-respiratory data during surgery and recovery were recorded. The dose of flumazenil injected, the time from flumazenil bolus injection to spontaneous eye opening and the time until the patient could identify himself were recorded. The child's mood on awakening was assessed by an independent observer using a structured observation score (Krane et al, 1987) and systolic arterial pressure, heart rate, ventilatory frequency and modified Steward coma scale (Robertson et al, 1977) were recorded at each blood sampling time after awakening. Any side effects occurring during and following flumazenil administration were noted and the time at which any child went back to sleep after eye-opening in recovery. Immediately when the patient became co-operative he was encouraged to complete the post-box toy in the quickest possible time. The child was offered the toy at 10, 30, 60, 120, 180 and 240 min after flumazenil administration and his fastest completion time on a single attempt recorded by the same investigator. At each assessment, a post-box toy completion-time ratio (the postoperative post-box toy

completion time / the child's best timed performance on the day prior to surgery) was calculated.

Blood samples (1.0 ml) were collected into tubes containing lithium heparin for measurement of the plasma concentration of midazolam immediately prior to induction of anaesthesia and then at 2, 4, 6, 8, 10, 15, 20, 30 min and immediately before flumazenil was given. Subsequent samples were then taken at 2, 4, 6, 8, 10, 15, 20, 30, 60, 120, 180, and 240 min after flumazenil administration. Post-operatively a bulked, 24 h urine specimen was collected from each of the patients. Plasma was obtained from blood after centrifugation for 15 min at 3000 r.p.m.. Plasma samples were then stored at -20°C before assay. Flumazenil and midazolam in plasma and urine samples were determined simultaneously using a high performance liquid chromatographic (HPLC) technique with UV detection at 220 nm using a programmable photodiode array detector (Waters 994) as described in the *Chapter II.* Flumazenil profiles were analysed using the statistical moment theory to obtain pharmacokinetic parameters as described in the methods section of this thesis (Gibaldi and Perrier, 1982).

# RESULTS

On arrival in the operating suite all children were assessed as awake and appearing calm, but on specific questioning two of the children were frightened of intravenous cannula placement for induction and two children expressed fear of postoperative pain. The mean (SD) [range] maximum increase in pulse rate and systolic pressure calculated during the induction period were 22.3 (24.4)[-28 to 54] beats $min^{-1}$ and 27.3 (28.3) [108 - 2] mm Hg respectively. The induction of anaesthesia was otherwise devoid of side effects. The awakening and cardio-respiratory data associated with flumazenil administration are given in Table **IV.1**. All patients opened their eyes within 5 min of the commencement of flumazenil administration and were able to give their name within a further 2 minutes. The average dose of flumazenil administered was 27 (6.1) $\mu g\ kg^{-1}$ and the mean (SD) concentration of midazolam on awakening was 163.1 (43.7) $ng\ ml^{-1}$.

**TABLE IV.1** Demographic, anaesthetic and awakening haemodynamics data in the 12 children. *Data are mean (SD) and [range].*

| | | |
|---|---|---|
| Age (yr) | 6.5 (1.4) | [5 -9] |
| Weight (kg) | 22.0 (6.7) | [14-38.5] |
| Anaesthesia duration (min) | 37.4 (8.4) | [29-58] |
| Time from giving flumazenil to eyes open (min) | 3.1 (1.1) | [1-5] |
| Time from giving flumazenil to self-identification (min) | 4.4 (1.4) | [2-7] |
| Mean dose of flumazenil administered ($\mu g\ kg^{-1}$) | 27.0 (6.1) | [16.8-39.6] |
| Mean concentration of flumazenil on awakening ($ng\ ml^{-1}$) | 29.9(16.1) | [7-62] |
| Mean concentration of midazolam on awakening ($ng\ ml^{-1}$) | 163.1(43.7) | [92-257] |
| Mean increase in heart rate after flumazenil ($beat\ min^{-1}$) | 8.0 (16.2) | [-24 to +37] |
| Mean increase in systolic blood pressure after flumazenil (mmHg) | 11.5 (17.0) | [-8 to +53] |
| Mean increase in respiratory rate after flumazenil ($breaths\ min^{-1}$) | 4.3 (5.5) | [-8 to +10] |

Psychomotor testing using the post-box toy completion-time ratio showed that, although the children tested had a faster completion time 3 hours postoperatively compared to their own **unpractised** preoperative performance, only one child could match his **best preoperative** performance four hours after operation (Table **IV.2**). The mean pre-induction midazolam level was 47.1(15.8)[29-38] $ng\ ml^{-1}$.

**TABLE IV.2** Assessment of the antagonism of midazolam by flumazenil. *Data are mean (SD) and [range].*

| Time after flumazenil administration | Toy completion ratio | Mean midazolam level (ng $ml^{-1}$) | Mean flumazenil level (ng $ml^{-1}$) |
|---|---|---|---|
| 10 min (n = 7) | 0.31(0.12)[0.17 - 0.50] | 147 (34.4) [83 - 197] | 32.1(21.5)[14-97] |
| 20 min (n = 2) | 0.41 (0.15)[0.31 - 0.52] | 131 (29.7) [72 - 184] | 19.5(9.5)[8-42] |
| 30 min (n = 8) | 0.40(0.12)[0.18 - 0.58] | 120 (27.1) [70 - 170] | 15.7(9.1)[7-38] |
| 60 min (n = 5) | 0.39(0.12)[0.25 - 0.55] | 91 (24.6) [52 - 138] | 10.1(6.3)[3-23] |
| 120 min (n = 5) | 0.44(0.15)[0.17 - 0.55] | 59 (15.4) [40 - 87] | 4.3(5.6)[0-16] |
| 180 min (n = 5) | 0.63(0.16)[0.44 - 0.83] | 41 (9.5) [29 - 55] | not detected |
| 240 min (n = 10) | 0.65(0.18) [0.34 - 0.95] | 27 (10.6) [15 - 52] | not detected |

not detected = flumazenil concentration below limit of detection

Half the children awoke irritable, crying and refusing to play with the toy and in total, 9 children refused to play on 30 occasions during the four hour postoperative study period. Although the study group is small, the children who were happy on awakening had the highest mean (SD) midazolam levels 181 (62.9) ng $ml^{-1}$; those children that were sleepy had the lowest mean (SD) flumazenil levels 17.3 (7.6) ng $ml^{-1}$ and those that were crying had the highest flumazenil levels 37.8 (13.6) ng $ml^{-1}$. Six children fell asleep again after giving their name and playing with the post-box toy but all were easily awakened (Table **IV.3**).

**TABLE IV.3** Resedation and mood assessment following flumazenil administration. *Data are mean (SD) and [range].*

| | **Midazolam level on awakening (ng ml$^{-1}$)** | **Flumazenil level on awakening (ng ml$^{-1}$)** |
|---|---|---|
| Average time of resedation after flumazenil (n=6) 80 (20.6) [60 - 120] (min) | 158.2 (19.5) [133 - 183] | 29.3 (15.0) [7 - 52] |
| Toy refusal on awakening (n = 6) | 139.4 (25.8) [164 - 92] | 25.4 (11.4) [7 - 42] |
| Mood on awakening: | | |
| happy, playful (n = 3) | 181 (62.9) [103 - 257] | 26.7 (17.9) [14 - 52] |
| calm, drowsy (n = 3) | 168.7 (25.80 [133 - 193] | 17.3 (7.6) [7 - 25] |
| irritable, crying (n = 6) | 151.3 (34.5) [92 - 208] | 37.8 (13.60 [62 -23] |

Mean blood concentrations of midazolam and flumazenil declined in all patients (Figures **IV.1** and **IV.2**). Flumazenil was not detectable at three hours and in 7 patients at 2 hours. Compartmental analysis of midazolam revealed a three-compartment model with elimination from a central compartment. The pharmacokinetic findings are summarised in Table **IV.4**.

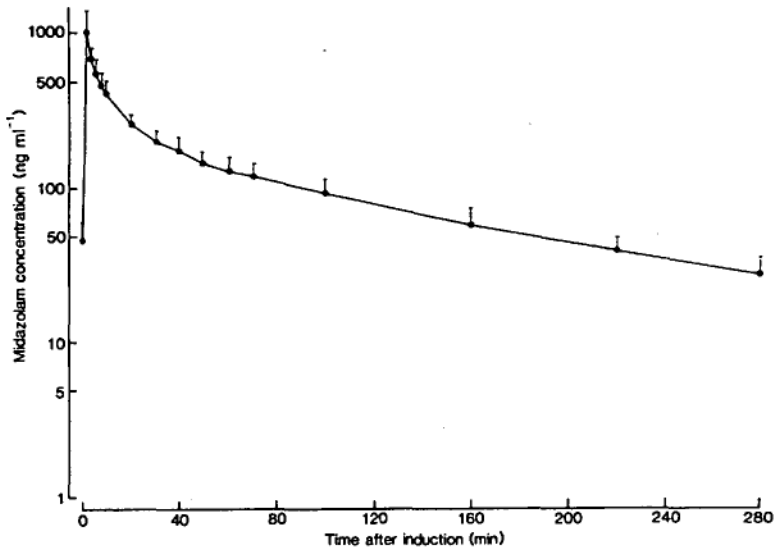


**FIGURE IV.1** Mean (SD) serum midazolam concentrations

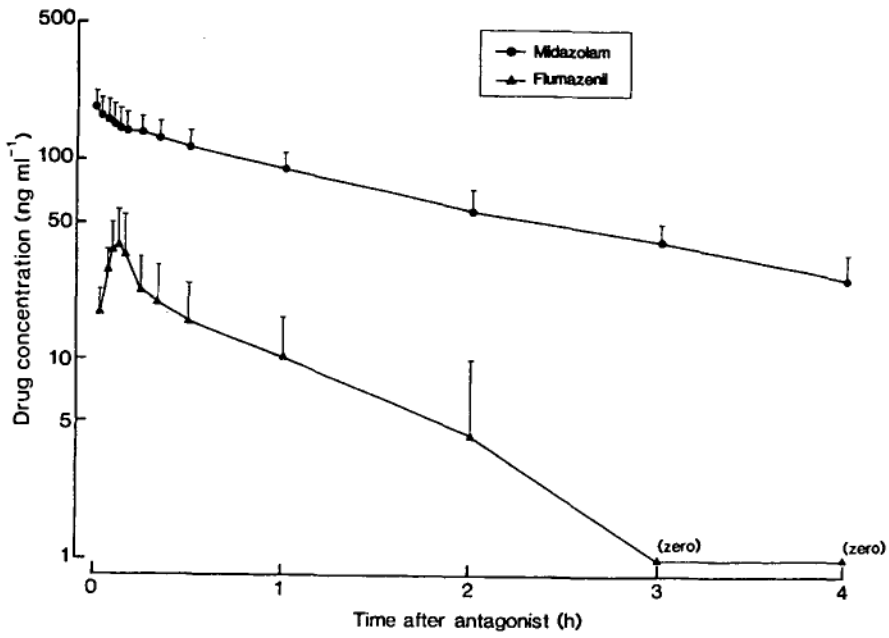


**FIGURE IV.2** Simultaneous mean (SD) serum flumazenil and midazolam concentrations.

**TABLE IV.4** Pharmacokinetic findings in the 12 children. *$V^{ss}$ =Volumes of distribution at steady state, $V^{\gamma}$=equilibrium, V=volume of the central compartment, Cl=total body clearance, $T½^{\alpha}$, $T½^{\beta}$, $T_{½}^{\gamma}$=half lives of the three phases and rate constants mean (SD) [range].*

| | Midazolam | Flumazenil |
|---|---|---|
| $V^{ss}$ (litre)<br>(litre $kg^{-1}$) | 41.1 (18.9) [21.5 - 93.7]<br>1.87 (0.57) [1.15 - 2.93] | 21.0 (7.1) [10.3 - 32.7]<br>1.0 (0.2) [0.7 - 1.6] |
| $V^{\gamma}$ (litre)<br>(litre $kg^{-1}$) | 48.8 (22.2) [25.2 - 106.5]<br>2.2 (0.7) [1.2 - 3.3] | 20.5 (6.7) [9.8 - 31.2]<br>0.9 (0.2) [0.7 - 1.6] |
| V (litre)<br>(litre $kg^{-1}$) | 7.2 (5.6) [1.8 - 23.3]<br>0.31 (0.17) [0.09 - 0.73] | |
| Cl (litre $min^{-1}$)<br>(ml $min^{-1}kg^{-1}$) | 344 (150) [199 - 736]<br>15.37 (3.16) [11.02 -23.00] | 469.83 (239.52) [136.27 - 963.17]<br>20.57 (6.92) [7.29 - 30.85] |
| **Terminal $T_{½}$** | 101.7 (31.9) [59.7 - 179.4] | 35.3 (13.8) [21.5 - 75.5] |
| $T_{½}^{\alpha}$ (min) | 2.55 (1.37) [0.84 - 5.00] | |
| $T_{½}^{\beta}$ (min) | 16.1 (6.8) [3.9 - 26.0] | |
| $T_{½}^{\gamma}$ (min) | 107.0 (30.2) [65.0 - 189.0] | |
| $k_{31}$ ($h^{-1}$) | 1.03 (0.37) [0.55 - 1.84] | |
| $k_{10}$ ($h^{-1}$) | 3.53 (1.74) [1.76 - 7.06] | |
| $k_{13}$ ($h^{-1}$) | 4.5 (3.83) [0.89 - 14.20] | |
| $k_{12}$ ($h^{-1}$) | 8.17 (6.93) [1.49 - 24.38] | |
| $k_{21}$ ($h^{-1}$) | 8.30 (5.52) [3.49 -23.67] | |
| $k_{31}$ : $k_{10}$ | 0.35 (0.18) [0.12 - 0.75] | |
| $k_{12}$ : $k_{21}$ | 1.14 (0.80) [0.06 - 3.00] | |

Bulked (0 - 24 h) urine samples were successfully obtained in 10 out of the 12 children. No unchanged midazolam was detected in these samples. A wide variation in the recovery, as a percentage of dose, of the hydroxyl metabolites and their glucuronides was observed: α - hydroxymidazolam (0 to 0.23%), α - hydroxymidazolam glucuronide (0.64 to 13.2%), 4 - hydroxymidazolam (0.03 to 1.12%) and 4 - hydroxymidazolam glucuronide (0.01 to 1.15%). One child was an extensive hydroxylator having a high recovery of hydroxyl metabolites and the glucuronide (denoted by the upper range). Unchanged flumazenil was recovered in all the urine samples ranging from 5.84% to 13.8% {mean (SD) 9.07 (2.96)} of the dose administered. The demethylated metabolite, desmethylflumazenil, was detected but was not measurable by the HPLC method because its analytical peak was too close to the solvent front of the chromatogram. The carboxylic acid metabolite of flumazenil was not resolved by the HPLC method described. The child demonstrating extensive hydroxylation of midazolam also excreted the largest amount of unchanged flumazenil in the urine (i.e. 13.8%), however his other pharmacokinetic and pharmacodynamic data were unremarkable.

# DISCUSSION

The clinical pharmacokinetics of drugs in anaesthetic practice may be influenced by the mutual pharmacokinetic interactions of drug distribution, metabolism and excretion. In their studies in healthy volunteers, Breimer and co-workers observed that flumazenil and midazolam at repeated therapeutic doses did not show any accumulation or saturation kinetics (Breimer et al, 1991). Therefore, it is unlikely in this present clinical study, that pharmacokinetic interaction occurred when midazolam and flumazenil were administered together. The effect of caudal epidural anaesthesia on midazolam pharmacokinetics in children has not been studied but central blockade is reported to protect the child from the stress (Giaufré et al, 1985) and metabolic responses associated with surgery (Gouyet et al, 1991). Central blocks produce minimal haemodynamic changes in children and no changes at all in those under 8 years old (Giaufré, 1990) and therefore it is unlikely that caudal anaesthesia altered hepatic blood flow in this study to such an extent as to effect drug disposition (Giaufré et al, 1990a, Giaufré et al, 1990b).

In all the Chinese children in this study, clearance of midazolam from the plasma may be best described by a tri-exponential function, however other workers have described a bi-exponential decline in plasma midazolam levels (Tolia et al, 1991; Salonen et al, 1987; Payne et al, 1989). This may be explained by the 2 min sampling interval during the initial distribution phase and the measurement of plasma concentrations for nearly 300 min compared to shorter sampling times in other studies. The kinetics of intravenous midazolam were superimposed on a 'background' concentration of the oral midazolam premedication. This was considered valid if,

within the constraints of clinical practice, it is assumed that first order kinetics existed. The midazolam pharmacokinetic data in this study show a mean $T_{½}^{\gamma}$ of 107 min (non-compartmental analysis), total body clearance of 15 ml $kg^{-1}min^{-1}$ and an apparent central volume of distribution of 0.3 l $kg^{-1}$. The smaller central volume of distribution and higher clearance in the subjects of this study should have resulted in a rapid initial and subsequent distribution half-lives, however the mean terminal elimination half-life data are intermediate when compared to other studies (Tolia et al, 1991; Clausen et al, 1988; Pentikainen et al, 1989). This may be explained by the different fat distribution in Chinese children, the differing anaesthetic techniques employed and the age related variation in metabolism of benzodiazepines which undergo oxidation as their main metabolic pathway of elimination (Greenblatt et al, 1984). The mean (SD) ratio of $k_{12}$ : $k_{21}$ was 1.14 (0.8) suggesting a rapid distribution of the i.v. midazolam from the central plasma compartment to the shallow compartment, and the mean (SD) ratio of $k_{31}$: $k_{10}$ was 0.35 (0.18), suggesting a slow return from the deep fat and muscle compartments before elimination.

Flumazenil pharmacokinetic data were suitably interpreted by non-compartmental analysis because of the bolus and infusion administration regimen used in this study. The mean plasma levels of the drug after the infusion appear to decline bi-exponentially (Figure **IV.2**), although this was not observed in several patients whose drug levels declined almost mono-exponentially in a similar manner to that described in adults (Klotz et al, 1984; Klotz and Kanto, 1988). The present HPLC assay was not sufficiently sensitive to measure flumazenil in plasma in these patients 120 min after dose administration. The terminal elimination half-life of flumazenil may therefore be underestimated. Nevertheless the kinetic data were derived using

statistical moment analysis which takes into account the total dose administered. The $V_{ss}$ in the children studied was about half that reported in adults, clearance values were similar and the flumazenil terminal half-life was 35 min in children compared to reported values of 60 -77 min in adults (Klotz et al, 1984; Breimer et al, 1991; Geller and Halpern, 1991). Both flumazenil and midazolam are water soluble drugs at low pH, but at physiological pH the imidazole ring forming part of the midazolam structure closes and lipid solubility is enhanced (Nilsson, 1991). The $V_{ss}$ and $V^{\gamma}$ for flumazenil was approximately half that of midazolam reflecting the latter drug's wider distribution and greater lipid solubility within the body. This is endorsed by the low $k_{31}$: $k_{10}$ ratio for midazolam and the absence of unchanged midazolam in the urine, implying that the slow release of the drug from the deep fat compartment enables complete metabolism by the liver before elimination (Greenblatt et al, 1984; Wills et al, 1990). The clearance of flumazenil from the plasma was more rapid compared to midazolam and unchanged flumazenil was recovered in the urine. Flumazenil rapidly attains equilibration in the central compartment, is only slightly bound to plasma proteins compared to midazolam and it is likely that more of the drug remains in the plasma compartment for a longer time because its lipid solubility is less than that of midazolam at physiological pH (Klotz et al, 1984). The small volume of distribution and high clearance of flumazenil resulted in a terminal half-life which was one third of the terminal half-life of midazolam in our children. Flumazenil levels in the plasma were minimal at 2 hr and not detectable by our method of analysis at 3 hr. The mean dose of flumazenil administered to the children in this study to attain awakening (27 $\mu g\ kg^{-1}$) was similar to that given by Klotz and colleagues (approx. 35 $\mu g\ kg^{-1}$) to adults and the measured levels of flumazenil at awakening were higher than the steady

state levels used by Breimer and colleagues in adults to reverse a single i.v. dose of midazolam (approx. 0.25 - 0.75 mg·kg$^{-1}$) (Breimer et al, 1988; Klotz et al, 1984).

Two hours after oral midazolam administration all of the children arrived in the operating suite awake, co-operative and apparently anxiety free, but on specific questioning 30% of the children expressed some fear. Their mean (SD) midazolam concentration was 47 (15.8) ng ml$^{-1}$ (Figure **IV.3**) which is close to the lower range of concentrations at which sedative effects are seen in adult intensive care patients (Michalk et al, 1986; Westphal et al, 1987; Maitre et al, 1989; Reves, 1984) but well below the amnesic threshold reported by Persson and colleagues (Persson et al, 1988). Each benzodiazepine has its own plasma decay curve and pattern of threshold concentrations (Reves et al, 1984). The anxiolytic effect of midazolam occurs at lower serum concentrations than those required for sedation and therefore most of the children were calm on arrival in the operating suite (Nilsson, 1991). To achieve a hypnotic effect with midazolam in adults, a plasma concentration of 300-500 ng ml$^{-1}$ is required (Lauven et al, 1985; Persson et al, 1987). Children require a rapid, pleasant, smooth induction of anaesthesia but the variability in clinical response to a given dose of midazolam requires that either a large dose is administered, or that a narcotic (in this series alfentanil) is also given to ensure these favourable characteristics (Kissin et al, 1990). The relatively small dose of alfentanil administered during induction (Hiller and Saarnivaara, 1992), it's short elimination half-life in children (Meistelman et al, 1987) and evidence that recovery is not prolonged after daycase anaesthesia (Millar and Jewkes, 1988) would suggest that alfentanil had little influence on the recovery characteristics recorded during this study. In all the children the induction was smooth, rapid and without incident and

the peak measured mean plasma midazolam level at 2 min was 1000 ng $ml^{-1}$ which declined to levels less than 300 ng $ml^{-1}$ at 20 min (Figure **IV.1**). At the time of antagonist administration, the children's mean plasma midazolam level (180 ng $ml^{-1}$) (Figure **IV.2**) was at the adult mid-range sedative level but was easily reversed with flumazenil 0.03 mg $kg^{-1}$. Half of the children awoke crying and refused to play with the post-box toy which may imply a mild inverse agonistic effect, reported by other workers in adults (Chiolero et al, 1986; Higgitt et al, 1986). Interestingly, these children also had the highest mean serum levels of flumazenil on awakening. These findings are in contrast to those described in the next chapter. Following flumazenil administration to children undergoing the same surgical procedure but using a spontaneously breathing anaesthetic technique employing halothane, only 20% of the children refused the toy or cried on awakening. The halothane supplemented children awoke more slowly but were given a lower mean dose of antagonist (0.024 mg $kg^{-1}$) than in this study. This is in accord with the findings of Geller and colleagues who demonstrated that flumazenil improved the quality of emergence from anaesthesia in patients given halothane anaesthesia without benzodiazepines (Geller et al 1987). Midazolam produces marked reduction of halothane MAC in humans at serum concentrations lower than that required to cause sleep (Inagaki et al, 1993) and to reduce the influence of the volatile agent on recovery and pharmacokinetic disposition, isoflurane was employed as the volatile agent in this study. The children who were happy and co-operative on awakening had higher serum midazolam levels compared to the children who were irritable, crying and refused to play with the post-box toy. Moreover, the children who were drowsy on awakening had a lower mean serum flumazenil level (Table **IV.3**). The sample size is too small for any statistical comparison, however the data are blind and lend credence to

pharmacokinetic-pharmacodynamic model of midazolam plasma concentration and effects which is being presently developed by other workers (Breimer et al,1991).

Flumazenil is distributed into the brain within minutes of i.v. administration and attains brain concentrations which are higher than those in plasma but then is rapidly cleared from the brain and excreted (Geller and Halpern, 1991). The clinical effect of flumazenil is dependent on the dose of midazolam, dose of flumazenil, pharmacokinetics of both drugs and the timing of antagonist administration. Despite being fully awake, the children who were willing to perform the post-box toy demonstrated mild residual psychomotor impairment for the first 2 hr postoperatively. At 4 hr all of the children tested performed close to their best, practised, unmedicated preoperative attempt. The sensitivity of the assay did not permit measurement of plasma flumazenil levels at 3 hr but the mean midazolam levels of the children at that time were in the adult anxiolytic range. The resedation seen in 6 of the patients was presumably due to the residual midazolam hypnotic effects being relatively unopposed by flumazenil (Table **IV.3**). These children went back to sleep approximately 80 minutes after initial awakening but were easily roused, albeit crying and irritable and similar to the "normal" small child who is abruptly awoken. The awakening mean plasma level of midazolam in the resedated children was less than the awakening mean midazolam levels in the happy or sleepy children inferring that midazolam was redistributed more rapidly to the deep compartment in these children resulting in later sedation when the midazolam returned to the central compartment, and furthermore that resedation per se was not due to the rapid redistribution of flumazenil from the central compartment. Relative plasma concentrations of agonist and antagonist seem to determine the quality of emergence from anaesthesia. A mild

inverse agonistic effect of flumazenil has been reported in adults and may also occur in children with large plasma concentrations of flumazenil (Higgitt et al, 1986).

A smooth induction of anaesthesia with midazolam in children is achieved only with high plasma drug concentrations, with the resultant drawback of prolonged sedation during the early recovery period. Flumazenil antagonised the hypnotic effects of midazolam rapidly and effectively and the pharmacokinetic disposition of flumazenil in children was similar to that defined in adults (Klotz et al, 1984). The popularity of the new induction agent propofol infers that it may confer advantages over midazolam, however a more complete description of the pharmacokinetic disposition of propofol in children is required before comparing these two drugs as induction agents.

# PHARMACOKINETICS OF PROPOFOL

Rapid recovery after general anaesthesia may be an advantage in paediatric patients, particularly those undergoing minor day care surgery. Propofol, the latest induction agent to be introduced into clinical practice seems to possess some advantage over other available agents in this respect (Mackenzie and Grant, 1985). The pharmacology of propofol has been recently reviewed by White (White, 1988) and there has been a rapid accumulation of clinical and pharmacological data but the description of the pharmacokinetics of propofol in children is incomplete (Valtonen et al, 1989; Saint-Maurice et al, 1989).

Age-related changes in body water, lean body mass, regional blood flow, renal and hepatic function (Friis-Hansen, 1971; Greenblatt et al, 1984, Björkman et al, 1987) affect drug distribution, metabolism and excretion (Cockshott, 1985; Kay et al, 1986; Servin et al, 1986). Furthermore, physiological changes associated with general anaesthesia and the racial characteristics of the study group may alter the disposition of anaesthetic drugs (Kumana et al, 1987). This study reports the pharmacokinetics of propofol in Chinese children.

## MATERIALS AND METHODS

Twelve Chinese children aged between 4 and 12 years were studied. All patients were ASA grade I and underwent circumcision for the treatment of phimosis. Children were specifically excluded from the study if there was a history of asthma or allergies, a previous adverse anaesthetic experience, halothane anaesthesia within the last month, hepatic, renal, respiratory, cardiac or haematological disease, developmental disability and if under two years of age.

Patients were premedicated with trimeprazine 3 mg $kg^{-1}$ (to a maximum of 90 mg) and atropine 0.03 mg $kg^{-1}$ by mouth two hours preoperatively. Two grams of EMLA emulsion cream (lignocaine 25 mg $g^{-1}$ and prilocaine 25 mg $g^{-1}$) was also applied to the dorsum of the left hand. In the operating suite, a 24-gauge cannula was inserted into a vein underlying the EMLA pretreated area. Procaine HCl 1 mg $kg^{-1}$ was administered 15 seconds prior to anaesthesia being induced with the aqueous emulsion formulation of propofol ('Diprivan') 2.5 mg $kg^{-1}$ injected over 30 seconds. Time zero was taken to be the incidence when the injection was completed. An 18-gauge cannula (for venous sampling) was then inserted into a vein in the contralateral antecubital fossa. Thereafter, anaesthesia was maintained with the patient spontaneously breathing nitrous oxide 67% in oxygen with halothane 1-3% delivered via a Mapleson F breathing system if under 25 kilograms and by a Mapleson A breathing system if more than 25 kilograms in body weight. The surgeon infiltrated each dorsal nerve at the root of the penis with 1.5 mls of 0.5% bupivacaine.

The sedative effectiveness of the premedication on arrival in the operating suite was assessed, categorised and recorded as one of the following: agitated or crying; aware and apparently anxiety free; drowsy; asleep but responsive to command (Jones et al, 1990). Induction was graded as good (absence of side effects), adequate (side effects present but not interfering with induction) and poor (side effects severe and protracted). Any evidence of excitatory phenomena on induction of anaesthesia was also recorded. During anaesthesia all patients were monitored with an E.C.G., non-invasive blood pressure cuff, pulse oximeter, capnograph and inspired oxygen concentration (Datex Cardiocap). Post operatively the patients' coma scale (Robertson et al, 1977) and a structured observation score (Krane et al, 1987) were assessed and noted at each of the blood sampling times detailed below. Also recorded in recovery were the awakening time (elapsed time from the discontinuation of general anaesthesia in the operating room to spontaneous eye-opening in recovery) and the time elapsed until the patient could identify himself.

Whole blood samples were collected for propofol estimation at the following times: 2, 5, 10, 15, 20, 30, 45, 60, 90, 120 and 180 minutes and 4, 6, 8, 10, 12, 18 and 24 hours. Each sample was thoroughly mixed in tubes containing lithium-heparin (Sarstedt LH/5) and stored at +4°C until assayed. Propofol concentration in whole blood was determined by a modified liquid chromatographic method (Gin et al, 1990). Propofol in whole blood [(0.5 ml samples rather than the 1.0 ml samples used by Plummer (Plummer, 1987)] and internal standard thymol, buffered with 0.1 M sodium dihydrogen phosphate, were extracted into cyclohexane. The mobile phase consisted of 75% (v/v) acetonitrile in distilled water containing 1% (v/v) glacial acetic acid. A $C_{18}$

reversed phase column (Nova-Pak), linked to a $C_{18}$ pre-column was used and the eluate was measured by a fluorometric detector with excitation and emission wavelengths set at 276 nm and 310 nm respectively (Chan and Gin, 1990). The calibration graphs were linear over the range 2 to 3000 ng $ml^{-1}$ with coefficients of variation ranging from 1.0 to 8.0%. The between batch coefficient of variance was 6.7% at 50 ng $ml^{-1}$ and 4.8% at 3000 ng $ml^{-1}$, while the limit of detection was approximately 2 ng $ml^{-1}$.

The blood concentration-time profiles of propofol were analysed by the BITRI computer programme (Gin et al, 1990; Chan et al, 1987) which utilises the method of residuals, whereby each curve is fitted with experimental data in terms of a bi-exponential or tri-exponential function. BITRI chooses the best fit such that the logarithms of squared deviation between exponential and computer values are minimised (Boxenbaum et al, 1974).

Distribution and elimination half-lives ($T_{½}^{\alpha}$ $T_{½}^{\beta}$ $T_{½}^{\gamma}$), apparent central volume of distribution (V), apparent volume of distribution at steady state ($V^{ss}$), apparent volume of distribution in the elimination phase ($V^{\gamma}$) and total body clearance (TBC) were calculated using standard formulae (Gibaldi and Perrier, 1982).

Association between age, clearance and elimination half-life was determined using linear regression with computer interactive statistical software (Minitab 1989).

# RESULTS

On arrival in the operating suite, 2 of the children were awake and apparently anxiety free, 7 patients were drowsy with intermittent eye opening and the remaining 3 children were asleep, but awoke on command. A fixed dose of propofol of 2.5 mg $kg^{-1}$ was given to all patients and resulted in induction being graded as free of side effects in 50% of patients and satisfactory in the remaining six. Five episodes of semi-purposeful movement occured, combined with breath holding, tremor and rigidity in two patients, and 1 patient developed hiccup. The demographic, haemodynamic changes during induction and anaesthesia details for the 12 boys are presented in Table **IV.5**.

**TABLE IV.5** Demographic, induction-haemodynamics and anaesthetic data in the 12 children. *Data are mean (SEM)[range].*

| | | |
|---|---|---|
| **Age (yr)** | 7.9 (0.8) | [4-12] |
| **Weight (kg)** | 25.8 (7.9) | [16-39] |
| **Mean increase in heart rate from pre-induction values (beats $min^{-1}$)** | 4.3 (6.4) | [-42 to +42] |
| **Mean decrease in systolic blood pressure from pre-induction values (mm Hg)** | -7.1 (4.4) | [-28 to +16] |
| **Maximal end-tidal carbon dioxide recorded during anaesthesia (kPa)** | 6.8 (0.3) | [5.3-7.8] |
| **Anaesthesia time (min)** | 28.8 (1.5) | [21-36] |
| **Awakening time (min)** | 30.5 (4.0) | [11-61] |

The maximum change in heart rate and systolic blood pressure from pre-induction values during the first five minutes of the induction period was computed. The mean maximum end tidal carbon dioxide value recorded during the surgical procedure was 50.9 mmHg, and the mean anaesthetic time for this group of children was 28.8 minutes. The mean awakening time was 30.5 minutes which occured at a mean blood propofol concentration of 165 $ng.ml^{-1}$. In all cases the children could adequately identify themselves within two minutes of opening their eyes spontaneously. Coma scores post-induction time are shown in Table **IV.6**.

**TABLE IV.6** Relationship between awakening and time after propofol administration. *(Values are the number of children)*

| **Time after induction (min)** | 45 | 60 | 90 | 120 | 240 |
|---|---|---|---|---|---|
| **Coma score <7** Asleep | 10 | 1 | 1 | 0 | 0 |
| **Coma score 7** Lightly asleep, eyes open on command | 1 | 8 | 6 | 1 | 0 |
| **Coma score 9** Fully awake, eyes open, conversing | 0 | 3 | 5 | 11 | 12 |
| **Total number of children** | 12 | 12 | 12 | 12 | 12 |

The mean (SEM) duration of anaesthesia was 30.5(5.13) min. The mean blood propofol concentration-time profile for the children is shown in Figure **IV.3**.

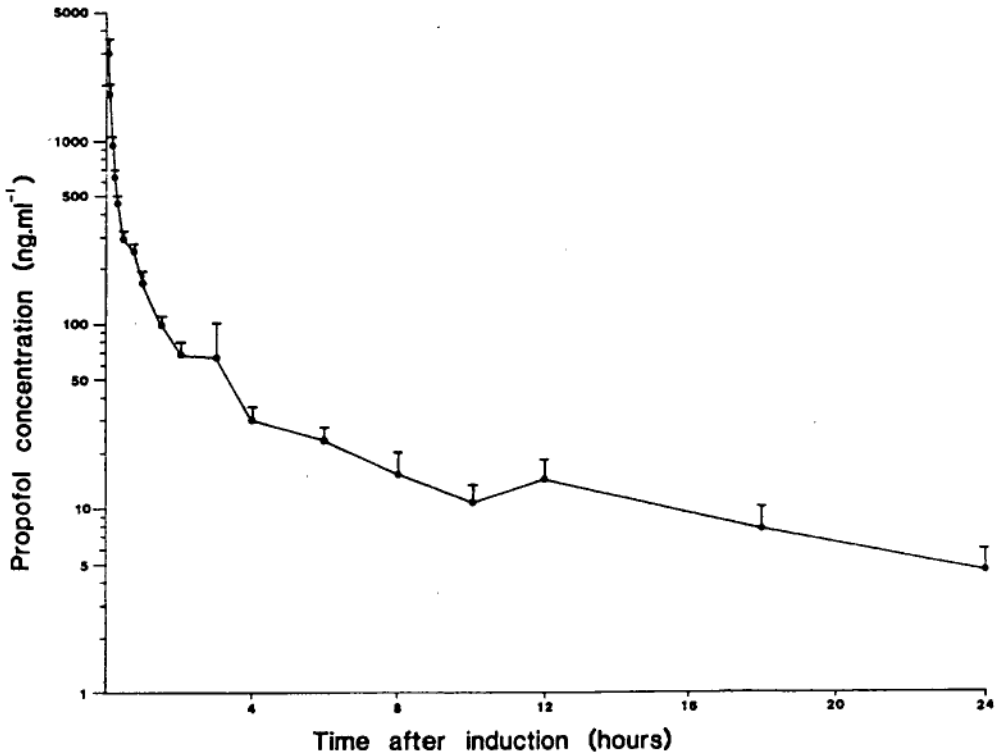


**FIGURE IV.3:** The mean (SEM) blood propofol concentration-time relationship in Chinese children.

Propofol concentrations declined in all patients but secondary peaks were present at 3 and 12 hours. Propofol concentrations were detectable in only 5 patients at 10 hours and only 2 patients at 24 hours. In all patients compartmental analysis of propofol concentrations revealed a three compartment model with elimination from a central compartment and the pharmacokinetic findings are summarised in Table **IV.7**.

**TABLE IV.7** Propofol pharmacokinetic findings in the 12 children. *$V^{ss}$=Volumes of distribution at steady state, $V^{\gamma}$= equilibrium, V=volume of central compartment, Cl=total body clearance, $T_{½}^{\alpha}$, $T_{½}^{\beta}$, $T_{½}^{\gamma}$=half-lives of the three phase and rate constants. Results are mean (SEM)[range].*

| | | |
|---|---|---|
| **$V^{ss}$ (litre)** | 133.34 (25.56) | [20.25-345.40] |
| **(litre $Kg^{-1}$)** | 5.01 (2.66) | [1.68-10.16] |
| **$V^{i}$ (litre)** | 325.47 (61.22) | [44.63-570.11] |
| **(litre $Kg^{-1}$)** | 12.38 (1.98) | [2.23-23.50] |
| **V (litre)** | 16.31 (3.77) | [2.45-41.94] |
| **(litre $Kg^{-1}$)** | 0.597 (0.10) | [0.08-1.23] |
| **Cl (litre $min^{-1}$)** | 1.11 (0.18) | [0.53-1.43] |
| **(litre $min^{-1}$ $Kg^{-1}$)** | 40.35 (3.60) | [25.70-66.75] |
| **$T_{½}^{\alpha}$ (min)** | 3.05 (0.43) | [1.01-6.44] |
| **$T_{½}^{\beta}$ (min)** | 24.33 (5.13) | [5.26-74.99] |
| **$T_{½}^{\gamma}$ (min)** | 209.22 (29.26) | [37.88-285.97] |
| **$k_{31}$ ($h^{-1}$)** | 0.55 (0.22) | [0.18-2.97] |
| **$k_{10}$ ($h^{-1}$)** | 6.40 (1.52) | [1.81-19.55] |
| **$k_{13}$ ($h^{-1}$)** | 2.84 (0.72) | [0.64-9.47] |
| **$k_{12}$ ($h^{-1}$)** | 5.79 (1.11) | [0.31-11.98] |
| **$k_{21}$ ($h^{-1}$)** | 4.85 (0.82) | [1.31-9.96] |
| **$k_{31}$ : $k_{10}$** | 0.169 (0.074) | [0.02-0.89] |
| **$k_{12}$ : $k_{21}$** | 1.435 (0.224) | [0.03-2.58] |

The mean ratio of $k_{12}$: $k_{21}$ was 1.435 ± 0.224 (mean ± SEM), suggesting a rapid distribution of the intravenous propofol bolus to the shallow compartment, and the mean ratio of $k_{31}$: $k_{10}$ was 0.1692 ± 0.074 (mean ± SEM) suggesting that the third

exponential phase was constrained by its slow return from the deep to the central compartment. Linear regression demonstrated a significant increase in the rate of elimination of propofol with increasing age ($p < 0.001$) (Figure **IV.4**), but there was no significant relationship between propofol clearance and age (Figure **IV.5**). No relationship was found between age and $V^{ss}$, V or $V^{\gamma}$ with linear regression analysis. Anaesthesia and recovery proceeded smoothly in all patients and there were no complications.

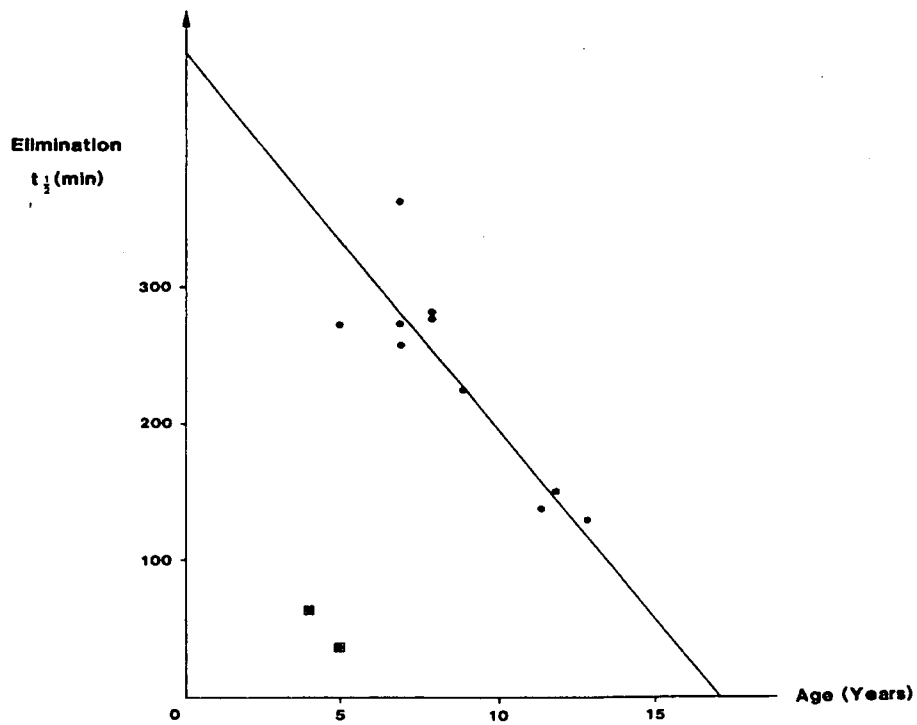


**FIGURE IV.4:** Relationship between age (years) and elmination half-life (minutes) for propofol. *The two outlying data points enclosed in the boxes were excluded from linear regression analysis ($r = 0.73$, $p < 0.001$).*

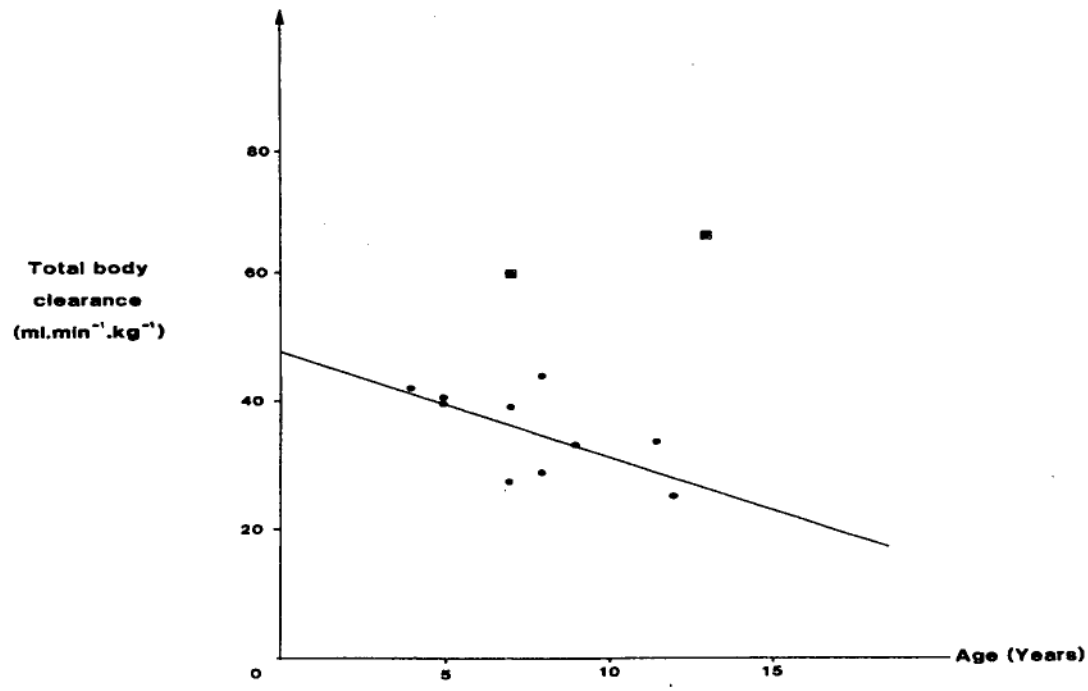


**FIGURE IV.5:** Relationship between age and clearance (ml $kg^{-1}$ $min^{-1}$) of propofol. *The two outlying data points enclosed in the boxes were excluded from linear regression analysis ( $r = 0.41$, $p = 0.046$ ).*

# DISCUSSION

Pharmacokinetic studies in children are often restricted by the limited amount of blood that can be removed from the patient; a consequence of which is a lack of definition of the elimination phase. Recently new strategies such as naive pooled data and the non-linear mixed-effects modelling approach have been introduced in an attempt to overcome this problem (Fisher, 1994). However the pharmacokinetics of propofol are well described by the standard two-stage method and the 'best' estimates of the pharmacokinetic parameters estimated using the mixed-effects approach did not offer any increased accuracy over the simpler two staged approach (Kateria et al, 1994). In this study blood propofol concentrations in the 12 children have been determined, using small volume samples, up to 24 hours post induction. Peripheral venous samples were used because the risk to the paediatric patient of arterial cannulation is not justified for a minor surgical procedure, like circumcision. In all these children, the clearance of the drug from the blood can best be described by a tri-exponential function. The pharmacokinetic data show a mean $T_{½}^{\gamma}$ of 209 minutes and a mean total body clearance of 1.11 litre.min$^{-1}$. This large total body clearance combined with a relatively small mean volume of equilibrium (325.5 litres) for a highly lipophilic drug, results in a fast elimination of propofol from the blood in children. As in another study in young adults (Kirkpatrick et al, 1988), the mean volume of distribution at steady state was less than half of the mean equilibrium volume of distribution, suggesting that after distribution from the blood to the tissues, and metabolic clearance from the blood, elimination is constrained by a slow return of propofol to the blood from the deep compartment.

Data from this study are compared with the pharmacokinetic findings of Valtonen (Valtonen et al, 1989) and Saint-Maurice (Saint-Maurice et al, 1989) and are summarised in Table **IV.8**.

**TABLE IV.8** Comparison of three pharmacokinetic studies of single dose propofol in children

| | **Valtonen (n = 8) Mean (SD)** | **Saint-Maurice (n = 8 + 2 for 4h) Mean (SEM)** | **Present study (n = 12) Mean (SEM)** |
|---|---|---|---|
| **$T_{½}^{\alpha}$ (min)** | 1.50 (1.56) | 4.15 (0.78) | 3.05 (0.43) |
| **$T_{½}^{\beta}$ (min)** | 9.3 (3.78) | 56.1 (6.30) | 24.3 (5.13) |
| **$T_{½}^{\gamma}$ (min)** | 214.6 (168.8) | 735.0 (82.7) | 209.22 (29.3) |
| **V (litre $kg^{-1}$)** | 0.530 (0.65) | 0.722 (0.11) | 0.597 (0.10) |
| **$V^{ss}$ (litre $kg^{-1}$)** | 2.16 (1.49) | 10.90 (1.20) | 5.01 (2.66) |
| **Cl (ml $min^{-1}$ $kg^{-1}$)** | 32.0 (16.8) | 30.6 (2.9) | 40.4 (3.6) |
| **Sampling times (min)** | 2, 4, 6, 10, 15, 30, 45, 60 | 2, 5, 10, 15, 20, 30, 40, 60, 90, 120 | 2, 5, 10, 15, 20, 30, 45, 60, 90, 120 |
| **(hr)** | 3, 6, 12, 24 | 3, 4, 5, 6, 7, 8, 10, 12, 24 | 3, 4, 6, 8, 10, 12, 18, 24 |
| **Surgery** | Elective surgery | Minor visceral<br>Minor orthopaedic | Circumcision |
| **Other drugs administered** | Atropine<br>Flunitrazepam<br>Lignocaine<br>Fentanyl<br>Pancuronium<br>Suxamethonium | <br><br><br>Fentanyl<br>Vecuronium | Atropine<br>Trimeprazine<br>Procaine HCl<br><br><br> |
| | | Halothane (n = 9)<br>Enflurane (n = 1) | Halothane |
| | $O_2$ : $N_2O$ | $O_2$ : $N_2O$ | $O_2$ : $N_2O$<br>Caudal bupivacaine |

The initial distribution half life determined in this study and that of Saint-Maurice are similar, perhaps reflecting the similar sampling times. The SD of Valtonen's data is equal to their mean $T_{½}^{\alpha}$. The elimination half life, central

compartment volume and plasma clearance values from Valtonen's study and this one are similar. The $V^{ss}$ in Saint-Maurice's study is twice the value found in this study and five times that of Valtonen's data, and the elimination half-life determined by Saint-Maurice's group is three times as long. The differences between these studies may be attributable to the different anaesthetic techniques employed, different types of surgical procedure, the different sample collection times and the small populations examined.

The smaller lean body mass of Chinese children may decrease $V^{ss}$, leading to a shorter elimination half life. Similar results have been found with the pharmacokinetics of diazepam in Chinese adults (Kumana et al, 1987). The influence of ethnic origin on metabolism may also contribute to these differences, as it does for example, with the increased oxidative demethylation of pethidine in oriental subjects (Chan et al, 1990). The present study was performed with a prescibed anaesthetic technique, the same simple surgical procedure in all cases and 24 hour sampling in twelve patients.

Despite the small population sample, and the exclusion of two outlying points from the linear regression analysis, the decrease in elimination half life with increasing age was statistically significant (Figure **IV.4**). Each of the outlying points belong to a different patient and do not show any relation to the clinical or blood analysis data. The only constant feature in these two patients was that propofol could not be detected in their blood samples after the 10 hour post induction blood sample. The patient blood samples were randomly assayed, standardised pre and post batch,

and collected in the same manner by the same investigator throughout the study. It is likely in this group of young children that their metabolising capacity is rapidly developing, as reflected by the inverse relationship of elimination half life and age. Propofol is primarily rapidly metabolised to the inactive glucuronide conjugate and the corresponding quinol glucuronide. Not only is glucuronidation an age dependent enzyme process but both hepatic mass and hepatic blood flow increase towards adulthood (Stanski et al, 1982). Two children aged seven years took the longest to fully awaken and both were included in the elimination / age regression data ($T_{½}^{\gamma}$ 262 and 276 min). Unfortunately the awakening data are confounded by the long half-life of the premedicant trimeprazine; nevertheless, 91% of the children had awoken within 30 minutes of termination of anaesthesia and could be returned from the recovery area to the ward. With the anaesthetic technique used in this study, awakening occurred at approximately twice the $T_{½}^{\beta}$ with a mean blood concentration of 165 $ng.ml^{-1}$. There are no comparable data in the literature, but it can be noted that adults premedicated with hydroxyzine (Destibats et al, 1987) or promethazine (Hartung and Freye, 1988), had mean recovery times (22 and 16.3 minutes respectively) approximately double those of unpremedicated adults.

Both this study and that of Valtonen's group (Valtonen et al, 1989) demonstrate a tri-exponential relationship between blood concentrations and time. The data from two patients in Saint-Maurice's study (Saint-Maurice et al, 1989) were not available after four hours and their pharmacokinetic parameter estimates for these patients were based on a two-compartment open mamillary model. However it is possible to make a comparison of propofol half-lives between non-pregnant adults and

children (Briggs et al, 1985; Kay et al, 1985; Mather et al, 1987), though interpretation should be prudent in view of the varying anaesthetic techniques. The present study on children demonstrated a similar $T_{½}^{\alpha}$ to adults. Estimation of the initial distribution half life of propofol is liable to error because the first sample was drawn at two minutes post induction and the initial distribution half life value is 3.05 (0.43) minutes. However it was shown that when blood sampling at 2,4,6,8, and 10 minutes, post induction with propofol, in women undergoing laparoscopy was compared to sampling at 2,5,10 and 15 minutes in women undergoing caesarean section, there was no significant difference in their kinetics (Gin et al, 1990). The $T_{½}^{\beta}$ of the children in this study was approximately half and their elimination half-life three times shorter than those of the young adults in Kirkpatrick's study (Kirkpatrick et al, 1988). Only two patients in this study had detectable propofol levels at 24 hours. This may imply that these Chinese children had rapid metabolic elimination of the drug. The volume of the central compartment when normalised for body weight did not differ significantly from the young adults, but $V^{ss}$ was approximately half. This may reflect the proportionately larger lipid content of the Caucasian adult compared to the Chinese child.

The rapid hepatic clearance of a highly protein bound drug like propofol (Mather et al, 1987) is primarily hepatic blood flow limited. Halothane reduces hepatic blood flow and may inhibit drug-metabolising liver enzymes (Björkman et al, 1987), but in Brigg's series the propofol levels in a group of patients whose anaesthesia included halothane were not significantly different from those in other groups (Briggs et al, 1985). However, unlike the children investigated in later studies,

the recorded haemodynamic changes on induction in this group were minimal. The effect of caudal epidural anaesthesia on propofol pharmacokinetics in children has not been studied but central blockade is reported to protect the child from the stress (Giaufré et al, 1985) and metabolic responses associated with surgery (Gouyet et al, 1991). Central blocks produce minimal haemodynamic changes in children and no changes at all in those under 8 years old (Giaufré, 1990) and therefore it is unlikely that caudal anaesthesia altered hepatic blood flow in this study to such an extent as to effect drug disposition (Giaufré et al, 1990a, Giaufré et al, 1990b).

This study has demonstrated that propofol pharmacokinetics in children are similar to adults and are consistent with a three compartment model with elimination from a central compartment. The elimination half-life of propofol in children is similar to that reported with a bolus intravenous administration of methohexitone in paediatric patients (Björkman et al, 1987), and approximately one third that reported with thiopentone (Sorbo et al, 1984). The rapid elimination of propofol and the minimal haemodynamic perturbation during induction qualify this agent as suitable for induction of anaesthesia in children.

The pharmacokinetic profile of midazolam described earlier in this chapter shows that although propofol clearance is twice as fast as midazolam, the elimination half-life of midazolam is half the duration of propofol and the terminal half-lives of the two drugs are very similar. Awakening times should only be compared if the patients were initially at the same depth of anaesthesia. This can be easily determined with inhalational agents by MAC equivalence but the analogous end point with

intravenous agents is not available. To some extent, the choice of a single surgical procedure and the very similar durations of anaesthesia may allow tentative conclusions to be considered. Halothane would also be expected to have some influence on the elimination of propofol and therefore care must be taken when comparing results, but awakening times were much faster following midazolam-induced anaesthesia antagonised with flumazenil, compared to awakening after propofol induced anaesthesia. In view of these results, a controlled comparison of midazolam and propofol would be valuable in assessing the place of midazolam as an induction agent in paediatric anaesthesia.

# HAEMODYNAMIC CHANGES ON INDUCTION OF ANAESTHESIA WITH MIDAZOLAM, PROPOFOL OR THIOPENTONE

The previous sections discussed the pharmacokinetic suitability of midazolam and propofol as anaesthetic induction agents in children. A number of authors have compared the induction characteristics of propofol and thiopentone (Runcie et al, 1993, Mirakhur, 1988, Purcell-Jones et al, 1987) but there have been no comparative studies with midazolam in children. Induction characteristic dose-equivalence studies for propofol and thiopentone in children have been determined (McCollum et al, 1986) but again there have been no comparative studies with midazolam in children and therefore a recommended induction dosage regimen was chosen for comparison (Salonen et al, 1987). Induction of anaesthesia in children is often associated with rapid cardiovascular change, the degree and duration of which depends upon the agent used and the physiological status of the patient. The aim of this study was to compare the haemodynamic perturbation associated with induction of anaesthesia with either midazolam, propofol or thiopentone in children using the Finapres™, a non-invasive continuous blood pressure monitor which was adapted to record continuous haemodynamic data for analysis. Exclusion criteria for the study were designed to provide subjects who would permit comparison of induction agent effect on haemodynamics, independent of patient pathology.

# METHODS

Thirty ASA grade I Chinese children, aged 4-12 yr, undergoing circumcision for treatment of phimosis were investigated in this study. The study was approved by the Faculty of Medicine Ethics Committee (The University of Hong Kong) and written informed consent obtained from the parents. Children were excluded from the study according to the criteria detailed in *Chapter II.*

On the day of surgery, EMLA emulsion cream 2 g (lignocaine 25 mg $g^{-1}$ and prilocaine 25 mg $g^{-1}$) was applied to the cubital fossa of the non-dominant arm 2 hr before premedication with midazolam 0.5 mg $kg^{-1}$ (maximum dose 15 mg) and atropine 0.02 mg $kg^{-1}$ by mouth. Immediately following administration of the premedicant, a 23-gauge cannula was inserted into a vein underlying the EMLA-pretreated area. Routine monitoring devices included an electrocardiograph, intermittent non-invasive arterial pressure recorder and pulse oximeter (Datex, Cardiocap CM-104). A small size Finapres cuff was applied to the middle phalanx of the middle finger of the hand strictly according to the manufacturer's instructions, and the output from the Finapres 2300e (Ohmeda, Colorado) was interfaced with an AST Premium exec 386SX/25 computer. On arrival in the operating suite, the child was assessed as agitated or crying, aware and apparently anxiety free, drowsy, or asleep but responsive to command. Before induction, pulse rate, blood pressure and time data were simultaneously stored to disc in ASCII format every 10 sec for 3 min and then during and after induction for a further 10 min, using data acquisition software written for this system (BPM, 1991). The children were randomly allocated to receive either

propofol 2.5 mg $kg^{-1}$ without lignocaine (Aun et al, 1992; Patel et al, 1988), midazolam 0.5 mg $kg^{-1}$ (Salonen et al, 1987) or thiopentone 4.0 mg $kg^{-1}$ (Sorbo et al, 1984) intravenously over 30 sec. Thereafter, anaesthesia was maintained with the patient breathing spontaneously 67% nitrous oxide and 1% halothane in oxygen via a Mapleson F (< 25kg) or a Mapleson A (>25 kg) breathing system. A caudal injection of 0.25% bupivacaine 0.5 ml $kg^{-1}$ was given to all children, 6 minutes after intravenous induction agent administration.

The haemodynamic data were treated as ordinal scale data and analysed using the computer interactive statistical program CSS:Statistica™. A statistical significant ($p < 0.05$) difference between the three induction agent groups was determined using the Kruskal-Wallis statistic incorporating consideration of Bonferroni inequality. Patient's demographic data were analyzed by general ANOVA and statistical significant differences before and after induction in the same individuals was determined using the Wilcoxon signed-rank test.

# RESULTS

There was no significant difference between the midazolam, propofol and thiopentone groups when comparing patient characteristics or mood immediately prior to induction (Table **IV.9**). One child presented to the operating suite asleep and the remainder were awake and apparently anxiety free.

**TABLE IV.9** Patient characteristics and premedicant effect in the induction agent groups. *Data are mean (SD)[range].*

| | Midazolam (n = 10) | Propofol (n = 10) | Thiopentone (n = 10) | *p* value | Statistical test |
|---|---|---|---|---|---|
| **Age (yr)** | 7.2(2.5)[4-11] | 7.4(2.0)[5-11] | 7.4(2.3)[5-12] | 0.97 | general anova |
| **Weight (kg)** | 21.4(4.5)[15-27] | 23.9(5.3)[16-33] | 23.7(7.4)[17-37] | 0.57 | |
| **Anaesthetic duration (min)** | 35.5(6.0)[27-48] | 29.9(4.6)[25-39] | 32.5(7.6)[21-47] | 0.15 | general anova |
| **Preoperative assessment** | | | | | |
| **asleep/drowsy** | 0 | 1 | 0 | | |
| **awake** | 10 | 9 | 10 | | |
| **crying** | 0 | 0 | 0 | | |

Haemodynamic changes on induction were compared between the three induction agents using conventional intermittent non invasive blood pressure measurement every minute (Cardiocap) and Finapres blood pressure measurement every 10 seconds (Figure **IV.6**). Due to various technical recording and data manipulation errors, complete data were only available for 25 patients. Subsequent analysis excludes the 5 patients for whom data were not available.

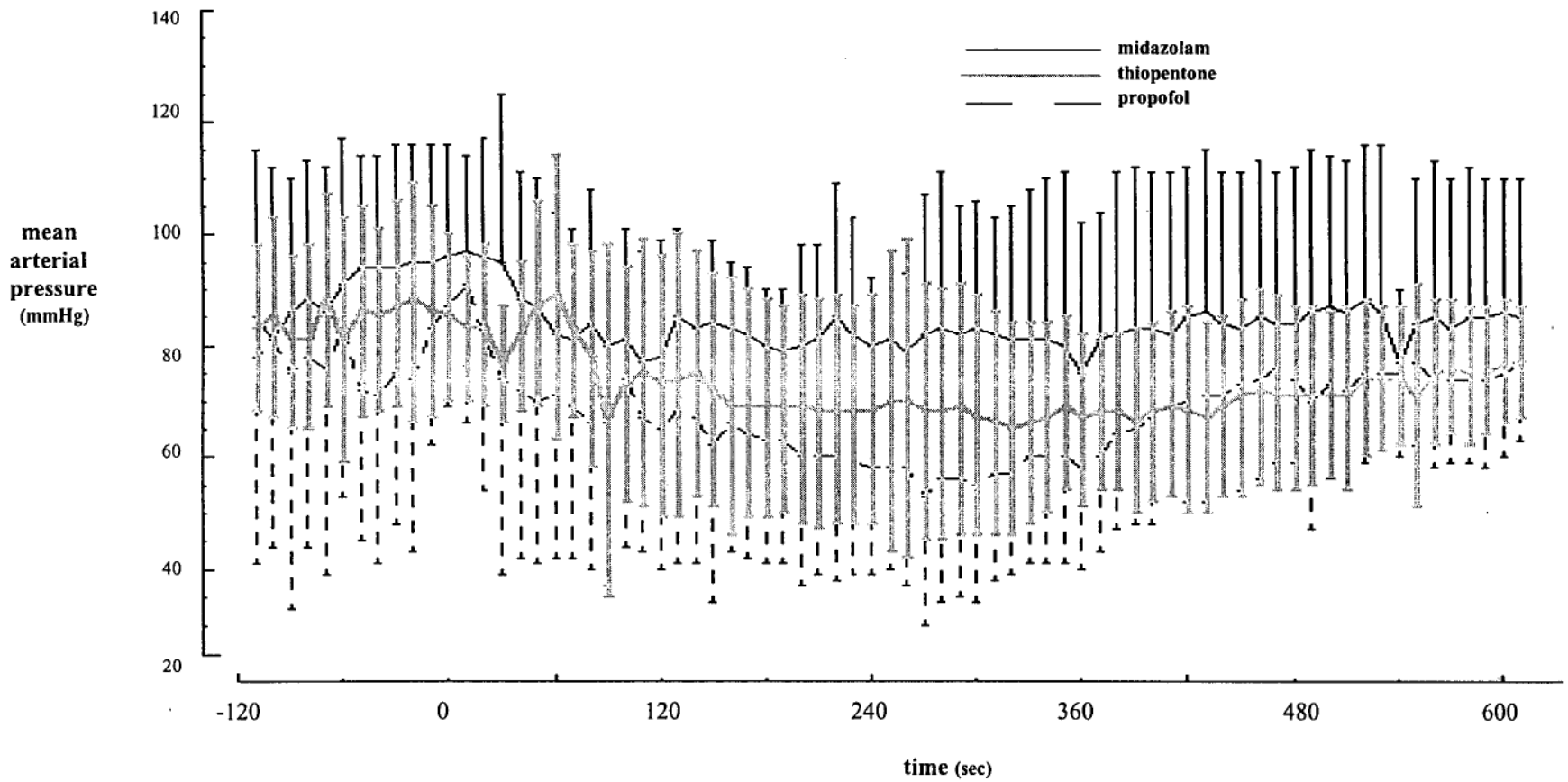


**FIGURE IV.6** Mean arterial pressure data measured by Finapres during induction with midazolam, thiopentone and propofol.

*Data are mean (SD).* (n = 25).

Maximum change in blood pressure and heart rate from the preinduction baseline were analysed during the first minute and the subsequent 5 minutes after induction (Table **IV.10**).

**TABLE IV.10** Haemodynamic data recorded by Finapres during the first and subsequent five minutes after induction. *Data are mean (SD)[range], blood pressure (mmHg), heart rate (beats min$^{-1}$).*

| | Midazolam (n = 8) | Propofol (n = 9) | Thiopentone (n = 8) | *p* value | Statistical test |
|---|---|---|---|---|---|
| **Mean maximum change in haemodynamic data recorded at first minute after induction** | | | | | |
| systolic pressure | -12.6(27.9)[-58 to 17] | -25.7(23.8)[-59 to 20] | -0.3(25.6)[-26 to 47] | 0.14 | Kruskal-Wallis statistic |
| diastolic pressure | -15.0(19.6)[-47 to 8] | -21.9(20.6)[-54 to 12] | 5.8(18.8)[-14 to 34] | 0.07 | |
| mean pressure | -16.0(21.4)[-53 to 10] | -28.4(17.4)[-53 to -10] | 6.1(24.3)[-20 to 43] | **0.03** | |
| heart rate | -2.5(28.9)[-23 to 59] | -18.3(31.9)[-78 to 25] | 15.3(22.1)[-24 to 49] | 0.05 | |
| **Mean maximum change in haemodynamic data recorded at subsequent five minutes after induction** | | | | | |
| systolic pressure | -24.7(32.4)[-58 to 49] | -50.2(21.8)[-91 to-11] | -27.1(44.0)[-71 to 70] | 0.16 | Kruskal-Wallis statistic |
| diastolic pressure | -19.9(23.3)[-47 to 30] | -37.2(27.6)[-67 to 24] | -14.3(30.7)[-40 to 59] | 0.05 | |
| mean pressure | -24.1(24.0)[-54 to 29] | -49.8(19.9)[-76 to -25] | -17.5(40.6)[-58 to 66] | **0.04** | |
| heart rate | -1.6(41.0)[-42 to 72] | -19.1(42.8)[-78 to 49] | 6.1(33.9)[-45 to 49] | 0.4 | |

The maximum decline in mean arterial pressure recorded with the Finapres showed a significant difference between the three induction agent groups at both 1 min and 5 min. Post-hoc analysis revealed a significant difference between the propofol and thiopentone groups at 1 minute ($p$=0.01), and between the propofol and midazolam groups at 5 minutes ($p$=0.02). Overall, thiopentone caused the least, propofol the greatest, fall in blood pressure, and midazolam was intermediate. The changing pattern in blood pressure and heart rate before and after induction is shown in figures **IV.7, IV.8** and **IV.9**.

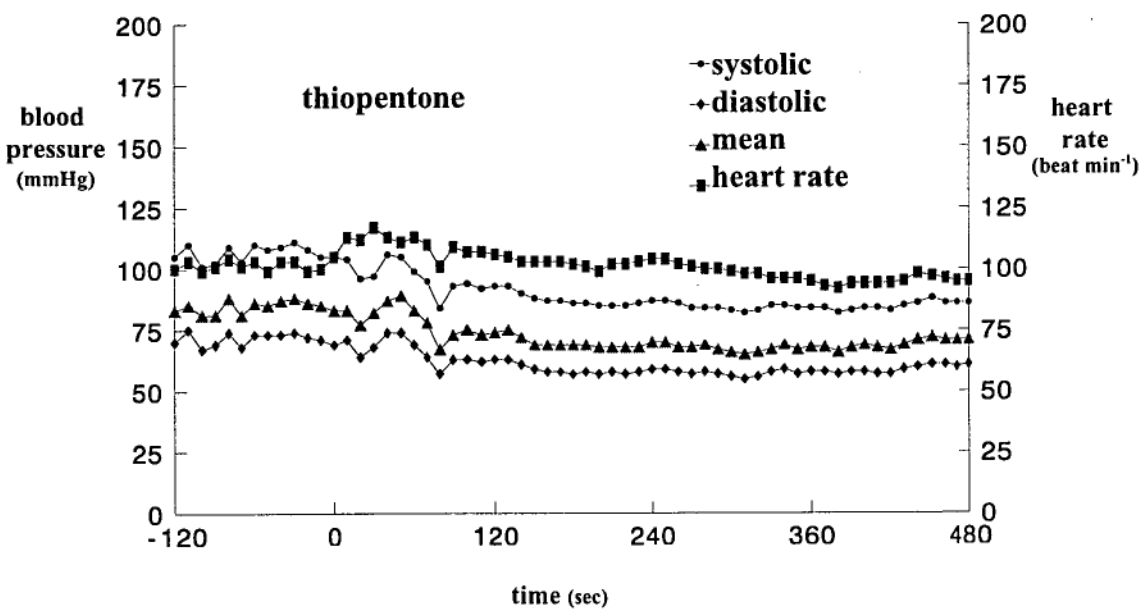


**FIGURE IV.7** Blood pressure and heart rate data measured by Finapres during induction of anaesthesia with thiopentone

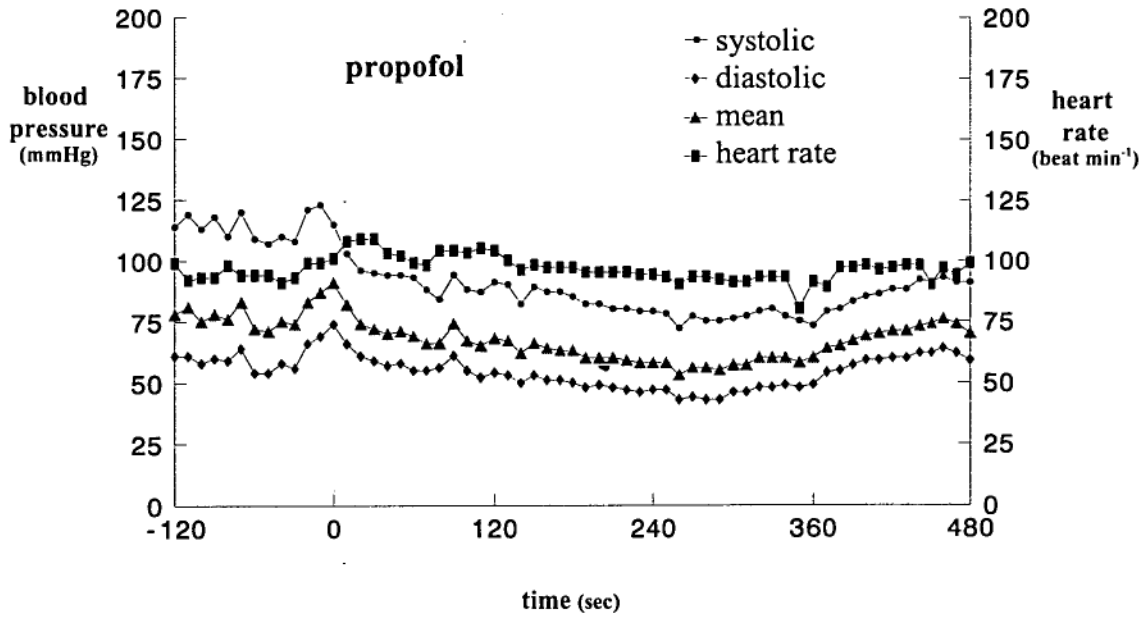


**FIGURE IV.8** Blood pressure and heart rate data measured by Finapres during induction of anaesthesia with propofol

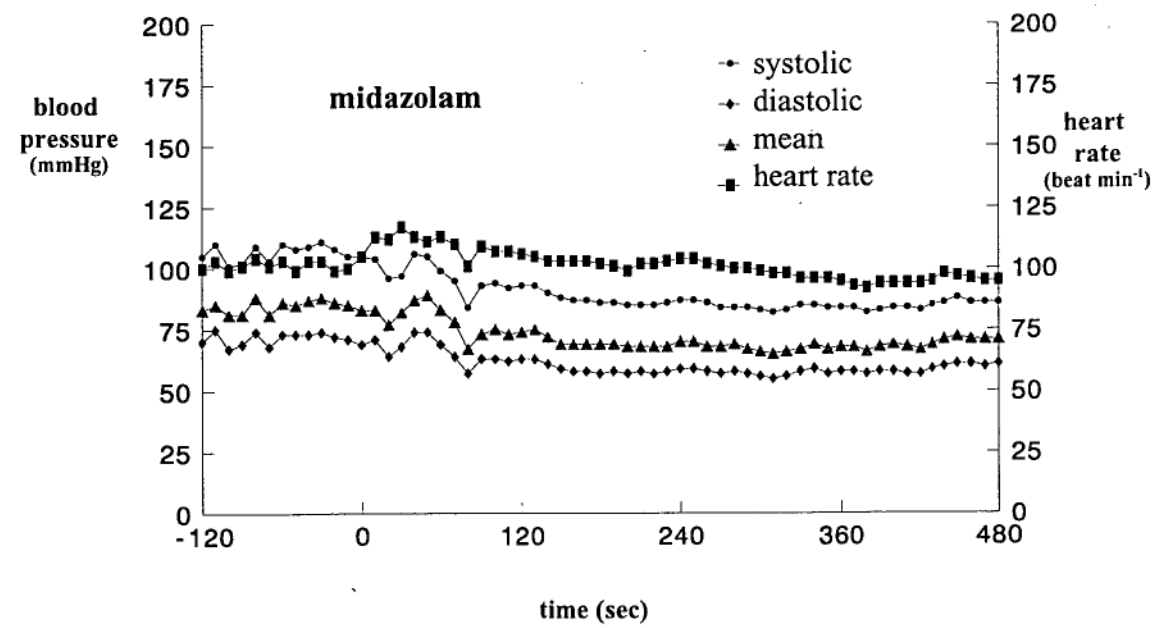


**FIGURE IV.9** Blood pressure and heart rate data measured by Finapres during induction of anaesthesia with midazolam.

The Cardiocap data failed to demonstrate any significant difference between the groups during either time period (Table **IV.11**).

**TABLE IV.11** Haemodynamic data recorded by Cardiocap during the first and subsequent five minutes after induction. *Data are mean (SD)[range], blood pressure (mmHg), heart rate (beats min$^{-1}$).*

| | Midazolam (n = 8) | Propofol (n = 9) | Thiopentone (n = 8) | *p* value | Statistical test |
|---|---|---|---|---|---|
| **Mean maximum change in haemodynamic data recorded in the first minute after induction** | | | | | |
| systolic pressure | -5.0(8.8)[-19 to 6] | -9.9(20.4)[-37 to 27] | -7.0(13.1)[-26 to 15] | 0.78 | Kruskal-Wallis statistic |
| diastolic pressure | -5.5(16.4)[-30 to 18] | -8.7(15.2)[-31 to 20] | -9.4(13.8)[-37 to 6] | 0.90 | |
| mean pressure | -5.1(14.8)[-34 to 20] | -8.9(15.1)[-31 to 20] | -8.0(12.9)[-33 to 7] | 0.77 | |
| heart rate | 8.1(17.6)[-11 to 41] | 6.3(16.6)[-18 to 34] | 15.5(15.9)[-7 to 35] | 0.75 | |
| **Mean maximum change in haemodynamic data recorded in the subsequent five minutes after induction** | | | | | |
| systolic pressure | -23.4(17.3)[-40 to 15] | -23.3(21.4)[-42 to 27] | -27.8(25.6)[-56 to 26] | 0.68 | Kruskal-Wallis statistic |
| diastolic pressure | -16.5(22.8)[-37 to 19] | -16.9(16.3)[-37 to 20] | -19.5(19.3)[-40 to 25] | 0.53 | |
| mean pressure | -14.9(22.1)[-34 to 20] | -18.7(15.8)[-33 to 20] | -20.9(19.3)[-42 to 24] | 0.70 | |
| heart rate | 13.0(28.3)[-33 to 45] | 0.6(22.1)[-24 to 34] | 4.3(27.2)[-28 to 37] | 0.48 | |

When all Finapres and Cardiocap data were compared there was a significantly greater fall in mean arterial pressure recorded by the Finapres ($p$=0.02) (Table **IV.12**).

**TABLE IV.12** Comparison of haemodynamic data recorded by Cardiocap and Finapres during the first and subsequent five minutes after induction, for all patients. *Data are mean (SD)[range], blood pressure (mmHg), heart rate (beats min$^{-1}$).*

| | FINAPRES (n = 25) | CARDIOCAP CM-104 (n = 25) | *p* value | Statistical test |
|---|---|---|---|---|
| **Mean maximum change in haemodynamic data recorded at first minute after induction** | | | | |
| systolic pressure | -13.4(26.9)[-59 to 47] | -7.4(14.7)[-37 to 27] | 0.43 | Wilcoxon |
| diastolic pressure | -10.8(22.4)[-54 to 34] | -7.9(14.6)[-37 to 20] | 0.62 | |
| mean pressure | -13.4(24.9)[-53 to 43] | -7.4(13.8)[-33 to 20] | 0.38 | |
| heart rate | -2.5(30.4)[-78 to 59] | 9.8(16.5)[-18 to 41] | 0.06 | |
| **Mean maximum change in haemodynamic data recorded at subsequent five minutes after induction** | | | | |
| systolic pressure | -34.7(34.2)[-91 to 70] | -24.8(20.9)[-56 to 27] | 0.23 | Wilcoxon |
| diastolic pressure | -24.3(28.1)[-67 to 59] | -17.6(18.7)[-40 to 25] | 0.12 | |
| mean pressure | -31.2(31.5)[-76 to 66] | -18.1(18.5)[-42 to 24] | **0.02** | |
| heart rate | -5.4(39.4)[-78 to 72] | 5.7(25.3)[-33 to 45] | 0.23 | |

There was poor correlation between Finapres and Cardiocap recorded blood pressures during each time period because of the difficulty in matching exact times of measurement between the two instruments and the limited number of Cardiocap measurements possible within the time period (correlation coefficients 0.07, 0.14, 0.16 and 0.17 for heart rate, systolic, diastolic and mean blood pressure), however there was less bias as more Cardiocap data became available for analysis during the 5 minute period (correlation coefficients being 0.24, 0.37, 0.37 and 0.46).

# DISCUSSION

A combined comparison of the induction agents midazolam, thiopentone and propofol has not previously been reported in children. Propofol caused the greatest and most protracted fall in blood pressure after an induction dose of 2.5 mg $kg^{-1}$ administered over 30 seconds into an antecubital vein. Thiopentone caused the least haemodynamic perturbation with the majority of changes being an increase in blood pressure. Midazolam administration was associated with a 15% decrease in mean arterial pressure (MAP) during the first minute after induction but the maximal decline in all pressures occurred at approximately 2 minutes when MAP was 20% below baseline values. Systolic, mean and diastolic blood pressures all declined by approximately 25% of baseline values following propofol administration, while pressures rose 0-5% following thiopentone induction. Propofol and thiopentone administration were associated with an average rise in heart rate of approximately 10% above baseline values, while the increase in pulse rate in midazolam group was 5%.

Continuous monitoring of arterial pressure is often desirable (Prys-Roberts, 1981, Kaplan, 1987) and is widely practised during anaesthesia, but arterial cannulation has associated morbidity (Slogoff et al, 1983, Runcie et al, 1989) and a noninvasive alternative is appropriate in ASA status I children undergoing minor surgical procedures. Although the Finapres demonstrates a wide variability in discrete values, it accurately reflects changes in pressure and was therefore able to display the haemodynamics in these children during the first minute following induction (Jones et

al, 1992b). The relatively slow sampling rate of the Cardiocap could not display these blood pressure changes during the early induction phase, and even though both instruments achieved more favourable correlation as more data points were acquired with time, this does not imply an improved ability to detect transient changes in blood pressure from a mean resting value. Blood pressure monitoring during the midazolam pharmacokinetic study discussed in the first section of this chapter was also performed with the Cardiocap. Recordings could only be made at 60 second intervals, and results showed an average **increase** of approximately 10% above baseline heart rate and blood pressure values. However, direct comparison between the two studies is inappropriate, as patients in the previous investigation were intubated.

There are few comparative data reported in the literature. The wide variation of ASA class, clinical condition, anaesthetic technique and interpatient response makes comparative interpretation of these results difficult. Early reports demonstrated no haemodynamic difference between midazolam and thiopentone, but data were collected at 5 minute intervals (Holloway et al, 1982). A comparative study of the haemodynamic sequelae associated with midazolam and propofol induction have not been reported but there are a number of controlled studies comparing thiopentone and propofol in children (Mirakhur, 1988, Purcell-Jones et al, 1987, Valtonen et al 1988). These studies showed the reduction of blood pressure to be less in the thiopentone groups compared to propofol but of less magnitude than the present study due to relatively infrequent data sampling. However, uncontrolled administration of propofol 1-3 mg $kg^{-1}$ over 10-30 seconds resulted in a decrease by more than 20% of baseline values in 48% of children who received halothane (Hannallah et al, 1991). Studies in

adults with ischaemic heart disease have demonstrated the relatively mild hypotensive effects of midazolam (Reves et al, 1979, Schulte-Sasse et al, 1982, Heikkila et al, 1984). Wilmot and colleagues found a 15% decrease in systolic blood pressure following propofol compared to a 0.7% decrease following a thiopentone induction in adults (Wilmot et al, 1993). Further factors confounding literature comparison are dose administered and rate of injection. Induction agents in this study were administered over 30 seconds. Unlike an increased dose of drug (Heikkila et al, 1984), fast rates of injection of propofol and midazolam do not appear to magnify the degree of hypotension associated with induction in ASA class I patients (Rolly et al, 1985, Alexander et al, 1992, Gillies and Lees, 1989).

Significant cardiovascular depression in terms of a decrease in arterial pressure is well documented in the elderly (McCollum et al, 1986, Fahy et al, 1985, Mirakhur et al, 1987) and more recently in children (Mirakhur, 1988, Hannallah, 1991) following propofol administration. A direct cardiac depressant effect, peripheral vasodilation and a reduction in ventricular preload have been proposed as likely causes of this hypotension (Coetzee et al, 1989). Decreasing diastolic pulmonary arterial pressure has been proposed as evidence of venous pooling after midazolam administration in adults, but a direct cardiac depressant effect has not been demonstrated in man in clinical doses (Massaut et al, 1983, Yip et al, 1992). Caudal anaesthesia in this series of children caused minimal haemodynamic disturbance and effectively abolished the usual increase in blood pressure associated with the commencement of surgery (Mirakhur, 1988).

This study demonstrates the clinically acceptable haemodynamic changes associated with midazolam induction in healthy children. Extrapolation of these data to other patient sub-groups is inappropriate. Care should be exercised if hypovolaemia is suspected because an exaggerated hypotensive response would be expected due to the venous pooling effect. Propofol administration in the presence of hypovolaemia or an otherwise compromised myocardium may result in severe, prolonged hypotension (Foëx et al,1991). On the other hand, a thiopentone induction undertaken in the manner described in this study should not be chosen, if an increased rate-pressure product is to be avoided.

When administered according to the described protocol, thiopentone caused the least average haemodynamic change on induction and propofol administration was associated with the greatest fall in blood pressure for the longest duration, in patients who were ASA I and undergoing a minor surgical procedure. The cardiovascular depressant effect of midazolam was intermediate between thiopentone and propofol.

# *CHAPTER V*

# RECOVERY FROM ANAESTHESIA

# ANTAGONISM OF THE HYPNOTIC EFFECT OF MIDAZOLAM

The previous chapters show that midazolam may have a place as an induction agent. However a wide variability in response and difficulty in predicting an induction end-point results in large doses of midazolam (0.6 mg $kg^{-1}$) being required for reliable induction of anaesthesia in children (Salonen et al, 1987; Gamble et al, 1981). There is therefore a consequent risk of prolonged post operative sedation. These risks can be reduced if the sedative effects of midazolam could be reliably antagonised and therefore provide greater safety in the recovery room and a more efficient usage of the operating suite.

The clinical efficacy and safety of flumazenil in rapidly antagonising the sedative effects of benzodiazepines administered to facilitate gastroscopy (Sanders et al, 1989), bronchoscopy (Geller et al, 1986) and other minor investigative procedures has been well established. The dose of flumazenil required for reversal of midazolam-induced anaesthesia, the incidence of resedation or incomplete respiratory depression reversal in children has not previously been reported.

Following midazolam induction of anaesthesia, this study assessed the efficacy of sedation antagonism in a flumazenil-treated and a placebo group, by comparing psychomotor performance with a modified post box toy test (Craig et al, 1982), using each patient as his own control.

## MATERIALS AND METHODS

Forty ASA grade I Chinese children, aged 3-12 yr., undergoing circumcision for the treatment of phimosis were studied. Children were excluded from the study if there was a history of asthma or allergies, previous adverse anaesthetic experience, halothane anaesthesia within the previous month, hepatic, renal, respiratory, cardiac or haematological disease, developmental disability and age less than 3 yr.

The day before surgery each child was familiarised with a post-box toy in the same manner as described in *chapter III.* The completion time of his best performance on seven attempts was recorded. On the day of surgery, the patients were premedicated with midazolam 0.5 mg $kg^{-1}$ (maximum dose 15 mg) and atropine 0.02 mg $kg^{-1}$ by mouth 2 hr before operation. EMLA emulsion cream 2 g (lignocaine 25 mg $g^{-1}$ and prilocaine 25 mg $g^{-1}$) was applied to the dorsum of a hand. On arrival in the operating suite the children were assessed and recorded as agitated or crying, aware and apparently anxiety free, drowsy, or asleep but responsive to command (Jones et al, 1990).

In the operating suite, a 24-gauge cannula was inserted into a vein underlying the EMLA-pretreated area. Anaesthesia was induced with midazolam 0.5 mg $kg^{-1}$ injected over 30 sec. Thereafter, anaesthesia was maintained with the patient breathing spontaneously 67% nitrous oxide and 1-3% halothane in oxygen via a Mapleson F (< 25 kg) or a Mapleson A (> 25 kg) breathing system. A caudal injection of bupivacaine 0.25%, 0.5 ml $kg^{-1}$ was given to all patients, 6 minutes after induction agent

administration. Routine monitoring devices included an electrocardiograph, non-invasive arterial pressure recorder, pulse oximeter, capnograph and inspired oxygen concentration (Datex, Cardiocap).

The duration of anaesthesia and the cardio-respiratory data during surgery were recorded. Three minutes after the child was transferred to the recovery room he was given 0.1 ml $kg^{-1}$ of a blinded solution intravenously, followed by 0.05 ml $kg^{-1}$ $min^{-1}$ until either the patient awoke or the 10 ml ampoule was exhausted. The blinded solution contained either flumazenil 1.0 mg in 10 mls or saline as placebo. The volume of blinded solution injected, the eye-opening time (time from the commencement of blinded solution injection to spontaneous eye opening) and the time until the patient could identify himself were recorded. During the administration of the blinded solution, the systolic blood pressure, heart rate, respiratory rate, modified Steward coma scale (Robertson et al, 1977) and a structured observation score (Krane et al, 1987) were assessed and recorded each minute for 10 min and then each 5 minutes until the patient awoke. Any untoward effects occurring during the recovery period were noted. The child's behaviour and speed of reversal were considered together by an independent observer in the recovery room and were graded as excellent, good, moderate or poor, determined by the eye opening time of <6 min, >6 < 12 min, >12 < 18 min and >18 min respectively.

Immediately the patient became cooperative he was encouraged to complete the post-box toy in the quickest possible time. The child was offered the post-box toy at 5, 10, 30, and 60 min and 2, 4, and 18 hr after operation and his fastest completion time

on a single attempt recorded by the same investigator with all children at all assessment times. The child's best, preoperative, unmedicated performance was divided by the child's postmedication toy-completion time at each assessment point, and the data expressed as the post box toy completion ratio (PBTR). The induction injection site was inspected at 18 hr post operatively for evidence of erythema, pain or venous thrombosis.

Statistical significance ($p<0.05$) was determined for patient characteristic data, duration of anaesthesia, awakening times, toy completion ratios and cardiorespiratory data comparison between the groups by analysis of variance. Premedication score and the efficacy of sedation antagonism was determined by Chi-square analysis (with Yates' correction) using the computer interactive statistical program MINITAB™. Correlation between awakening data and flumazenil administration was determined by calculating Spearman's rank correlation coefficient (adjusted for ties) and multivariate analysis of variance was determined using MRSP™ (Bacon-Shone and Laurent, 1989).

# RESULTS

The premedication scores for the two groups were significantly different ($p$<0.02)(Table **V.1**). On arrival in the operating suite, three of the children in the flumazenil group were crying, whereas two of the placebo group were asleep but awoke on command. The mean duration of anaesthesia was 36(14) min in the flumazenil group and 33(11) min in the placebo group ($p$=0.4)(Table **V.1**).

**TABLE V.1** A comparison of the demograhic data, duration of anaesthesia and premedication score in the Flumazenil and placebo groups. *Data are mean (SD)[range].*

| | **Flumazenil group (n = 20)** | **Placebo group (n = 20)** | ***p* value** |
|---|---|---|---|
| Age (yr) | 7.2 [3.5-11.5] | 6.9 [3.0-12.5] | 0.9 |
| Weight (kg) | 21.2 (5.1) [13.5-30.5] | 22.7 (6.9) [15.5-44.0] | 0.5 |
| Premedication score | | | |
| Asleep | 0 | 2 | |
| Drowsy | 0 | 0 | |
| Awake | 17 | 18 | |
| Crying | 3 | 0 | 0.02 |
| Duration anaesthesia (min) | 36 (14) [17-80] | 33 (11) [19-69] | 0.4 |

The average dose of flumazenil administered to the children was 0.024 (0.019) mg $kg^{-1}$. Fifty five percent of the children receiving flumazenil were given 10 mls of the blinded solution prior to awakening, compared to 100% of the placebo group. The time to eye opening and identification was significantly faster in the flumazenil treated patients ($p<0.001$). The effectiveness of anaesthesia reversal was qualitatively assessed by a second anaesthetist as superior in all but one of the flumazenil group (Figure **V.1**).

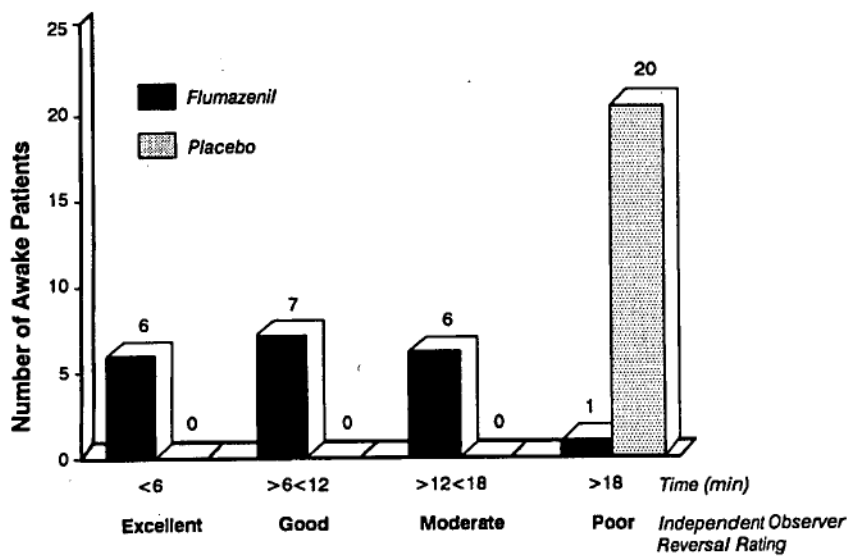


**FIGURE V.1** Effectiveness of the reversal solution assessed by the independent observer and by eye-opening time. (Spearman's correlation $p<0.001$).

The coma scores at 5 and 10 min were significantly higher in the flumazenil group ($p<0.008$ and $p<0.001$) (Table **V.2**).

**TABLE V.2** Awakening data after reversal. *Data are mean (SD)[range].*

| | **Flumazenil group (n = 20)** | **Placebo group (n = 20)** | ***p* value** |
|---|---|---|---|
| Volume of antagonist solution administered (ml) | 8.6 (1.7) [5.0-10.0] | 10 (10) | <0.001 |
| Time to eye-opening (min) | 10.4 (6.6) [2-32] | 37.9 (15.5) [21-76] | <0.001 |
| Time to self-identification (min) | 17.1 (12) [6-52] | 45.1 (15.5) [22-77] | <0.001 |
| Assessment of antagonism | | | |
| Excellent | 6 | 0 | |
| Good | 7 | 0 | |
| Moderate | 6 | 0 | |
| Poor | 1 | 20 | <0.001 |
| Modified Steward Coma Scale at: | | | |
| 5 min | 4.5 (2.0) [2-9] | 1.7 (0.9) [0-4] | <0.001 |
| 10 min | 7.4 (2.1) [3-9] | 1.9 (0.9) [0-4] | <0.001 |

There was a significant increase in the coma score associated with the lightening of consciousness within the flumazenil group between the 5 and 10 minute assessments but not in the placebo group ($p<0.001$). There was a significant increase in systolic arterial pressure on awakening during flumazenil administration compared to those patients receiving placebo ($p<0.02$) but other measured cardio-respiratory parameters were similar (Table **V.3**).

**TABLE V.3** Changes in cardiorespiratory data during administration of the blinded solution. *Data are mean (SD)[range].*

| | Flumazenil group (n = 20) | Placebo group (n = 20) | p value |
|---|---|---|---|
| Ventilation frequency (b.p.m.) | -1.2 (2.4) [-4 to 2] | -0.3 (1.6) [-4 to 2] | 0.1 |
| Systolic arterial pressure (mmHg) | 11.5 (12.7) [-11 to 35] | 2.6 (10.8) [-11 to 31] | 0.02 |
| Heart rate (beat $min^{-1}$) | 5.8 (29.4) [-44 to 66] | -5.4 (16.4) [-45 to 22] | 0.14 |

The postoperative assessment of the children's mood on awakening is shown in Table **V.4** and a comparison of post box toy completion ratios between the flumazenil and placebo groups is shown in Table **V.5**.

**TABLE V.4** Postoperative assesssment of the mood of the children on awakening.

| Postoperative assessment | Flumazenil group (n = 20) | Placebo group (n= 20) |
|---|---|---|
| Toy refusal on awakening | 3 | 5 |
| Crying on awakening | 4 | 2 |
| Resedation | 4 | 5 |
| Dissociated | 1 | 0 |
| Antagonism assessed as satisfactory | 17 | 0 |

**TABLE V.5** Post-box toy completion assessment. *Data are mean (SD)[range].*

| | Assessable children at prescribed times (n) | Flumazenil group (n = 20) | Assessable children at prescribed times (n) | Placebo group (n = 20) | *p* value |
|---|---|---|---|---|---|
| Fastest completion before operation (sec) | | 20 (10) [8-52] | | 19 (8) [9-43] | 0.9 |
| Completion ratio after operation | | | | | |
| 10 min | 12 | 0.34(0.08) [0.20-0.48] | 0 | | |
| 30 min | 16 | 0.48(0.16) [0.17-0.74] | 2 | 0.08(0.06) [0.04-0.13] | <0.001 |
| 60 min | 16 | 0.49(0.15) [0.29-0.72] | 12 | 0.18(0.10) [0.07-0.41] | <0.001 |
| 2 hr | 18 | 0.57(0.20) [0.25-1.08] | 15 | 0.47(0.17) [0.18-0.72] | 0.14 |
| 4 hr | 20 | 0.69(0.32) [0.31-1.80] | 20 | 0.65(0.19) [0.30-1.07] | 0.95 |
| 18 hr | 20 | 0.84(0.25) [0.43-1.42] | 20 | 0.84(0.26) [0.56-1.61] | 0.8 |

There was no difference between the two groups in the preoperative fastest completion time. However, during the first 2 hr postoperation, the flumazenil group performed significantly better than the placebo group. ($p$<0.02)(Figure **V.2**).

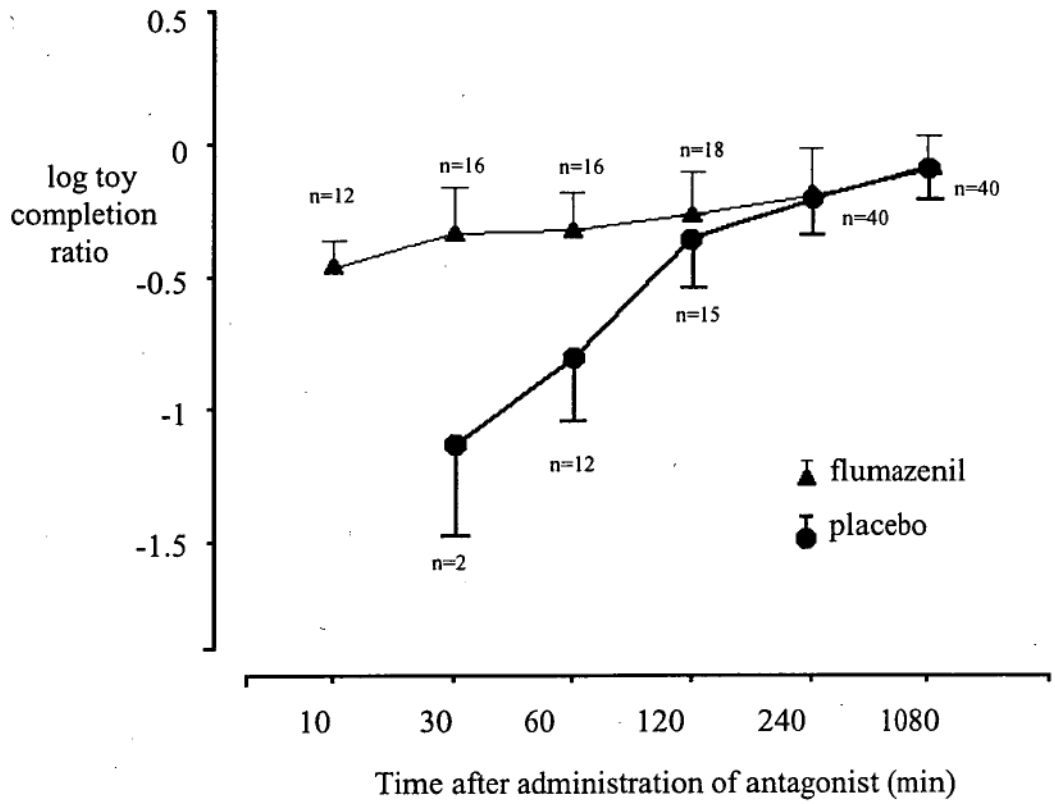


**FIGURE V.2** Log toy completion ratio at different times after administration of reversal solution. *Data are mean (SD)[range], n = number of patients assessable at the prescribed times.*

Postoperatively one child in the flumazenil group appeared dissociated for a period of approximately 3 min. An equal number of children in both groups went back to sleep after eye-opening but all of the flumazenil treated children were easily awakened. None of the children who received flumazenil became resedated. There

were no significant differences between the placebo and flumazenil groups in relation to refusal to play with the toy or crying on awakening (Table **V.4**). There was a significant correlation between the volume of flumazenil administered and the eye opening time ($p<0.001$) and the self-identification time ($p<0.02$). Multivariate analysis revealed no relationships of statistical significance.

# DISCUSSION

This study demonstrates that flumazenil effectively reverses the residual hypnotic effect of midazolam induction of anaesthesia in children. All aspects of arousal assessment during the first 2 hr postoperatively demonstrated flumazenil administration to be significantly superior to the placebo. The mean dose of flumazenil required to reverse the effects of midazolam was 0.024 mg $kg^{-1}$. The dose of flumazenil reported to awaken adult patients in whom midazolam was used to induce anaesthesia is approximately 0.5 mg (Wolff, 1988; Nilsson et al, 1988; Alon et al, 1987). In our children the dose administered ranged from 0.5 to 1.0 mg, and 55% of the flumazenil group were given a maximum dose of 1.0 mg before awakening. Despite the relatively large dose per kilogram of midazolam (0.5 mg $kg^{-1}$) used to induce our children, reversal was achieved with a dose of flumazenil similar to that given to adults. However there was only a weakly significant relationship between body weight and the flumazenil dose required for awakening ($p<0.04$) and this showed no correlation with age.

The onset and mode of action of midazolam depends in part on the relationship between the benzodiazepine receptor and the gamma-amino-butyric acid (GABA) receptor complex (Haefely, 1988). It has been demonstrated that the rate of chloride uptake by cultured neurons following midazolam administration is dose dependent (Thompson et al, 1988). The onset of anaesthesia with midazolam is faster in children (Salonen, 1987) and this may be due to a greater free midazolam concentration around the benzodiazepine receptor or a stronger affinity of midazolam

for the benzodiazepine receptor. Flumazenil reversal of benzodiazepine effects depends on the number of receptors occupied at the time of flumazenil administration (Haefely, 1988). It is postulated that the hypnotic effects of benzodiazepines occur with 60-90% receptor occupancy and anxiolytic properties at 20-30% receptor occupancy (Amrein and Hetzel, 1990). High doses of midazolam are therefore necessary for hypnosis but low doses of flumazenil convert the adult from the hypnotic to the sedated state (Amrein and Hetzel, 1990). It is surprising that there was no demonstrable relationship between the midazolam induction and flumazenil reversal dose. The variable response to midazolam and dose requirement of flumazenil in relation to body weight in children requires further investigation. Children may differ from adults in their pharmacokinetic profile, plasma protein binding, receptor occupancy rate, chloride channel opening frequency and the amount of GABA present at the GABA receptor (Thompson et al,1988).

This study shows that mean eye-opening and identification time was approximately three times as fast in the flumazenil group compared to the placebo group. One child in the flumazenil group did not awaken for 30 min after flumazenil administration and behaved in a manner identical to the placebo group. This may have been caused by an undue sensitivity to midazolam, resistance to flumazenil, unusual pharmacokinetic profile of these drugs or the unlikely event of there not being any active drug in that particular ampoule of blinded solution. The remaining flumazenil treated children awoke within 18 min of administration while the placebo treated group demonstrated a wide variation in awakening times from 20 to 77 min. The modified Steward coma scales at 5 and 10 minutes were statistically and clinically

superior in the flumazenil treated children. These children demonstrated a rapid regaining of consciousness and airway control compared to the placebo group who required vigilant observation for a long period of time.

The observer assessed both the rate and quality of reversal (Table **V.2**). One child awoke after flumazenil adminstration and remained uncommunicative in a dissociated state for about three minutes. The child then began to cry and appeared normal. All other flumazenil treated children awoke faster and were more co-operative, more rapidly calmed if distressed and if they went back to sleep they were easily aroused. Resedation after midazolam reversal in our children did not present the same problem as in adults (Whitwam, 1990). This may be because they were given a single intravenous dose of midazolam, their lack of concomitant disease and the absence of synergistic drugs (excluding halothane) for supplementation of anaesthesia. Interestingly, Geller and colleagues found that although flumazenil did not actually reverse halothane anaesthesia, it had a definite effect on hastening recovery as well as making it more pleasant (Geller et al, 1988). The reversal of the midazolam-induced deep hypnosis by careful titration of flumazenil appears to leave the anxiolytic properties of midazolam intact (Amrein et al, 1988). The placebo group in this study had a higher toy participation refusal rate, were irritable on awakening and were still somnolent after eye-opening.

Vomiting, tremor and involuntary movements reported in adults after flumazenil administration (Haefely, 1988), were not seen in any of our children. The low incidence of vomiting may be explained by the brief duration of anaesthesia for

peripheral surgery in children, the midazolam premedication and a caudal epidural being preferred to narcotics for the provision of analgesia.

The post-box toy completion time ratio provided a sensitive psychomotor assessment, a measure of the speed of recovery from anaesthetic agents and took into account the practice effect associated with performing a complex motor task. During the first 2 hr postoperatively the flumazenil group performed significantly faster when compared to the placebo treated children. This is in accord with previous clinical experience in adults (Raeder et al, 1988; Geller et al, 1988) and the pharmacokinetic profiles of midazolam and flumazenil (Hunkeler, 1988; Gerecke, 1983). At 4 hr the mean toy completion ratios were identical between the two patient groups and their performance was less than twice their preoperative **fastest** completion time. Despite the large dose of midazolam given at premedication and induction of anaesthesia, both the flumazenil treated and placebo treated children demonstrated a degree of recovery from anaesthesia which would allow them to be safely discharged home four hours postoperatively.

The mean change in cardio-respiratory parameters from pre-reversal administration were small and similar in both groups of patients. The only statistically significant finding was a minimal increase in systolic blood pressure after flumazenil administration corresponding to the normal awakening, a similar finding to Geller and colleagues in adults (Geller et al, 1986).

Flumazenil provides safe reversal of the residual sedative effects of midazolam induced hypnosis in children. Of particular benefit is the rapid return of consciousness

and upper airway control during early recovery and the preservation of the anxiolytic properties of midazolam anaesthesia. To provide a more complete understanding of the place of midazolam in clinical paediatric anaesthetic practice, a comparison of recovery following anaesthesia induced with other commonly used agents is necessary.

# RECOVERY FOLLOWING INDUCTION OF ANAESTHESIA WITH MIDAZOLAM, PROPOFOL OR THIOPENTONE

Paediatric surgery is being increasingly performed on a day-stay basis because of rising hospital costs. Ambulatory care also reduces displacement anxiety in the child and decreases exposure to nosocomial infection (Kapur, 1992). Circumcision is a suitable procedure for ambulatory surgery because the procedure is of short operative duration, has a low incidence of complications and postoperative pain relief can be easily and reliably provided (Hannallah and Epstein, 1991). Circumcision patients form a suitable subgroup for assessment of induction agents because the procedure permits delivery of a standard anaesthetic technique of relatively constant duration. Furthermore, the control of intra and postoperative pain with caudal anaesthesia allows assessment of anaesthetic recovery without pain confounding the data (Runcie et al, 1993).

Recovery after anaesthesia is multidimensional (Zuurmond et al, 1989). Of particular interest in ambulatory care is the immediate recovery of protective reflexes following surgery and a later return to "street fitness" prior to discharge from the ward. A variety of tests of psychomotor performance, cognition and memory have been used to assess recovery in adults (Cashman and Power, 1989) but patient compliance makes assessment of psychomotor recovery difficult in children. The aim of this study was to evaluate two tests of recovery and describe any relative advantages following induction with either thiopentone, propofol or midazolam, in children undergoing circumcision.

## MATERIALS AND METHODS

Thirty ASA grade I Chinese children, aged 4-12 yr, undergoing circumcision for treatment of phimosis were investigated. The study was approved by the Faculty of Medicine Ethics Committee (The University of Hong Kong) and written informed consent obtained from the parents. Children were excluded from the study if they failed to conform with the criteria as described in *Chapter II.* The day prior to surgery, each child was familiarised with a post-box toy (PBT) and the completion time of his best seven attempts recorded (Jones et al, 1991). The children also underwent a Wechsler intelligence scale (WISC-R) coding performance assessment, matched for race (The Hong Kong Wechsler Intelligence Scale for Children, 1981). Long term memory recall was assessed by a simplified Williams test (Williams, 1968), whereby the children were shown a simple picture of a school scene for 30 s and asked to name and remember five depicted objects. The following morning before premedicant administration, the child was asked to recall the objects from the picture shown to him the previous evening and scored according to his degree of success.

On the day of surgery, EMLA emulsion cream 2 g (lignocaine 25 mg $g^{-1}$ and prilocaine 25 mg $g^{-1}$) was applied to the cubital fossa of the non-dominant arm 2 hr before premedication with midazolam 0.5 mg $kg^{-1}$ (maximum dose 15 mg) and atropine 0.02 mg $kg^{-1}$ by mouth. On administration of the premedicant, a 23-gauge cannula was inserted into a vein underlying the EMLA-pretreated area. Prior to transfer to the operating suite the child was again shown another simple picture of a family scene for 30 sec and asked to name and remember five depicted objects. On

arrival in the operating suite, all children were assessed by the same attendant anaesthetist as agitated or crying, aware and apparently anxiety free, drowsy, or asleep but responsive to command (Jones et al, 1990). The awake children were then asked if they felt frightened and if so, to specify the cause of their anxiety. Routine monitoring devices included an electrocardiograph, intermittent non-invasive arterial pressure recorder and pulse oximeter (Datex, Cardiocap CM-104). The children were randomly allocated to receive either propofol 2.5 mg $kg^{-1}$(Aun et al 1992; Patel et al 1988), midazolam 0.5 mg $kg^{-1}$ (Salonen et al, 1987) or thiopentone 4.0 mg $kg^{-1}$ (Sorbo et al, 1984) intravenously over 30 sec. Thereafter, anaesthesia was maintained with the patient breathing spontaneously 67% nitrous oxide and 1% halothane in oxygen via a Mapleson F (< 25kg) or a Mapleson A (>25 kg) breathing system. A caudal injection of 0.25% bupivacaine 0.5 ml $kg^{-1}$ was administered to all children.

The duration of anaesthesia and cardio-respiratory data during surgery and recovery were recorded. The time to spontaneous eye opening and self-identification were recorded by an anaesthetist blinded to the agent used for induction of anaesthesia. The child's co-operation, mood and sedative level were recorded were recorded on awakening using a structured observation score (Krane et al, 1987) and the modified Steward coma score (Robertson et al, 1977), and a 1 ml blood sample taken. The blood samples were collected into tubes containing lithium-heparin (Sarstedt LH/5) for measurement of the plasma or whole blood concentration of the induction agent. As soon as the child became co-operative he was encouraged to complete the post-box toy in the quickest possible time and the WISC-R coding performance was scored. At each of the blood collection times the child was offered

the post-box toy and his fastest completion time at a single attempt recorded. The child was also asked to complete the WISC-R coding test within 2 min and scored according to his performance. The raw WISC-R data was then scaled to produce score equivalents adjusted for the child's age. The child's best, preoperative, unmedicated performance was divided by the child's postmedication performance at each assessment point for both the PBT and WISC-R, and the data expressed as the post box toy completion ratio (PBTR) and WISC-R scale ratio. The child was offered the toy and coding test at 60, 120 ,180 and 240 min after awakening and a 1 ml blood sample was taken immediately after completion of each psychomotor assessment. Four hours after awakening the child was asked to recall 5 objects from the picture shown to him immediately preoperatively and scored according to his degree of success. Each assessment of psychomotor function was performed by the same investigator on all occasions in all patients.

Whole blood propofol concentrations, midazolam and thiopentione plasma concentrations were determined employing an HPLC technique as described in *Chapter II.*

Statistical significance ($p < 0.05$) was determined for the three induction agent groups for demographic and awakening data by analysis of variance using the Newman-Keuls test for post-hoc comparisons. Pearson product moment correlation was used to determine any relationship between postoperative awakening and duration of anaesthesia, PBT and WISC-R ratios, and, drug concentration and psychomotor test. A significant difference between the coma scores at each postoperative

assessment for the three induction agents was determined using the Kruskal-Wallis statistic and chi-square analysis (with Yates' correction) was used to analyse the mood data. Memory recall before and after induction in the same individuals was analysed using Wilcoxon signed-rank test. Data computation was performed using the computer interactive statistical program CSS:Statistica™ (Complete Statistical System, 1991).

# RESULTS

There was no significant difference between the midazolam, propofol and thiopentone groups when comparing patient characteristics, anaesthetic duration and psychomotor assessment by WISC-R or post box toy (PBT) on the evening before surgery or after midazolam premedication (Table **V.6**). One child presented to the operating suite asleep and the remainder were awake and apparently anxiety free. No child required any post operative analgesic supplementation.

**TABLE V.6** Demographic data, anaesthetic duration and preinduction assessment in the three induction agent groups. *Data are mean (SD)[range].*

| | Midazolam (n = 10) | Propofol (n = 10) | Thiopentone (n = 10) | *p* value | Statistical test |
|---|---|---|---|---|---|
| **Age (yr)** | 7.2(2.5)[4-11] | 7.4(2.0)[5-11] | 7.4(2.3)[5-12] | 0.97 | general anova |
| **Weight (kg)** | 21.4(4.5)[15-27] | 23.9(5.3)[16-33] | 23.7(7.4)[17-37] | 0.57 | |
| **Anaesthetic duration (min)** | 35.5(6.0)[27-48] | 29.9(4.6)[25-39] | 32.5(7.6)[21-47] | 0.15 | general anova |
| **Preoperative state** | | | | | |
| **asleep/drowsy** | 0 | 1 | 0 | | |
| **awake** | 10 | 9 | 10 | | |
| **crying** | 0 | 0 | 0 | | |

Testing the association between anaesthetic duration and the time to self-identification in all patients revealed a correlation coefficient of 0.17 (Table **V.7**).

**TABLE V.7** Postoperative awakening and psychomotor performance data in the three induction agent groups. *Data are mean (SD)[range]. * r value = correlation coefficient for the relationship between postoperative self-identification time and the duration of anaesthesia for each induction agent.*

| | Midazolam (n = 10) | Propofol (n = 10) | Thiopentone (n = 10) | *p* value | Statistical test |
|---|---|---|---|---|---|
| **Eye opening time (min)** | 31.8(10.8)[21-57] | 21.9(7.6)[10-33] | 25.2(7.0)[16-36] | 0.05 | General anova |
| **Identification time (min)** | 36.3(10.0)[24-57] | 22.9(8.1)[10-34] | 27.0(7.7)[16-40] | **0.01** | General anova Newman-Keuls |
| **Postoperative PBTR** | | | | | |
| **Awake** | 0.2(0.2)[0.1-0.6] | 0.4(0.2)[0.1-0.8] | 0.4(0.2)[0.2-1.0] | **0.03** | General anova |
| **60** | 0.5(0.3)[0.1-0.9] | 0.8(0.2)[0.3-1.2] | 0.6(0.2)[0.3-0.8] | 0.18 | Newman-Keuls |
| **120** | 0.8(0.2)[0.5-1.1] | 0.7(0.2)[0.5-1.2] | 0.8(0.2)[0.6-1.2] | 0.34 | |
| **180** | 0.9(0.2)[0.4-1.1] | 0.9(0.2)[0.6-1.3] | 0.8(0.1)[0.6-0.9] | 0.83 | |
| **240** | 0.9(0.2)[0.7-1.4] | 0.9(0.2)[0.6-1.1] | 0.9(0.2)[0.6-1.2] | 0.63 | |
| **Postoperative WISC-R scale R** | | | | | |
| **Awake** | 0.1(0.1)[0.1-0.2] | 0.5(0.4)[0.1-1.0] | 0.4(0.2)[0.1-0.7] | **0.02** | General anova |
| **60** | 0.6(0.3)[0.1-1.0] | 0.7(0.4)[0.1-1.0] | 0.6(0.4)[0.1-1.0] | 0.44 | Newman-Keuls |
| **120** | 0.9(0.2)[0.3-1.0] | 0.9(0.4)[0.1-1.2] | 1.0(0.2)[0.7-1.5] | 0.60 | |
| **180** | 1.0(0.1)[0.8-1.1] | 1.0(0.2)[0.7-1.3] | 1.1(0.2)[0.9-1.6] | 0.50 | |
| **240** | 1.0(0.1)[0.8-1.1] | 1.1(0.1)[0.9-1.3] | 1.1(0.2)[0.9-1.6] | 0.32 | |
| ***r value** | 0.36 | 0.22 | 0.56 | | Pearson product moment correlation |

The midazolam group of children took a significantly longer time to identify themselves compared to both the propofol ($p$=0.005) and thiopentone groups

($p$=0.02), however there was no difference between the groups in the time to eye opening ($p$=0.05). The propofol group were able to identify themselves 13 minutes faster than the midazolam group. On awakening, both PBT and WISC-R ratios were significantly lower in the midazolam group compared to propofol ($p$=0.03 and 0.01) and thiopentone groups ($p$=0.01 and 0.02). However, after 1 hr, there was no statistical difference between the groups with either method of assessment. Most children had recovered to 80% of their best recorded performance four hours after awakening, irrespective of the induction agent administered (Figure **V.3**).

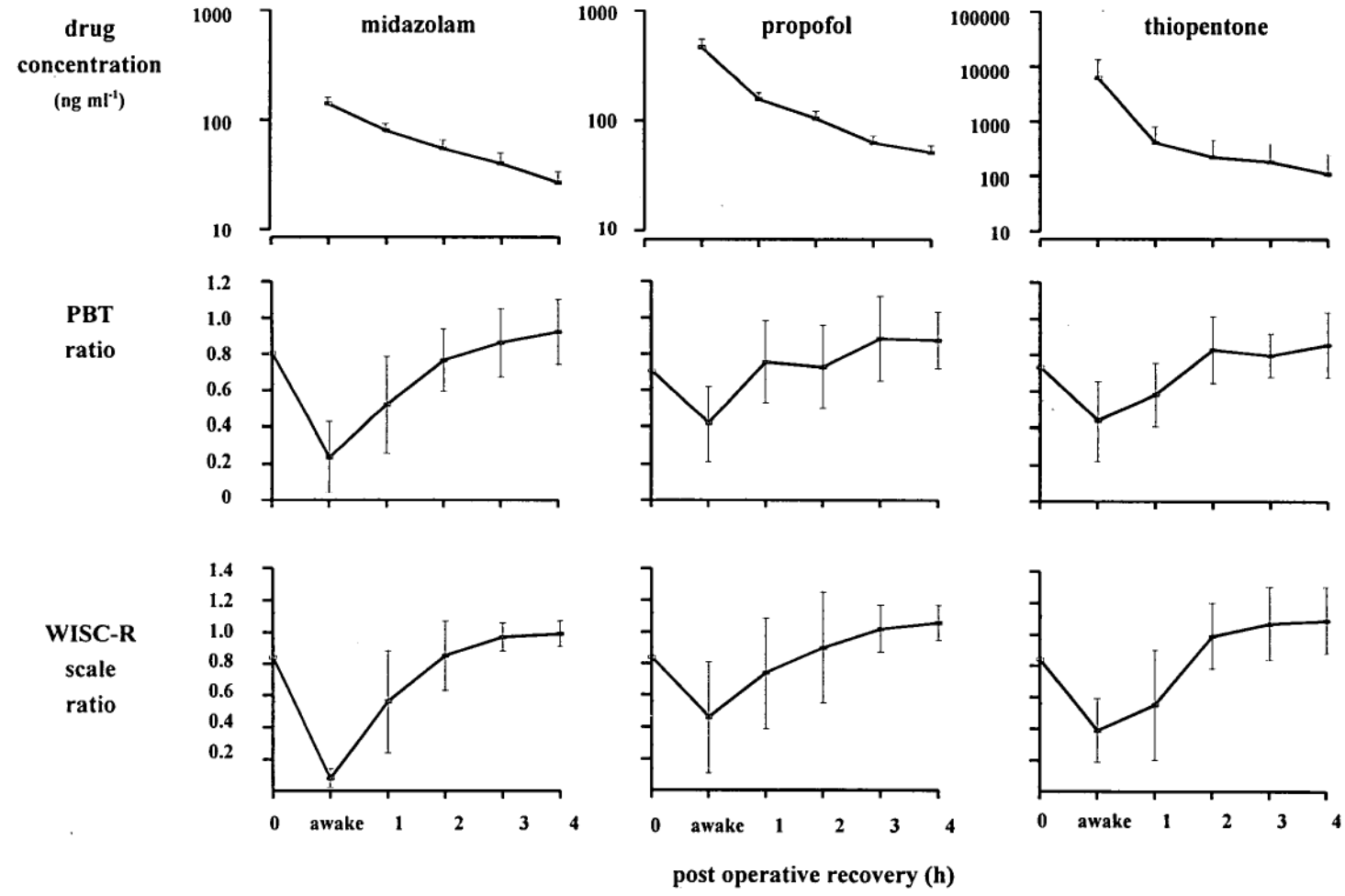


**FIGURE V.3** Postoperative drug concentrations of the induction agents midazolam, thiopentone and propofol and hourlly assessments of psychomotor recovery using the PBT and WISC-R ratios. (n=10).

The Pearson product moment correlation testing the association between PBT and WISC-R ratios for all psychometric data was 0.7 (Figure **V.4**).

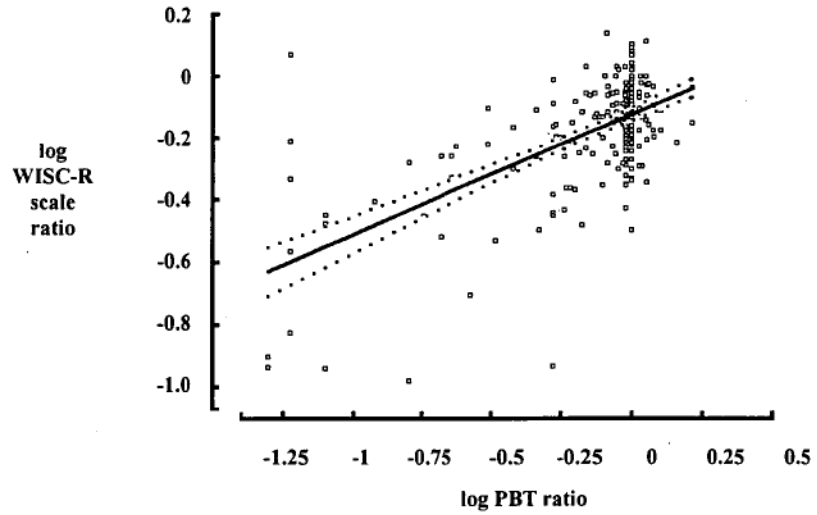


**FIGURE V.4** Pearson product moment correlation testing the association between PBT and WISC-R ratios for all psychometric data. (n=30).

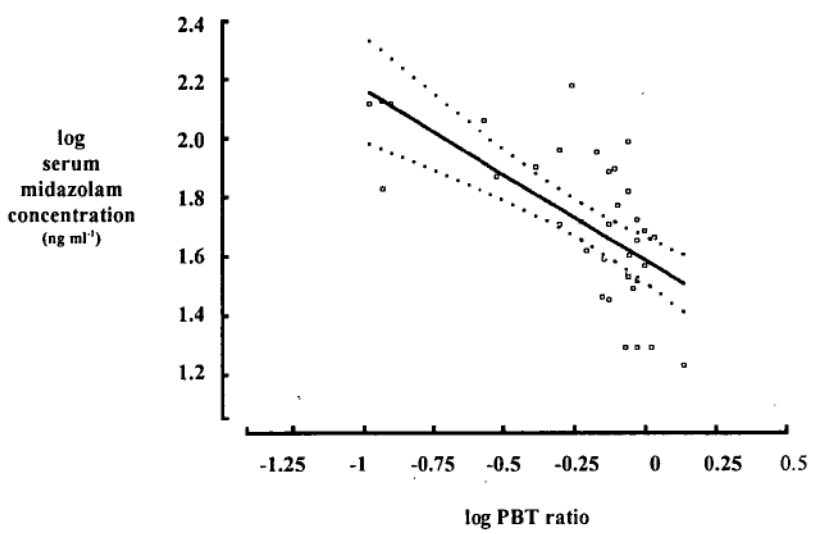


**FIGURE V.5** Pearson product moment correlation testing the association between serum midazolam concentration and PBT ratio. (n=10).

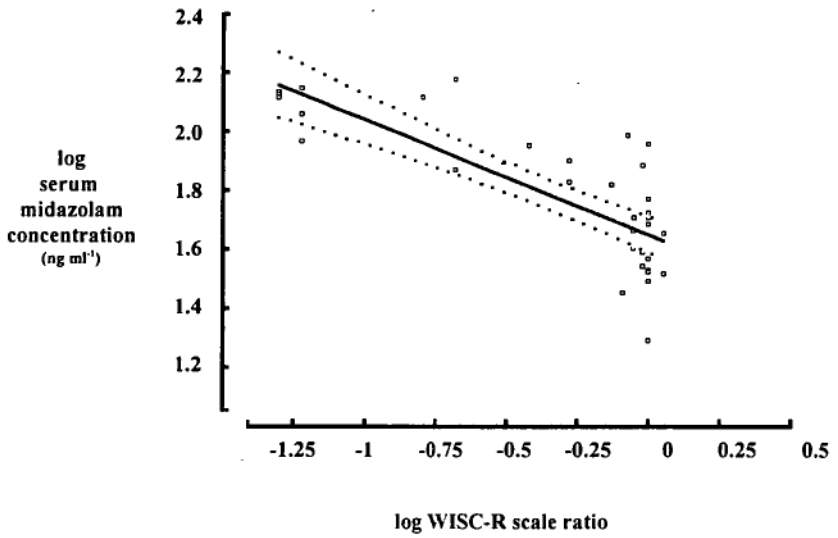


**FIGURE V.6** Pearson product moment correlation testing the association between serum midazolam concentration and WISC-R ratio. (n=10).

The correlation coefficients between PBT and serum midazolam (Figure **V.5**), thiopentone and blood propofol concentrations were 0.67, 0.38 and 0.37 respectively. WISC-R testing and serum drug concentrations showed correlation coefficients for midazolam (Figure **V.6**), propofol and thiopentone of 0.78, 0.63 and 0.52 respectively.

Mood score, incidence of sleep and coma score analysis showed no significant differences between the three drug groups, however memory recall after anaesthesia was significantly better than after natural, unmedicated sleep, although the performance error rates in all groups were small (Table **V.8**). The mean number of

errors in preoperative overnight memory recall for all three groups of children was 2.0(1.6)[1-6], that of postoperative errors was 1.2(0.6)[1-4]. Thiopentone group showed significant less number of recall errors postoperatively ($p$=0.02). In the propofol and midazolam groups, there was no statistical significant difference in the number of preoperative and postoperative memory recall errors ($p$=0.27 and 0.14 respectively).

**TABLE V.8** Mood, sedation and memory data for the three induction agent groups. *Data are mean (SD)[range].*

| | **Midazolam** (n = 10) | **Propofol** (n = 10) | **Thiopentone** (n = 10) | ***p* value** | **Statistical analysis** |
|---|---|---|---|---|---|
| **Co-operation** | | | | | |
| refused | 1 | 0 | 0 | | Chi-square |
| willing | 9 | 10 | 10 | 0.36 | analysis |
| **Sleep assessment** | | | | | |
| aleep | 4 | 3 | 2 | | Chi-square |
| awake | 6 | 7 | 8 | 0.71 | analysis |
| **Mood score** | | | | | |
| 1-3 = happy | 7 | 9 | 8 | | Chi-square |
| 4, 5= unhappy | 3 | 1 | 2 | 0.61 | analysis |
| **Postoperative Coma Score** | | | | | |
| Awake | 5.9(1.2)[4-8] | 6.1(1.3)[4-8] | 6.2(1.9)[3-9] | 0.9 | |
| | 7.4(1.2)[5-9] | 8.1(1.2)[6-9] | 6.9(2.4)[3-9] | 0.42 | |
| 120 min | 8.6(1.0)[6-9] | 8.5(1.1)[6-9] | 9.0(0.0)[9-9] | 0.33 | Kruskal-Wallis |
| 180 min | 9.0(0.0)[9-9] | 8.9(0.3)[8-9] | 9.0(0.0)[9-9] | 0.37 | statistic |
| 240 min | 8.8(0.6)[7-9] | 9.0(0.0)[9-9] | 9.0(0.0)[9-9] | 0.37 | |
| **No. of recall errors overnight** | 2.2(2.0)[1-6] | 1.4(0.7)[1-3] | 2.3(1.8)[1-6] | 0.43 | Kruskal-Wallis statistic |
| **No. of recall errors post-operatively** | 1.2(0.4)[1-2] | 1.3(1.0)[1-4] | 1.1(0.3)[1-2] | 0.80 | Kruskal-Wallis statistic |

# DISCUSSION

The time taken for the child to identify himself was independent of the duration of anaesthesia and predominantly influenced by the induction agent administered, although identification after thiopentone administration was more closely associated with anaesthetic duration than midazolam or propofol. Children awoke more quickly after propofol compared to thiopentone and midazolam however this only reached statistical significance when self identification time was compared between the three groups and not the time of eye opening ($p$=0.05). This illustrates the greater sensitivity of cognitive awareness compared to the more simple physical tests of awakening which presumably require greater patient numbers to demonstrate significance and prevent a type II statistical error. Furthermore, time to eye opening is not related to time of attaining hospital discharge criteria in children following anaesthesia with sevoflurane (Sarner et al, 1995).

Psychomotor performance on awakening was worst in the midazolam group but 1 hour later there was no statistical difference between the groups, and by 4 hours all groups were virtually identical in performance with both tests. Psychomotor improvement paralleled drug redistribution and metabolism but some children were able to perform at unmedicated levels after 1 hour, despite significant induction agent blood levels. The narrower range of awakening drug concentrations in patients induced with midazolam may be associated with greater predictability of recovery, whereas like other workers, this study demonstrated that the awakening blood concentrations of thiopentone and propofol varied widely (Kay et al, 1985). The more

gradual decline of midazolam levels produces more somnolent patients in the early postoperative phase, which under some circumstances may be advantageous. All patients could be discharged 3 hours after awakening having achieved 90% of their unmedicated psychomotor performance, confirming the work of Runcie and colleagues (Runcie et al, 1993).

The association between serum midazolam levels and PBTR and WISC-R ratio was stronger than both propofol and thiopentone in the postoperative period, inferring a closer relationship between blood levels and cerebral effect and therefore a more predictable pattern of postoperative awakening in children induced with midazolam. Coma score and mood assessment lacked both specificity and sensitivity in recovery assessment and were not helpful in differentiating between the induction agents. This was disappointing as previous work discussed in *Chapter IV* had shown that children receiving midazolam and flumazenil appeared calmer and more compliant in accord with the anxiolytic properties of the drug and serum levels (Geller et al, 1988).

Despite the specific effect of benzodiazepines on recall and recognition components of memory which rely on personal experiences within specific contexts (Ghoneim and Mewaldt, 1990), memory recall of a picture card viewed 2 hours after oral administration of midazolam and anaesthesia, was better than memory recall after unmedicated, natural sleep. This finding is probably not clinically meaningful as the sample groups were small, the error rate in one child could have a disproportionate influence on the group as a whole and like Twersky and colleagues we found a higher

number of false positive recall responses in children less than six years (Twersky et al, 1993). It is inappropriate to covary emeory scores for age and false positive 'guess' responses because of the small uncontrolled (no placebo) sample groups, the descriptive nature of this part of the study and the lack of age based norms. Furthermore the serum midazolam levels were not in the adult amnesic range 2 hours after oral administration and the children may have experienced heightened awareness in the unfamiliar operating theatre environment (File and Lister, 1982).

This study has demonstrated the suitability of the post box toy ratio for measurement of psychomotor performance in children because of its simplicity and ease of use in the clinical environment, although it suffers the limitations of familiarity as do other tests of this type. Rapid recovery of cognitive function in the recovery room is best achieved with propofol but 4 hours after awakening all children were equally suitable for discharge irrespective of the induction agent administered.

# *CHAPTER VI*

# DISCUSSION

# &

# CONCLUSIONS

Midazolam possesses many of the properties of an ideal anaesthetic agent but introduction of the drug into paediatric anaesthetic practice requires an evaluation of its suitability in children. The objectives of this thesis were

- to investigate the effects of midazolam on psychomotor function and oxygen desaturation when administered as a premedicant in children
- to describe the pharmacokinetic disposition of midazolam, flumazenil and propofol in children
- to investigate the induction pharmacodynamics and psychomotor recovery following administration of midazolam in elective paediatric anaesthetic practice, and compare these data with midazolam antagonised with flumazenil, propofol and thiopentone.

## Premedication

The incidence of oxygen desaturation episodes during the 2 hours immediately before induction of anaesthesia, following administration of midazolam 0.5 mg $kg^{-1}$ orally, was low and of minimal clinical significance (Jones et al, 1993b). Neither the time spent desaturated, the degree of desaturation or the frequency of desaturation episodes was significantly different from normal, unmedicated sleep. Furthermore, the incidence of desaturation after midazolam was not significantly different to that found after administration of another commonly prescribed premedicant, pethidine. The possibility exits for concluding that midazolam has no effect on oxygen saturation, when in reality it does. In drawing conclusions, the small sample size and data

variability described in this thesis risk Type II error and should be born in mind when interpreting data where no difference was demonstarted with a beta error of < 0.05. However, computerised aquisition of large volumes of data may result in unmanageable data sets. For example, with respect to the oxygen saturation data, a sample size of 1100 per group would be required to give a probability of 0.8 of rejecting the null hypothesis of equal means if the alternative holds (Dallal, 1990).

Orally administered midazolam in this dose was associated with no dangerous effects in the small samples investigated and is effective without the unwanted effects associated with higher dosage that have been reported by other workers (McMillan et al, 1992). The peak desaturation episode incidence did not coincide with expected peak serum concentrations of midazolam suggesting that any depressant effect on ventilation was independent of serum levels. This is the only study reported to date which has attempted to filter out artefactual desaturation data associated with probe movement and calls into question the findings of other studies which have drawn conclusions directly from raw data (de Santos et al, 1991, Roelofse and de-V-Joubert, 1990).

Oral midazolam resulted in peak serum levels 60 minutes after administration however other workers have described peak sedation at 30 minutes following the same oral dose of midazolam (Weldon et al, 1992) and the maximum decline in psychomotor performance also occurred at 30 minutes in this study. The improved psychomotor performance at 60 minutes may be due to a "test-retest' practice effect, despite increasing serum concentrations of midazolam. An alternative explanation

may be that the rate of increase of midazolam concentration rather than its absolute value, has a maximal agonist effect on the benzodiazepine receptor-modulated chloride channels, resulting in a coincident maximal decline in psychomotor performance. The benzodiazepine/GABA receptor complex requires a minimum amount of GABA to be present for a benzodiazepine to be effective (Thompson et al, 1988), and the basal state of the receptors in these children is unknown. The incidence of sleep was uniformly distributed throughout the two hour assessment period and was unrelated to serum drug levels. The majority of children presented to the operating room awake, with a quiet and cooperative mood, and on specific questioning, 66% of the children denied feeling frightened. The measured serum midazolam levels at 2 hr remained in the anxiolytic range described for adults (Dundee et al, 1984) and the assessed mood of the children described in this thesis, reinforces the superiority of the drug to placebo (Parnis et al, 1992). Preinduction serum midazolam concentrations were below those associated with anterograde amnesia, and retrograde amnesia was not demonstrated.

## Induction

Midazolam is the only hypnotic induction agent that has a specific antagonist. The disposition of midazolam in children has been studied by a number of workers (Salonen et al, 1987; Payne et al, 1989; Rey et al, 1991) but the contemporaneous disposition of flumazenil in children has not previously been reported. In contrast to other workers (Tolia et al, 1991; Salonen et al, 1987; Payne et al, 1989), clearance of midazolam from the plasma was best described by a tri-exponential function because

of an increased sampling rate during the early redistribution phase and better definition of the elimination phase. Differences in pharmacokinetic data can be explained by the different fat distribution in Chinese children, the differing anaesthetic techniques and the age related variation in metabolism of benzodiazepines (Greenblatt et al, 1984).

Flumazenil pharmacokinetic data were suitably interpreted by non-compartmental analysis because of the combined bolus and infusion administration regimen used to reverse midazolam. The steady state volume of distribution of flumazenil was about half that reported in adults, clearance values were similar and the terminal half-life was about 35 minutes (Klotz et al, 1984). The small volume of distribution and high clearance of flumazenil resulted in a terminal half-life which was one third that of midazolam. These findings provide some insight into the resedation controversy (Ashton, 1985). Resedation was presumably due to the residual mild sedative effects of midazolam being relatively unopposed by flumazenil. The decline in serum flumazenil concentration was paralleled by a concomitant decline in serum midazolam concentration, resulting in the children being easily aroused from sleep.

The clinical efficacy of flumazenil in rapidly antagonising the sedative effects of midazolam induction in children had not been previously reported. The flumazenil treated children were significantly more orientated, co-operative and demonstrated better comprehension when compared to the placebo group. The children in this study were both premedicated and induced with midazolam, and all but one child awoke

within 21 minutes of the termination of anaesthesia. This compares very favourably with the children in the propofol pharmacokinetic study. The benzodiazepine receptor is a positive modulatory subunit of the gamma-amino-butyric acid (GABA) receptor complex (Amrein and Hetzel, 1990). Flumazenil antagonism of benzodiazepine effects depends in part, on the number of receptors occupied at the time of flumazenil administration and also the amount of GABA present at the GABA receptor (Haefely, 1988). Neither these receptor models nor the reciprocal dose dependent effects of midazolam and flumazenil fully explain the variable dose response to midazolam and the variable dose requirement of flumazenil in relation to body weight in children, and this requires further investigation. Recommendations to use an antagonist with a shorter half-life than a parent compound must be made with reservation, especially when the response to the agents is variable.

Propofol is the latest intravenous induction agent to be introduced into clinical practice and its reported rapid postoperative recovery prompted a comparison with a midazolam induction technique antagonised by flumazenil. However, pharmacokinetic data for propofol were incomplete in children and a meaningful comparison required that propofol first be investigated in a similar study population. The blood clearance of propofol was best described by a tri-exponential function. The large total body clearance and relatively small volume of distribution for a highly lipophilic drug resulted in a relatively fast elimination of propofol from the blood in children which was constrained by the slow return of propofol to the blood from the deep compartment. Differences from other propofol pharmacokinetic studies may be attributable to the different anaesthetic techniques employed, different types of

surgical procedure, the different sample collection times and the small patient populations examined (Valtonen et al, 1989; Saint-Maurice et al, 1989). The higher clearance and smaller steady state volume of distribution results in a $T_{½}^{\gamma}$ which was half, and a $T_{½}^{\beta}$ which was 66% that of propofol. Children in the pharmacokinetic study of propofol awoke within 30 minutes of the termination of anaesthesia but unfortunately these data were confounded by the long half-life of the premedicant trimeprazine. Furthermore, compartmental kinetic analysis, although standard practice, has limited direct clinical application because of the between subject variability for many of the parameters.

A number of authors have compared the induction characteristics of propofol and thiopentone but there have been no comparative studies with midazolam in children (Runcie et al, 1993; Mirakhur, 1988). Propofol caused the greatest and most protracted fall in blood pressure after an induction dose of 2.5 mg $kg^{-1}$ administered over 30 seconds into an antecubital vein. Thiopentone 4.0 mg $kg^{-1}$ caused the least haemodynamic perturbation and midazolam 0.5 mg $kg^{-1}$ was associated with a maximum decrease of 20% below baseline mean arterial pressure. Exclusion criteria for this study were designed to provide a homogeneous patient sample who would permit comparison of the induction agent effect on haemodynamics, independent of patient pathology. The relatively slow sampling rate of the Cardiocap could not display the acute haemodynamic changes seen with the noninvasive continuous monitoring of the Finapres during the early induction phase. Although the Finapres demonstrates a wide variability in discrete values, it accurately reflects changes in pressure (Jones et al, 1992b). Thiopentone provided smooth induction conditions in

nearly all children, with an occasional brief period of apnoea being the only side effect. Propofol induction was associated with pain and semi-purposeful arm movement in 50% of patients, while the end point of midazolam induction was less distinct than with the other two agents.

## Recovery

Recovery after anaesthesia is multidimensional (Zuurmond et al, 1989). Of particular interest in ambulatory care in children is the immediate recovery of protective reflexes following surgery and the later return to "street fitness" prior to discharge from the ward. Sophisticated tests of psychomotor recovery are not practical in children and a simple, practical, repeatable assessment of suitability for discharge would be useful. Work in this thesis showed the post box toy ratio to be equally as sensitive and specific as the Wechsler intelligence scale ratio-R (matched for race), for the assessment of psychomotor recovery, however the latter assessment was more difficult to perform, particularly in younger children. The residual influence of anaesthesia diminished discrimination between the physical and cognitive components of each test, resulting in an improvement in their correlation. Psychomotor performance on awakening was worst in patients induced with midazolam but not antagonised by flumazenil. At one hour postoperatively there was no statistical difference in psychomotor performance between midazolam, propofol and thiopentone induced children and at 4 hours all children were equally suitable for discharge irrespective of the induction agent administered. Awakening was fastest in

the midazolam children given flumazenil and was equal in quality to the propofol group.

This thesis confirms the hypothesis that midazolam is a suitable and effective premedicant in elective paediatric anaesthetic practice but its acceptance could be improved if the taste of the drug was more efficiently disguised. As an intravenous induction agent, the hypnotic onset of action of midazolam reaches a peak 2-3 minutes after administration in children, unlike propofol and thiopentone which produce hypnosis in one arm-brain circulation time. This relatively slow induction time and indefinite end point limit the application of midazolam as the sole-agent for induction of anaesthesia, however recent work in adults has demonstrated the synergistic effects of pretreatment with midazolam prior to induction with another agent (Tverskoy et al, 1988; Short and Chui, 1991). The place of coinduction and induction agent synergism in children, requires further investigation. There are inherent risks in using an antagonist with a shorter half-life than the parent compound and therefore patient observation must be continued for an appropriate duration.

# CONCLUSIONS

1. Midazolam, in a dosage of 0.5 mg $kg^{-1}$, is a satisfactory oral premedicant in children less than 30 kg.
2. Oral administration of 0.5 mg $kg^{-1}$ midazolam in the children studied did not result in increased incidence of episodic arterial oxygen desaturation above that accompanying normal, unmedicated sleep.
3. Oral administration of 0.5 mg $kg^{-1}$ midazolam as a premedicant in children is not associated with a delay in postoperative recovery or discharge from the ward.
4. Midazolam has a faster clearance and shorter elimination half-life than propofol in healthy Chinese children.
5. Mild resedation occurs following antagonism of an induction dose of midazolam with flumazenil in healthy children because the terminal half-life of flumazenil is one third that of midazolam.
6. In recommended clinical doses, propofol induction is associated with hypotension which is more severe in degree and duration compared to midazolam and thiopentone, in healthy children undergoing minor surgery.
7. Midazolam antagonised with flumazenil produced a rapid immediate recovery of consciousness, equivalent in quality to propofol.
8. Two hours postoperatively there was no significant difference in psychomotor performance, irrespective of which induction agent was administered and all patients were assessed as "street-fit" for discharge from the ward at four hours.

9. The post box toy ratio was not only as effective as the Wechsler intelligence scale ratio in assessing postoperative psychomotor function, but was more easily performed in children.

10. Accurate interpretation of pulse oximetry profiles require prior exclusion of artefactual data.

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# APPENDICES

# APPENDIX A

## Presentations & Publications

## Presentations:

### Reversal of the hypnotic effect of midazolam in children.

8th Asian-Australasian Congress of Anaesthesiologists

Seoul, Korea, 23-28 September, 1990.

### Continuous pulse oximetry data acquisition.

6th Congress of the Western Pacific Association of Critical Care Medicine

Bangkok, Thailand, 1-4 December, 1991.

### The upgraded 'FINAPRES' continuous non-invasive blood pressure monitor.

6th Congress of the Western Pacific Association of Critical Care Medicine

Bangkok, Thailand, 1-4 December, 1991.

### Pharmacokinetics of flumazenil and midazolam in paediatric patients.

5th World Congress of Clinical Pharmacology and Therapeutics

Yokohama, Japan, 26-31 July, 1992.

### An HPLC assay for flumazenil, midazolam and their in the plasma and urine of paediatric patients.

British Pharmacological Society Meeting

Aberdeen, Scotland, April, 1993.

## Publications:

1. **Jones R.D.M.**, Chan K., Andrew L.J. (**1990**). The pharmacokinetics of propofol (Diprivan) in children. *British journal of anaesthesia* **65**: 661-667.
2. **Jones R.D.M.**, Andrew L.J., Lawson A.D., Gunawardene W.M.S., Bacon-Shone J. (**1991**). Antagonism of the hypnotic effect of midazolam in children: A randomised, double blind study of placebo and flumazenil administered after midazolam-induced anaesthesia. *British journal of anaesthesia* **66**: 660-666.
3. **Jones R.D.M.**, Brown A.G., Roulson C.J., Smith I.D., Chan S.C. (**1992**). A clinical evaluation of the upgraded "Finapres" 2300e continuous non-invasive blood pressure monitor. *Anaesthesia* **47**: 701-705.
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5. **Jones R.D.M.**, Chan K., Roulson C.J., Brown A.G., Smith I.D., Mya G.H. (**1993**). The pharmacokinetics of flumazenil and midazolam in paediatric patients. *British journal of anaesthesia* **70**: 286-292.
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7. **Jones R.D.M.**, Visram A.R., Kornberg J.P., Irwin M.G., Roulson C.R., Gunawardene W.M.S. (**1994**). The effect of premedication on oxygen saturation during the post-premedication period in 20 Chinese children undergoing elective surgery. *European journal of anaesthesiology* **11**: 307-311.

8. Chan K. and **Jones R.D.M.** (**1993**). Simultaneous determination of flumazenil, midazolam and metabolites in human biological fluids by liquid chromatography. *Journal of chromatography* **619**: 153-160.

9. Visram A.R., **Jones R.D.M.**, Kornberg J.P., Irwin M.G. (**1994**). Use of oximeters to investigate a method of movement artefact rejection using photoplethysmographic signals. *British journal of anaesthesia* **72**: 388-392.

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11. **Jones R.D.M.**, Chan M.M.Y., Bacon-Shone J., Mya G.H., Visram A.R., Irwin M.G. (**1994**). A comparison of three induction agents in paediatric anaesthesia - cardiovascular effects and recovery. *Anaesthesia and intensive care* **22**: 545-555.

# APPENDIX B

## Ethics committee approval & written consent

UNIVERSITY OF HONG KONG
FACULTY OF MEDICINE
7, SASSOON ROAD, HONG KONG
TELEPHONE 8199111
TELEX: 71919 CEREB HX
Fax: 852-8559742

January 18, 1991

Dr A.D. Lawson,
Department of Anaesthesiology

Dear Dr Lawson,

EC 375-90

Thank you for your letter of 7 January, 1991.

I write to inform you that the Committee, after consideration, has approved your captioned research protocol entitled "Pulse Oximetry and Premedication in Children".

Yours sincerely,

Y.C. Lee
Secretary
Ethics Committee

c.c. Dr R.D.M. Jones, Dept of Anaesthesiology
Dr S. Gunawardene, Dept of Anaesthesiology

YCL/yl
MM1/ETHICSCIR/6

UNIVERSITY OF HONG KONG
FACULTY OF MEDICINE
7, SASSOON ROAD, HONG KONG
TELEPHONE 5-8199111
TELEX: 71919 CEREB HX
FAX: 852-5-8559742

July 11, 1989

Dr. RDM Jones
Department of Anaesthesiology

Dear Dr. Jones,

Ethics Committee - EC 321-89

In reply to your letter of June 15, 1989, I write to inform you that your captioned research protocol entitled "The Pharmacokinetics of Propofol (Diprivan) in Chinese Children" has the approval of the Committee.

Yours sincerely,

Dora Yue
Secretary
Ethics Committee

DY/ll

cc: Dr. LJ Andrew
Dr. K Chan

UNIVERSITY OF HONG KONG
FACULTY OF MEDICINE
7, SASSOON ROAD, HONG KONG
TELEPHONE 8199111
TELEX: 71919 CEREB HX
Fax: 852-8559742

January 28, 1991

Dr RDM Jones
Department of Anaesthesiology

Dear Dr Jones,

EC 372-90

Thank you for your letter of January 15, 1991.

I write to inform you that the Committee, after consideration, has approved your captioned research protocol entitled "The pharmacokinetics of flumazenil and midazolam in children".

Yours sincerely,

Y.C. LEE
Secretary
Ethics Committee

YCL/wt
WT/ethics/4

UNIVERSITY OF HONG KONG
FACULTY OF MEDICINE
7, SASSOON ROAD, HONG KONG
TELEPHONE 5-8199111
TELEX: 71919 CERES HX

November 21, 1989

Dr. R.D.M. Jones,
Department of Anaesthesiology.

Dear Dr. Jones,

EC 330-89

Thank you for your letter dated September 26, 1989.

I write to inform you that the Ethics Committee, having considered your aforementioned reply, has approved your research protocol entitled "Reversal of Midazolam with Anexate in Paediatric Patients".

Yours sincerely,

Dora Yue
Secretary
Ethics Committee

DY/ac
MM1/ETHICSCIR/8

香港大學 THE UNIVERSITY OF HONG KONG
醫學院 FACULTY OF MEDICINE
院長：馬錦可教授 Dean: Professor H.K. Ma O.B.E., M.B., B.S., F.R.C.O.G., J.P.
副院長：梁憲孫 Associate Dean: Dr. Raymond H.S. Liang M.B., B.S., M.D., F.R.C.P. (E.)
副院長：王登川 Associate Dean: Dr. Y.C. Wong B.Sc., M.Sc., Ph.D., C.Biol., M.I.B.

July 8, 1992

Dr. R.D.M. Jones,
Department of Anaesthesiology

Dear Dr. Jones,

EC 433-92

Thank you for your reply dated May 20, 1992.

I write to inform you that the Committee, after consideration, has approved your aforementioned research protocol entitled " An investigation of the postoperative sedative effects of three anaesthetic induction agents in children ".

Yours sincerely,

(Mrs.) Vivian Lee
Secretary
Ethics Committee

VL/cl
YC/ethics3/2

# 大口環兒童骨科醫院"氧氣分析"病人同意書
# INFORMED CONSENT FOR OXIMETRY PATIENTS AT DCH

我是鍾斯德醫生．　香港大學麻醉科高級講師．
My name is Dr. Jones.  I am a Senior Lecturer in Anaesthesia at the Hong Kong University.

我們將對閣下的小孩在手術前及手術後測量血的含氧量對睡眠的影響.
We are measuring the effect of sleep on the level of oxygen in your child's blood before and after the operation.  The oxygen level is measured by shining a light through the skin of your child's toe.  It is painless and will not hurt your child.  This machine is one which is routinely attached in the operating room.

## 同意書
## CONSENT

本人　　同意我的小孩　　參與
I,.....hereby consent for my child .....to be placed in the study described above which I fully understand.  I understand that I may choose to my child from the study at any time without affecting treatment.

上述研究，並對其過程完全明白．
在以上過程中我亦可隨時取消以上研究而下會影響其治療．

簽名　　家長或監護人簽署
SIGNED ..... Parent Signature

證人　　護士
Witnessed.....Nurse

日期
Date  /  / 1991

# 太口瑪麗皇后產科醫院"包皮環割術"病人同意書
# INFORMED CONSENT FOR CIRCUMCISION PATIENTS AT DCH

我是鍾斯醫生， 香港大學麻醉科高級講師。
My name is Dr. Jones. I am a Senior Lecturer in Anaesthesia at the Hong Kong University.
我們將對閣下的小孩做量一量該導管24小時，量度抽血共7毫升，
We would like to measure by repeated blood sampling through a venous cannula which is left
以測定其中一種麻醉藥的清除率，其副作用和發炎的機會是很少的，
in place for 24 hours, the rate of clearance from the blood of one of the drugs which is
used to anaesthetise your child. A total of 7 mls of blood only will be taken. There is
only minimal chance of side effects or infection occuring.
所有之麻醉程序，會全部經由本人執行及精密儀器監察以
I shall be present at all the anaesthetics administered. Your child will be monitored with
確保閣下小孩的安全。
sophisticated monitoring equipment throughout the operation to ensure that all precautions
have been carried out.

## 同意書
## CONSENT

本人 同意我的小孩 參與
I,.....hereby consent for my child .....to be placed in
上述檢查， 本人已明白其過程， 我亦明白這項研究
the trial described above and fully understand the procedure. I also understand that
程序會照其標準的過程一樣小心進行，在以上過程中我亦可隨時要求
this trial will be conducted with all the precaution and safety that would be applied
以上檢查而不會影響其治療。
to any other procedure, and I may choose to withdraw my child from the trial at any time,
without affecting the usual treatment.

家長或監護人簽署

簽名日期 太口瑪麗皇后產科醫院
SIGNED THIS .....DAY OF 198 AT DUCHESS OF KENT HOSPITAL Parent Signature.....

護士 日期
Nurse:..... Date.....

# 大口環兒童骨科醫院"清除麻醉藥"研究同意書
# INFORMED CONSENT FOR PATIENTS UNDERGOING DRUG CLEARANCE RESEARCH AT DKH

我是鍾斯醫生． 香港大學麻醉科高級講師．
My name is Dr. Jones. I am a Senior Lecturer in Anaesthesia at the Hong Kong University.
我們將對閣下的小孩放置一靜脈導管4小時，重複抽血共10毫升，
We would like to measure by repeated blood sampling through a venous cannula which is left
我現進行一項研究．其副作用和發炎的機會是很少的．
in place for 4 hours, the rate of clearance from the blood of two of the drugs which are
used to anaesthetise your child. A total of 10 mls of blood only will be taken. There is
only mininal chance of side effects or infection occuring.
所有之麻醉程序，會全部經由本人執行及精密儀器輔助監察以
I shall be present at all the anaesthetics administered. Your child will be monitored with
確保閣下小孩的安全．
sophisticated monitoring equipment throughout the operation to ensure that all precautions
have been carried out.

同意書
CONSENT

本人 同意我的小孩 參與
I.....horeby consent for my child .....to be placed in
上述研究， 亦完全明白其過程， 我亦明白這項研究
the trial described above and fully understand the procedure. I also understand that
程序會與其他的過程一樣小心進行．在以上研究中我亦可隨時取消
this trial will be conducted with all the precaution and safety that would be applied
以上檢查而不會影響其治療．
to any other procedure, and I may choose to withdraw my child from the trial at any time,
without affecting the usual treatment.

家長或監護人簽署
簽名日期 大口環兒童骨科醫院
SIGNED THIS .....DAY OF 199 AT DUCHESS OF KENT HOSPITAL Parent Signature.....

護士 日期
Nurse:..... Date.....

# 大口環兒童骨科醫院"包皮環割術"病人同意書
# INFORMED CONSENT FOR CIRCUMCISION PATIENTS AT DCH

我是瓊斯醫生． 香港大學麻醉科高級講師．
My name is Dr. Jones. I am a Senior Lecturer in Anaesthesia at the Hong Kong University.
我們將量度一種用於閣下兒子麻醉後的甦醒藥之效果．
We would like to measure the effectiveness of a new drug used to wake children up after
在手術接近完畢時，閣下兒子將接受注射該種新藥或生理鹽水，
anaesthesia. At the end of the operation, your child will be given either saline
及會以玩具遊戲來測定知覺．
intravenously or the new drug, and the time taken to complete a simple game measured.
所有之麻醉程序，會全部經由本人執行及精密儀器輔助監管以
I shall be present at all the anaesthetics administered. Your child will be monitored with
確保閣下兒子之安全．
sophisticated monitoring equipment throughout the operation to ensure that all precautions
have been carried out.

## 同意書
## CONSENT

本人 同意我的小孩 參與
I,.....hereby consent for my child .....to be placed in
上述試驗研究，亦完全明白其過程， 我亦明白這項研究
the trial described above and fully understand the procedure. I also understand that
程序會與其他的 程序一樣小心進行. 在以上過程中我亦可隨時取
this trial will be conducted with all the precaution and safety that would be applied
消以上檢查而不會影響其治療．
to any other procedure, and I may choose to withdraw my child from the trial at any time,
without affecting the usual treatment.

家長或監護人簽署
簽名日期 大口環兒童骨科醫院
SIGNED THIS .....DAY OF 198 AT DUCHESS OF KENT HOSPITAL Parent Signature.....

護士 日期
Nurse:..... Date.....

# 大口環兒童骨科醫院"包皮環割術"病人同意書
# INFORMED CONSENT FOR CIRCUMCISION PATIENTS AT DCH

我是鍾斯醫生． 香港大學麻醉科高級講師．
My name is Dr. Jones. I am a Senior Lecturer in Anaesthesia at the Hong Kong University.
我們將對閣下的小孩放置一靜脈導管4小時，重複抽血共10毫升，
We would liko to measure by repeated blood sampling through a venous cannula which is left
以測量血液裏麻醉藥的份量及使小孩安靜的水平． 其副作用和發炎的
in place for 4 hours, the amount of anaesthetic drug in the blood and the level of
機會是很少的．
sedation in your child. A total of 10 mls of blood only will be taken. There is only
mininal chance of side effects or infection occuring.
所有之麻醉程序，會全部經由本人執行及精密儀器輔助監察以
I shall be present at all the anaesthetics administered. Your child will be monitored with
確保閣下小孩的安全．
sophisticated monitoring equipment throughout the operation to ensure that all precautions
have been carried out.

同意書
CONSENT

本人 同意我的小孩 參與
I,.....hereby consent for my child .....to be placed in
上述檢查． 亦完全明白其過程． 我亦明白這項研究
the trial described above and fully understand the procedure. I also understand that
程序會與其他的過程一樣小心進行．在以上過程中我亦可隨時取消
this trial will be conducted with all the precaution and safety that would be applied
以上檢查而不會影響其治療．
to any other procedure, and I may choose to withdraw my child from the trial at any time,
without affecting the usual treatment.

家長或監護人簽署
簽名日期 大口環兒童骨科醫院
SIGNED THIS .....DAY OF 198 AT DUCHESS OF KENT HOSPITAL Parent Signature.....

護士 日期
Nurse:..... Date.....

# APPENDIX C

## Psychometric data

| Patient number | Body weight (kg) | Age (yr) | Duration of anaesthesia (min) | Time to eye opening after flumazenil (sec) | Time to self identification after flumazenil (sec) | Dose of flumazenil administered (mg) | Mood on awakening (**) |
|---|---|---|---|---|---|---|---|
| **1** | 18.7 | 6 | 31 | 240 | 360 | 0.62 | D |
| **2** | 16.0 | 5 | 33 | 120 | 240 | 0.46 | D |
| **3** | 20.0 | 6 | 39 | 120 | 240 | 0.60 | D |
| **4** | 20.0 | 6 | 35 | 240 | 300 | 0.60 | C |
| **5** | 32.0 | 8.5 | 43 | 240 | 300 | 0.82 | B |
| **6** | 38.5 | 9 | 40 | 180 | 180 | 0.75 | C |
| **7** | 14.0 | 5 | 31 | 180 | 420 | 0.56 | B |
| **8** | 24.0 | 7 | 58 | 300 | 360 | 0.56 | D |
| **9** | 20.0 | 8 | 31 | 150 | 270 | 0.53 | C |
| **10** | 17.0 | 5 | 31 | 180 | 180 | 0.35 | D |
| **11** | 25.0 | 7.5 | 29 | 60 | 120 | 0.42 | B |
| **12** | 19.0 | 5 | 48 | 240 | 300 | 0.58 | D |
| **mean** | 22.0 | 6.5 | 37.4 | 187.5 | 272.5 | 0.60 | |
| **SD** | 6.7 | 1.4 | 8.4 | 65.0 | 82.6 | 0.10 | |
| **min** | 14.0 | 5.0 | 29.0 | 60 | 120 | 0.40 | |
| **max** | 38.5 | 9.0 | 58.0 | 300 | 420 | 0.80 | |

**APPENDIX C 1: Anaesthetic and awakening data from Jones et al (1993).**

(**) **A:** laughing, euphoric **B:** happy, contented, playful **C:** calm, drowsy, asleep **D:** crying but calmed, irritable **E:** severe pain, screaming, inconsolable

| Patient number | Age (yr) | Weight (kg) | Premed effect (*) | Loss of eye-lash reflex (sec) | Anaes. duration (min) | Time to eye open (min) | Time to giving name (min) | Dose of drug (ml) | Oserved effect (**) | Tolerance of injection (***) | Coma score at 5 min | Coma score at 10 min |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 7.5 | 25.0 | 2 | 85 | 37 | 4 | 6 | 6.3 | 1 | 1 | 4 | 8 |
| **4** | 5.5 | 18.0 | 2 | 14 | 30 | 6 | 30 | 6.8 | 1 | 1 | 4 | 8 |
| **7** | 3.5 | 17.0 | 2 | 79 | 41 | 15 | 52 | 7.2 | 3 | 2 | 4 | 4 |
| **8** | 8.5 | 22.0 | 2 | 84 | 80 | 9 | 11 | 10.0 | 2 | 2 | 3 | 7 |
| **9** | 9.0 | 25.0 | 2 | 33 | 31 | 8 | 12 | 10.0 | 2 | 1 | 5 | 8 |
| **10** | 6.0 | 15.1 | 2 | 49 | 23 | 14 | 35 | 10.0 | 3 | 3 | 4 | 4 |
| **14** | 4.5 | 17.3 | 2 | 123 | 39 | 6 | 6 | 5.0 | 1 | 1 | 7 | 8 |
| **16** | 11.5 | 28.5 | 2 | 72 | 47 | 2 | 6 | 7.5 | 1 | 1 | 7 | 9 |
| **18** | 11.0 | 30.5 | 2 | 18 | 38 | 5 | 8 | 7.0 | 1 | 1 | 6 | 9 |
| **20** | 11.0 | 27.0 | 2 | 106 | 32 | 5 | 9 | 8.0 | 1 | 1 | 9 | 9 |
| **23** | 4.5 | 17.5 | 2 | 90 | 17 | 9 | 11 | 10.0 | 2 | 1 | 3 | 9 |
| **24** | 10.0 | 25.5 | 2 | 32 | 25 | 7 | 9 | 9.0 | 2 | 2 | 2 | 8 |
| **25** | 9.0 | 25.0 | 2 | 83 | 63 | 15 | 18 | 10.0 | 3 | 1 | 4 | 4 |
| **26** | 4.5 | 17.8 | 2 | 120 | 24 | 9 | 17 | 10.0 | 2 | 1 | 4 | 9 |
| **29** | 11.0 | 28.0 | 1 | 52 | 33 | 16 | 16 | 10.0 | 3 | 1 | 2 | 9 |
| **31** | 4.5 | 18.5 | 1 | 64 | 43 | 10 | 12 | 10.0 | 2 | 1 | 8 | 9 |
| **33** | 4.0 | 13.5 | 2 | 71 | 25 | 32 | 36 | 10.0 | 4 | 1 | 3 | 3 |
| **34** | 6.5 | 20.0 | 2 | 61 | 28 | 13 | 14 | 10.0 | 3 | 1 | 3 | 5 |
| **38** | 5.0 | 14.3 | 2 | 117 | 32 | 7 | 8 | 6.0 | 2 | 2 | 5 | 9 |
| **39** | 6.0 | 17.8 | 2 | 32 | 31 | 16 | 26 | 10.0 | 3 | 3 | 2 | 9 |

**APPENDIX C 2:** **Patient and anaesthetic data from the flumazenil group in Jones et al (1991).**
**(*) : 1 = agitated and crying, 2 = aware, apparently anxiety free, 3 = drowsy, 4 = asleep, responds to commands**
**(**)(***) : 1 = excellent, 2 = good, 3 = moderate, 4 = poor**
**Coma score refer *Chapter II*, page 21**

| Patient number | Age (yr) | weight (kg) | Premed effect (*) | Loss of eye-lash reflex (sec) | Anaes. duration (min) | Time to eye open (min) | Time to giving name (min) | Dose of drug (ml) | Observed effect (**) | Tolerance of injection (***) | Coma score at 5 min | Coma score at 10 min |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **2** | 3.0 | 17.5 | 2 | 87 | 27 | 31 | 31 | 10 | 4 | 1 | 3 | 3 |
| **3** | 8.0 | 23.0 | 2 | 17 | 25 | 47 | 47 | 10 | 4 | 1 | 1 | 1 |
| **5** | 6.0 | 16.5 | 2 | 52 | 46 | 33 | 39 | 10 | 4 | 1 | 2 | 2 |
| **6** | 7.0 | 23.0 | 2 | 43 | 33 | 23 | 49 | 10 | 4 | 1 | 1 | 1 |
| **11** | 5.8 | 18.-0 | 2 | 20 | 27 | 76 | 77 | 10 | 4 | 1 | 1 | 1 |
| **12** | 5.5 | 19.0 | 2 | 40 | 26 | 28 | 27 | 10 | 4 | 1 | 2 | 2 |
| **13** | 5.5 | 18.5 | 2 | 40 | 25 | 57 | 61 | 10 | 4 | 1 | 2 | 2 |
| **15** | 12.5 | 44.0 | 2 | 21 | 29 | 21 | 22 | 10 | 4 | 1 | 2 | 2 |
| **17** | 3.8 | 17.0 | 2 | 118 | 43 | 25 | 32 | 10 | 4 | 1 | 2 | 2 |
| **19** | 8.0 | 24.5 | 2 | 94 | 69 | 23 | 43 | 10 | 4 | 1 | 0 | 0 |
| **21** | 4.5 | 18.5 | 2 | 24 | 38 | 22 | 31 | 10 | 4 | 1 | 2 | 2 |
| **22** | 11.5 | 30.5 | 2 | 88 | 26 | 32 | 34 | 10 | 4 | 1 | 3 | 3 |
| **27** | 5.6 | 29.0 | 2 | 27 | 35 | 30 | 33 | 10 | 4 | 1 | 1 | 2 |
| **28** | 8.0 | 26.0 | 2 | 110 | 45 | 30 | 30 | 10 | 4 | 1 | 1 | 1 |
| **30** | 6.8 | 19.7 | 4 | 60 | 22 | 47 | 63 | 10 | 4 | 1 | 2 | 2 |
| **32** | 7.0 | 21.5 | 2 | 26 | 19 | 31 | 60 | 10 | 4 | 1 | 1 | 2 |
| **35** | 10.5 | 34.0 | 2 | 72 | 30 | 46 | 54 | 10 | 4 | 1 | 1 | 3 |
| **36** | 5.5 | 15.5 | 2 | 72 | 25 | 38 | 43 | 10 | 4 | 1 | 1 | 1 |
| **37** | 9.0 | 20.5 | 2 | 51 | 28 | 66 | 67 | 10 | 4 | 1 | 4 | 4 |
| **40** | 5.0 | 18.0 | 4 | 20 | 33 | 53 | 59 | 10 | 4 | 1 | 2 | 2 |

**APPENDIX C 3:** **Patient and anaesthetic data in the placebo group from Jones et al (1991).**
**(*) : 1 = agitated and crying, 2 = aware, apparently anxiety free, 3 = drowsy, 4 = asleep, responds to commands**
**(**)(***) : 1 = excellent, 2 = good, 3 = moderate, 4 = poor**
**Coma score refer *Chapter II*, page 21**

| | Coma Scale | | | | | | | | Mood Score | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient number | 2 | 5 | time (min) | 30 | 60 | 120 | 240 | 18 hr | 2 | 5 | 10 | time (min) | 60 | 120 | 240 | |
| 1 | 4 | 8 | 8 | 8 | 9 | 9 | 9 | 9 | 1 | 2 | 2 | 2 | 3 | 3 | 3 | 3 |
| 4 | 4 | 4 | 8 | 9 | 9 | 9 | 9 | 9 | 0 | 1 | 2 | 2 | 1 | 1 | 3 | 3 |
| 7 | 2 | 4 | 4 | 5 | 9 | 9 | 9 | 9 | 0 | 2 | 1 | 1 | 3 | 3 | 3 | 3 |
| 8 | 2 | 3 | 7 | 9 | 9 | 8 | 9 | 9 | 1 | 2 | 2 | 3 | 3 | 1 | 3 | 3 |
| 9 | 2 | 5 | 8 | 8 | 8 | 9 | 9 | 9 | 1 | 1 | 2 | 1 | 1 | 3 | 3 | 3 |
| 10 | 1 | 4 | 4 | 5 | 5 | 8 | 9 | 9 | 0 | 1 | 1 | 1 | 1 | 1 | 3 | 3 |
| 14 | 1 | 7 | 8 | 8 | 8 | 9 | 9 | 9 | 0 | 2 | 3 | 3 | 3 | 3 | 3 | 3 |
| 16 | 5 | 7 | 8 | 9 | 9 | 9 | 9 | 9 | 1 | 2 | 2 | 3 | 3 | 3 | 3 | 3 |
| 18 | 1 | 6 | 6 | 8 | 7 | 9 | 9 | 9 | 0 | 2 | 2 | 2 | 1 | 1 | 3 | 3 |
| 20 | 5 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 0 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 23 | 1 | 3 | 9 | 9 | 7 | 9 | 9 | 9 | 0 | 0 | 3 | 3 | 2 | 2 | 3 | 3 |
| 24 | 2 | 2 | 8 | 8 | 6 | 6 | 6 | 9 | 0 | 0 | 2 | 2 | 2 | 2 | 2 | 3 |
| 25 | 4 | 4 | 4 | 6 | 6 | 9 | 9 | 9 | 0 | 0 | 0 | 1 | 1 | 3 | 3 | 3 |
| 26 | 0 | 4 | 9 | 9 | 9 | 9 | 9 | 9 | 0 | 2 | 3 | 3 | 3 | 3 | 3 | 3 |
| 29 | 0 | 2 | 3 | 9 | 8 | 9 | 9 | 9 | 0 | 0 | 0 | 3 | 3 | 3 | 3 | 3 |
| 31 | 1 | 8 | 9 | 9 | 9 | 9 | 9 | 9 | 0 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 33 | 2 | 3 | 3 | 8 | 9 | 9 | 9 | 9 | 0 | 0 | 0 | 2 | 3 | 3 | 3 | 3 |
| 34 | 2 | 2 | 5 | 9 | 9 | 9 | 9 | 9 | 0 | 0 | 2 | 3 | 3 | 3 | 3 | 3 |
| 38 | 1 | 5 | 9 | 9 | 9 | 9 | 9 | 9 | 0 | 2 | 3 | 3 | 3 | 3 | 3 | 3 |
| 39 | 0 | 0 | 9 | 9 | 9 | 9 | 9 | 9 | 0 | 0 | 3 | 3 | 3 | 3 | 3 | 3 |

**APPENDIX C 4: Coma and mood scores following flumazenil administration from Jones et al (1991). Coma and mood scale refer *Chapter II*, page 21.**

| | Coma Scale | | | | | | | | Mood Score | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient number | 2 | 5 | time | (min) 30 | 60 | 120 | 240 | 18 hr | 2 | 5 | 10 | time | (min) 60 | 120 | 240 | |
| 2 | 0 | 2 | 2 | 7 | 9 | 9 | 9 | 9 | 0 | 1 | 1 | 1 | 3 | 3 | 3 | 3 |
| 3 | 1 | 4 | 4 | 4 | 6 | 9 | 9 | 9 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 3 |
| 5 | 1 | 1 | 1 | 1 | 8 | 9 | 9 | 9 | 0 | 0 | 0 | 0 | 2 | 3 | 3 | 3 |
| 6 | 1 | 1 | 3 | 4 | 4 | 8 | 9 | 9 | 0 | 0 | 0 | 0 | 0 | 1 | 3 | 3 |
| 11 | 1 | 1 | 2 | 2 | 2 | 9 | 9 | 9 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 3 |
| 12 | 1 | 2 | 2 | 3 | 3 | 9 | 9 | 9 | 0 | 0 | 0 | 2 | 1 | 3 | 3 | 3 |
| 13 | 1 | 1 | 1 | 1 | 5 | 4 | 9 | 9 | 0 | 0 | 0 | 0 | 2 | 3 | 3 | 3 |
| 15 | 1 | 1 | 2 | 2 | 1 | 6 | 7 | 9 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 3 |
| 17 | 1 | 3 | 3 | 5 | 8 | 5 | 9 | 9 | 0 | 1 | 2 | 2 | 2 | 1 | 3 | 3 |
| 19 | 0 | 0 | 0 | 6 | 6 | 9 | 9 | 9 | 0 | 0 | 0 | 1 | 1 | 3 | 3 | 3 |
| 21 | 0 | 2 | 2 | 9 | 9 | 9 | 9 | 9 | 0 | 0 | 0 | 3 | 1 | 3 | 3 | 3 |
| 22 | 0 | 2 | 2 | 4 | 9 | 9 | 9 | 9 | 0 | 0 | 0 | 1 | 3 | 3 | 3 | 3 |
| 27 | 2 | 2 | 2 | 9 | 9 | 9 | 9 | 9 | 0 | 0 | 0 | 3 | 3 | 3 | 3 | 3 |
| 28 | 2 | 2 | 2 | 6 | 9 | 9 | 9 | 9 | 0 | 0 | 0 | 2 | 3 | 3 | 3 | 3 |
| 30 | 0 | 1 | 1 | 1 | 6 | 9 | 9 | 9 | 0 | 0 | 0 | 0 | 1 | 3 | 3 | 3 |
| 32 | 1 | 1 | 1 | 1 | 1 | 8 | 8 | 9 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 3 |
| 35 | 2 | 2 | 2 | 2 | 7 | 9 | 9 | 9 | 0 | 0 | 0 | 0 | 2 | 3 | 3 | 3 |
| 36 | 1 | 1 | 1 | 2 | 9 | 9 | 9 | 9 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 3 |
| 37 | 3 | 3 | 3 | 3 | 3 | 7 | 7 | 7 | 0 | 0 | 0 | 0 | 0 | 1 | 3 | 3 |
| 40 | 2 | 2 | 2 | 3 | 9 | 8 | 9 | 9 | 0 | 0 | 0 | 0 | 3 | 1 | 3 | 3 |

**APPENDIX C 5: Coma scale and mood scores following placebo administration from Jones et al (1991). Coma and mood scale refer *Chapter II*, page 21.**

| | Mood Score | | | | | | | | | Coma Score | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | Preoperative time (min) | | | | Postoperative time (min) | | | | | Preoperative time (min) | | | | Postoperative time (min) | | | | |
| number | 30 | 60 | 90 | 120 | awake | 60 | 120 | 180 | 240 | 30 | 60 | 90 | 120 | awake | 60 | 120 | 180 | 240 |
| 4 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 3 | 9 | 9 | 9 | 9 | 6 | 8 | 9 | 9 | 7 |
| 7 | 2 | 2 | 2 | 2 | 4 | 3 | 3 | 3 | 2 | 9 | 9 | 9 | 9 | 5 | 7 | 8 | 9 | 9 |
| 9 | 2 | 2 | 3 | 3 | 5 | 4 | 2 | 2 | 2 | 9 | 9 | 7 | 7 | 7 | 7 | 9 | 9 | 9 |
| 11 | 2 | 3 | 3 | 3 | 5 | 3 | 2 | 2 | 2 | 9 | 9 | 9 | 9 | 6 | 7 | 9 | 9 | 9 |
| 12 | 2 | 2 | 2 | 2 | 3 | 3 | 4 | 4 | 3 | 9 | 9 | 9 | 9 | 7 | 7 | 9 | 9 | 9 |
| 14 | 2 | 2 | 2 | 2 | 3 | 3 | 2 | 2 | 2 | 9 | 9 | 9 | 9 | 8 | 9 | 9 | 9 | 9 |
| 19 | 3 | 3 | 3 | 2 | 3 | 3 | 2 | 2 | 2 | 9 | 9 | 9 | 9 | 5 | 8 | 9 | 9 | 9 |
| 20 | 2 | 3 | 3 | 2 | 3 | 3 | 3 | 3 | 2 | 9 | 9 | 9 | 9 | 6 | 7 | 9 | 9 | 9 |
| 23 | 3 | 3 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 8 | 8 | 9 | 9 | 4 | 9 | 9 | 9 | 9 |
| 26 | 3 | 3 | 3 | 3 | 4 | 3 | 3 | 4 | 4 | 9 | 9 | 9 | 9 | 5 | 5 | 6 | 9 | 9 |
| 2 | 2 | 2 | 2 | 3 | 3 | 3 | 2 | 2 | 3 | 9 | 9 | 9 | 9 | 5 | 6 | 9 | 9 | 9 |
| 5 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 2 | 9 | 9 | 8 | 9 | 6 | 7 | 7 | 9 | 9 |
| 6 | 3 | 3 | 3 | 3 | 4 | 3 | 2 | 2 | 2 | 8 | 8 | 8 | 8 | 5 | 7 | 9 | 9 | 9 |
| 13 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 9 | 9 | 9 | 9 | 8 | 9 | 9 | 9 | 9 |
| 16 | 2 | 2 | 2 | 2 | 3 | 3 | 2 | 2 | 2 | 9 | 9 | 9 | 9 | 7 | 7 | 9 | 9 | 9 |
| 17 | 2 | 2 | 2 | 2 | 3 | 3 | 2 | 2 | 2 | 9 | 9 | 9 | 9 | 6 | 9 | 9 | 9 | 9 |
| 18 | 2 | 3 | 3 | 3 | 3 | 2 | 2 | 2 | 2 | 9 | 9 | 9 | 7 | 6 | 9 | 9 | 8 | 9 |
| 22 | 3 | 3 | 3 | 3 | 4 | 4 | 2 | 2 | 2 | 9 | 9 | 9 | 9 | 4 | 9 | 9 | 9 | 9 |
| 25 | 4 | 3 | 3 | 4 | 2 | 3 | 3 | 2 | 2 | 9 | 9 | 9 | 9 | 6 | 9 | 6 | 9 | 9 |
| 30 | 3 | 4 | 4 | 4 | 3 | 3 | 3 | 2 | 2 | 9 | 9 | 9 | 9 | 8 | 9 | 9 | 9 | 9 |
| 1 | 2 | 3 | 3 | 3 | 4 | 4 | 2 | 2 | 2 | 9 | 9 | 9 | 9 | 5 | 7 | 9 | 9 | 9 |
| 3 | 2 | 2 | 3 | 3 | 3 | 3 | 2 | 2 | 2 | 9 | 9 | 9 | 9 | 6 | 9 | 9 | 9 | 9 |
| 8 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 2 | 2 | 9 | 9 | 9 | 9 | 7 | 7 | 9 | 9 | 9 |
| 10 | 3 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| 15 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 9 | 9 | 9 | 9 | 8 | 9 | 9 | 9 | 9 |
| 21 | 3 | 3 | 3 | 3 | 3 | 4 | 2 | 1 | 1 | 4 | 4 | 8 | 9 | 8 | 8 | 9 | 9 | 9 |
| 24 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 2 | 2 | 8 | 8 | 8 | 8 | 4 | 5 | 9 | 9 | 9 |
| 27 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 9 | 8 | 8 | 8 | 6 | 3 | 9 | 9 | 9 |
| 28 | 3 | 3 | 2 | 3 | 3 | 3 | 2 | 2 | 2 | 9 | 9 | 9 | 9 | 3 | 3 | 9 | 9 | 9 |
| 29 | 3 | 3 | 2 | 2 | 5 | 3 | 3 | 4 | 3 | 9 | 9 | 9 | 9 | 6 | 9 | 9 | 9 | 9 |

**APPENDIX C 6: Preoperative and postoperative mood score and coma scale data from Jones et al (1993 c & d).**

| Patient number | Age (yr) | Unmedicated preoperative post box toy completion attempts (sec) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 1st | 2nd | 3rd | 4th | 5th | 6th | 7th | fastest completion time |
| 1 | 6 | 34 | 31 | 23 | 34 | 37 | 26 | 26 | **23** |
| 2 | 5 | 34 | 63 | 30 | 24 | 25 | 24 | 20 | **20** |
| 3 | 6 | 22 | 22 | 20 | 15 | 18 | 21 | 18 | **15** |
| 4 | 6 | 16 | 24 | 15 | 19 | 19 | 16 | 13 | **13** |
| 5 | 8.5 | 17 | 15 | 16 | 15 | 11 | 14 | 11 | **11** |
| 6 | 9 | 33 | 18 | 17 | 20 | 17 | 22 | 15 | **15** |
| 7 | 5 | 19 | 20 | 23 | 23 | 22 | 23 | 20 | **19** |
| 8 | 7 | 25 | 27 | 26 | 17 | 23 | 26 | 19 | **17** |
| 9 | 8 | 29 | 21 | 17 | 16 | 22 | 18 | 13 | **13** |
| 10 | 5 | 115 | 31 | 27 | 21 | 44 | 33 | 28 | **21** |
| 11 | 7.5 | 25 | 21 | 23 | 22 | 13 | 16 | 18 | **13** |
| 12 | 5 | 38 | 28 | 33 | 24 | 23 | 20 | 27 | **20** |

**APPENDIX C 7: Unmedicated preoperative post box toy completion time learning curve data om Jones et al (1993).**

| Patient number | Pre-op Fastest CT (sec) | Post operation | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | First awake | | 10 min | 20 min | 30 min | | 60 min | | 120 min | | 180 min | | 240 min | |
| | | Time (min) | CT (sec) | PBT ratio | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio |
| 1 | 23 | 10 | 70 | 3.04 | | 40 | 1.74 | R | | R | | R | | R | |
| 2 | 20 | 20 | 65 | | 3.25 | R | | A | | A | | R | | 37 | 1.85 |
| 3 | 15 | 10 | 30 | 2.00 | | 35 | 2.33 | R | | A | | 30 | 2.00 | 28 | 1.87 |
| 4 | 13 | 20 | 25 | | 1.92 | 34 | 2.62 | 41 | 3.15 | R | | R | | 38 | 2.92 |
| 5 | 11 | 10 | 35 | 3.18 | | 22 | 2.00 | 20 | 1.82 | 20 | 1.82 | 14 | 1.27 | 17 | 1.55 |
| 6 | 15 | 10 | 90 | 6.00 | | 55 | 3.67 | 40 | 2.67 | 32 | 2.13 | 18 | 1.20 | 19 | 1.27 |
| 7 | 19 | 10 | 48 | 2.53 | | 40 | 2.11 | A | | 40 | 2.11 | R | | 25 | 1.32 |
| 8 | 17 | R | R | | R | R | | R | | R | | R | | R | |
| 9 | 13 | 10 | 42 | 3.13 | | 31 | 2.31 | 54 | 4.03 | A | | R | | 28 | 2.09 |
| 10 | 21 | R | R | | R | 120 | 5.71 | A | | 124 | 5.90 | 48 | 2.29 | 30 | 1.43 |
| 11 | 13 | 10 | 78 | 6.00 | | 41 | 3.15 | 28 | 2.15 | 25 | 1.92 | 20 | 1.54 | 18 | 1.38 |
| 12 | 20 | R | R | | R | R | | R | | R | | 36 | 1.80 | 21 | 1.05 |
| mean | 16.7 | | 48.3 | 3.70 | 2.59 | 34.8 | 2.90 | 16.6 | 2.30 | 21.9 | 2.30 | 15.1 | 1.40 | 23.7 | 1.50 |
| SD | 3.7 | | 26.1 | 1.51 | 1.51 | 31.1 | 1.20 | 19.9 | 1.30 | 35.3 | 1.80 | 16.3 | 0.70 | 10.1 | 0.70 |
| n | | | 9 | 7 | 2 | 9 | | 5 | | 5 | | 6 | | 10 | |
| min | 11 | | 25 | 2.00 | 1.92 | 22 | 1.74 | 20 | 1.82 | 20 | 1.82 | 14 | 1.20 | 17 | 1.05 |
| max | 23 | | 90 | 6.00 | 3.25 | 120 | 5.71 | 54 | 4.03 | 124 | 5.90 | 48 | 2.29 | 38 | 2.92 |

**APPENDIX C 8:** **Psychomotor data from Jones et al (1993).** Post box toy completion time and completion time ratios.
**PBT** = post box toy, **CT** = completion time, **A** = asleep, **R** = refused the toy.

| Patient number | Age (yr) | Unmedicated preoperative post box toy completion attempts (sec) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 1st | 2nd | 3rd | 4th | 5th | 6th | 7th | fastest completion time |
| **1** | 7.5 | 16 | 14 | 17 | 14 | 17 | 14 | 13 | **13** |
| **4** | 5.5 | 32 | 37 | 28 | 24 | 27 | 27 | 25 | **24** |
| **7** | 3.5 | 52 | 50 | 55 | 63 | 29 | 51 | 43 | **29** |
| **8** | 8.5 | 29 | 24 | 18 | 18 | 14 | 16 | 15 | **14** |
| **9** | 9 | 13 | 17 | 16 | 18 | 16 | 16 | 14 | **13** |
| **10** | 6 | 35 | 34 | 35 | 29 | 27 | 28 | 31 | **27** |
| **14** | 4.5 | 40 | 33 | 31 | 38 | 23 | 27 | 34 | **23** |
| **16** | 11.5 | 18 | 15 | 13 | 14 | 14 | 14 | 12 | **12** |
| **18** | 11 | 14 | 26 | 17 | 12 | 15 | 12 | 14 | **12** |
| **20** | 11 | 18 | 18 | 10 | 12 | 20 | 9 | 13 | **9** |
| **23** | 4.5 | 58 | 42 | 29 | 42 | 22 | 20 | 22 | **20** |
| **24** | 10 | 20 | 15 | 14 | 14 | 13 | 13 | 11 | **11** |
| **25** | 9 | 18 | 15 | 10 | 9 | 9 | 8 | 11 | **8** |
| **26** | 4.5 | 40 | 36 | 30 | 35 | 29 | 25 | 29 | **25** |
| **29** | 11 | 24 | 17 | 18 | 17 | 20 | 18 | 15 | **15** |
| **31** | 4.5 | 45 | 47 | 39 | 27 | 27 | 31 | 28 | **27** |
| **33** | 4 | 53 | 70 | 52 | 78 | 55 | 60 | 53 | **52** |
| **34** | 6.5 | 40 | 28 | 37 | 23 | 21 | 29 | 19 | **19** |
| **38** | 5 | 88 | 71 | 44 | 51 | 47 | 37 | 34 | **34** |
| **39** | 6 | 17 | 19 | 21 | 18 | 24 | 18 | 21 | **17** |

**APPENDIX C 9:** **Unmedicated preoperative post box toy completion time learning curve data for the flumazenil group from Jones et al (1991).**

| Patient number | Pre-op Fastest CT (sec) | Post-operation | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 10 min | | 30 min | | 60 min | | 120 min | | 240 min | | 18 hr | |
| | | CT (sec) | PBT Ratio | CT (sec) | PBT Ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio |
| 1 | 13 | 36 | 2.79 | 28 | 2.17 | 20 | 1.55 | 19 | 1.47 | 18 | 1.40 | 13 | 1.01 |
| 4 | 24 | | | 97 | 4.04 | 83 | 3.46 | 95 | 3.96 | 33 | 1.37 | 22 | 0.92 |
| 7 | 29 | | | | | 66 | 2.28 | 63 | 2.17 | 58 | 2.00 | 57 | 1.97 |
| 8 | 14 | 69 | 4.93 | 22 | 1.57 | 25 | 1.79 | 22 | 1.57 | 18 | 1.29 | 18 | 1.29 |
| 9 | 13 | 45 | 3.46 | 24 | 1.85 | 19 | 1.46 | 17 | 1.31 | 25 | 1.92 | 15 | 1.15 |
| 10 | 27 | | | | | | | | | 15 | 0.56 | 19 | 0.70 |
| 14 | 23 | 56 | 2.43 | 54 | 2.35 | 32 | 1.39 | 37 | 1.61 | 33 | 1.43 | 31 | 1.35 |
| 16 | 12 | 37 | 3.08 | 20 | 1.67 | 21 | 1.75 | 21 | 1.75 | 15 | 1.25 | 12 | 1.00 |
| 18 | 12 | 47 | 3.92 | 20 | 1.67 | 21 | 1.75 | 27 | 2.25 | 17 | 1.42 | 17 | 1.42 |
| 20 | 9 | 28 | 3.11 | 18 | 2.00 | 25 | 2.78 | 16 | 1.78 | 15 | 1.67 | 7 | 0.78 |
| 23 | 20 | 50 | 2.50 | 27 | 1.35 | 32 | 1.60 | 35 | 1.75 | 20 | 1.00 | 19 | 0.95 |
| 24 | 11 | 34 | 3.09 | 28 | 2.55 | 27 | 2.45 | 27 | 2.45 | 33 | 3.00 | 15 | 1.36 |
| 25 | 8 | | | 47 | 5.87 | | | 30 | 3.75 | 26 | 3.25 | 14 | 1.75 |
| 26 | 25 | | | | | | | 50 | 2.0 | 29 | 1.16 | 34 | 1.36 |
| 29 | 15 | 46 | 3.07 | 27 | 1.73 | 34 | 2.27 | 30 | 2.0 | 31 | 2.07 | 18 | 1.20 |
| 31 | 27 | | | | | | | | | 43 | 1.59 | 30 | 1.11 |
| 33 | 52 | | | | | 154 | 2.96 | 48 | 0.92 | 55 | 1.06 | 184 | 2.00 |
| 34 | 19 | 44 | 2.32 | 39 | 2.05 | 33 | 1.74 | 24 | 1.26 | 40 | 2.11 | 44 | 2.32 |
| 38 | 34 | 71 | 2.09 | 58 | 1.71 | 112 | 3.29 | 47 | 1.38 | 60 | 1.76 | 38 | 1.12 |
| 39 | 17 | | | 60 | 3.53 | 58 | 3.41 | 40 | 2.35 | 42 | 2.47 | 23 | 1.35 |

**APPENDIX C 10: Post box toy completion time and completion time ratio in the flumazenil group from Jones et al (1991).**

| Patient number | Age (yr) | Unmedicated preoperative post box toy completion attempts (sec) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 1st | 2nd | 3rd | 4th | 5th | 6th | 7th | fastest completion time |
| **2** | 3 | 227 | 57 | 50 | 58 | 55 | 43 | 56 | **43** |
| **3** | 8 | 25 | 21 | 16 | 20 | 15 | 19 | 17 | **15** |
| **5** | 6 | 46 | 46 | 56 | 46 | 46 | 38 | 31 | **31** |
| **6** | 7 | 102 | 51 | 114 | 21 | 36 | 19 | 24 | **19** |
| **11** | 5.5 | 37 | 23 | 26 | 46 | 32 | 30 | 23 | **23** |
| **12** | 5.5 | 28 | 22 | 22 | 16 | 21 | 16 | 13 | **13** |
| **13** | 5.5 | 60 | 35 | 31 | 40 | 50 | 29 | 29 | **29** |
| **15** | 12 | 26 | 14 | 18 | 18 | 14 | 10 | 9 | **9** |
| **17** | 4 | 44 | 41 | 31 | 51 | 30 | 29 | 31 | **29** |
| **19** | 8 | 18 | 45 | 28 | 21 | 23 | 20 | 19 | **18** |
| **21** | 4.5 | 119 | 49 | 47 | 40 | 35 | 41 | 24 | **24** |
| **22** | 11.5 | 27 | 17 | 18 | 15 | 13 | 14 | 14 | **13** |
| **27** | 5.5 | 47 | 57 | 27 | 30 | 28 | 24 | 21 | **21** |
| **28** | 8 | 11 | 15 | 13 | 18 | 12 | 15 | 13 | **11** |
| **30** | 7 | 28 | 24 | 28 | 24 | 23 | 15 | 15 | **15** |
| **32** | 7 | 24 | 21 | 16 | 14 | 14 | 13 | 13 | **13** |
| **35** | 10.5 | 19 | 16 | 13 | 11 | 10 | 11 | 12 | **10** |
| **36** | 5.5 | 44 | 30 | 27 | 31 | 26 | 19 | 20 | **19** |
| **37** | 9 | 22 | 18 | 19 | 15 | 15 | 13 | 13 | **13** |
| **40** | 5 | 21 | 24 | 24 | 23 | 50 | 26 | 20 | **20** |

**APPENDIX C 11:** **Unmedicated preoperative post box toy completion time learning curve data for the placebo group from Jones et al (1991).**

| Patient number | Pre-op Fastest CT (sec) | Post-operation | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 10 min | 30 min | | 60 min | | 120 min | | 240 min | | 18 hr | |
| | | CT (sec) | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio |
| 2 | 43 | | | | | | | | | | 36 | 0.84 |
| 3 | 15 | | | | 123 | 8.20 | 28 | 1.87 | 31 | 2.07 | 14 | 0.93 |
| 5 | 31 | | | | 125 | 4.03 | 48 | 1.55 | 45 | 1.45 | 26 | 0.84 |
| 6 | 19 | | | | | | | | 30 | 1.58 | 29 | 1.53 |
| 11 | 23 | | | | 176 | 7.65 | 45 | 1.96 | 27 | 1.17 | 28 | 1.22 |
| 12 | 13 | | | | 32 | 2.46 | 20 | 1.54 | 20 | 1.54 | 15 | 1.15 |
| 13 | 29 | | | | | | | | 27 | 0.93 | 18 | 0.62 |
| 15 | 9 | | | | | | 20 | 2.22 | 25 | 2.78 | 16 | 1.78 |
| 17 | 29 | | | | | | | | 32 | 1.10 | 41 | 1.41 |
| 19 | 18 | | | | | | 42 | 2.33 | 25 | 1.39 | 24 | 1.33 |
| 21 | 24 | | 192 | 8.00 | | | 60 | 2.50 | 80 | 3.33 | 40 | 1.67 |
| 22 | 13 | | | | 185 | 8.08 | 18 | 1.38 | 15 | 1.15 | 15 | 1.15 |
| 27 | 21 | | 508 | 24.19 | 111 | 5.29 | 50 | 2.38 | 29 | 1.38 | 30 | 1.43 |
| 28 | 11 | | | | 59 | 5.36 | 17 | 1.55 | 14 | 1.27 | 18 | 1.64 |
| 30 | 15 | | | | | | 84 | 5.60 | 29 | 1.93 | 16 | 1.07 |
| 32 | 13 | | | | 50 | 3.85 | 23 | 1.77 | 26 | 2.00 | 15 | 1.15 |
| 35 | 10 | | | | 45 | 4.5 | 24 | 2.40 | 19 | 1.90 | 15 | 1.50 |
| 36 | 19 | | | | 250 | 13.16 | 90 | 4.74 | 30 | 1.58 | 22 | 1.16 |
| 37 | 13 | | | | 194 | 14.92 | 55 | 4.23 | 25 | 1.92 | 19 | 1.46 |
| 40 | 20 | | | | 215 | 10.75 | | | 37 | 1.85 | 33 | 1.65 |

**APPENDIX C 12: Post box toy completion time and completion time ratio in the placebo group from Jones et al (1991).**

| Patient number | Age (yr) | Unmedicated preoperative post box toy completion attempts (sec) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 1st | 2nd | 3rd | 4th | 5th | 6th | 7th | fastest completion time |
| 1 | 6 | 28 | 38 | 48 | 25 | 25 | 27 | 22 | 22 |
| 2 | 8.5 | 25 | 18 | 22 | 19 | 18 | 16 | 14 | 14 |
| 3 | 10 | 16 | 13 | 14 | 14 | 14 | 13 | 11 | 11 |
| 4 | 5 | 23 | 21 | 25 | 23 | 25 | 22 | 26 | 21 |
| 5 | 11 | 15 | 16 | 14 | 13 | 12 | 12 | 15 | 12 |
| 6 | 9 | 18 | 18 | 15 | 13 | 17 | 18 | 16 | 13 |
| 7 | 9 | 19 | 23 | 21 | 15 | 17 | 18 | 21 | 15 |
| 8 | 7 | 25 | 21 | 18 | 20 | 22 | 18 | 16 | 16 |
| 9 | 5 | 42 | 32 | 29 | 28 | 21 | 22 | 25 | 21 |
| 10 | 6 | 41 | 24 | 23 | 25 | 22 | 23 | 20 | 20 |
| 11 | 8 | 15 | 13 | 13 | 14 | 19 | 12 | 16 | 12 |
| 12 | 4 | 76 | 38 | 35 | 41 | 32 | 39 | 25 | 25 |
| 13 | 6 | 22 | 19 | 20 | 20 | 19 | 16 | 17 | 16 |
| 14 | 6 | 59 | 53 | 21 | 18 | 23 | 22 | 20 | 18 |
| 15 | 12 | 16 | 14 | 15 | 14 | 13 | 14 | 14 | 13 |
| 16 | 6 | 39 | 24 | 27 | 25 | 27 | 28 | 24 | 24 |
| 17 | 5 | 37 | 38 | 79 | 36 | 23 | 20 | 25 | 20 |
| 18 | 6 | 59 | 39 | 21 | 26 | 21 | 21 | 20 | 20 |
| 19 | 9 | 20 | 18 | 18 | 14 | 20 | 16 | 15 | 14 |
| 20 | 10 | 15 | 13 | 13 | 13 | 14 | 12 | 13 | 12 |
| 21 | 5 | 39 | 32 | 35 | 30 | 28 | 23 | 23 | 23 |
| 22 | 9 | 20 | 18 | 14 | 15 | 17 | 15 | 15 | 14 |
| 23 | 11 | 23 | 23 | 20 | 19 | 17 | 19 | 15 | 15 |
| 24 | 8 | 19 | 17 | 13 | 15 | 15 | 16 | 13 | 13 |
| 25 | 8 | 24 | 18 | 16 | 15 | 14 | 13 | 13 | 13 |
| 26 | 4 | 66 | 61 | 37 | 48 | 79 | 63 | 57 | 37 |
| 27 | 8.5 | 26 | 22 | 19 | 18 | 19 | 17 | 16 | 16 |
| 28 | 5 | 33 | 34 | 30 | 29 | 30 | 36 | 38 | 29 |
| 29 | 6 | 38 | 34 | 30 | 23 | 21 | 25 | 22 | 21 |
| 30 | 5 | 61 | 23 | 26 | 22 | 34 | 25 | 22 | 22 |

**APPENDIX C 13: Unmedicated preoperative post box toy completion time learning curve data for the midazolam, propofol and thiopentone groups from Jones et al (1993 c & d).**

| Patient number | Age (yr) | Fastest CT | Preoperative data after premedication | | | | | | | | Postoperative performance | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 30 min | | 60 min | | 90 min | | 120 min | | Awakening | | 60 min | | 120 min | | 180 min | | 240 min | |
| | | | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio |
| 4 | 5 | 21 | 39 | 0.54 | 28 | 0.75 | 22 | 0.96 | 25 | 0.84 | 38 | 0.55 | 24 | 0.88 | 26 | 0.81 | 24 | 0.88 | 26 | 0.81 |
| 7 | 9 | 15 | 19 | 0.79 | 16 | 0.94 | 14 | 1.10 | 20 | 0.75 | R | | A | | 19 | 0.79 | 17 | 0.88 | 16 | 0.94 |
| 9 | 5 | 21 | 58 | 0.38 | 45 | 0.47 | 47 | 0.45 | 44 | 0.48 | R | | 180 | 0.12 | 29 | 0.72 | 24 | 0.88 | 23 | 0.91 |
| 11 | 8 | 12 | 15 | 0.80 | 15 | 0.80 | 17 | 0.71 | 14 | 0.86 | R | | 24 | 0.50 | 16 | 0.75 | 12 | 1.00 | 14 | 0.86 |
| 12 | 4 | 25 | 84 | 0.30 | 49 | 0.51 | 46 | 0.54 | 27 | 0.93 | A | | A | | R | | 40 | 0.63 | 35 | 0.71 |
| 14 | 6 | 18 | 28 | 0.64 | 23 | 0.78 | 24 | 0.75 | 21 | 0.86 | 171 | 0.11 | 24 | 0.75 | 30 | 0.60 | 18 | 1.00 | 19 | 0.95 |
| 19 | 9 | 14 | 17 | 0.82 | 17 | 0.82 | 19 | 0.74 | 19 | 0.74 | 121 | 0.12 | 46 | 0.30 | 16 | 0.88 | 15 | 0.93 | 15 | 0.93 |
| 20 | 10 | 12 | 13 | 0.92 | 19 | 0.63 | | | 20 | 0.60 | 96 | 0.13 | 29 | 0.41 | 24 | 0.50 | 27 | 0.44 | 16 | 0.75 |
| 23 | 11 | 15 | 25 | 0.60 | 20 | 0.75 | 17 | 0.88 | 14 | 1.10 | 55 | 0.27 | 22 | 0.68 | 14 | 1.10 | 16 | 0.94 | 11 | 1.36 |
| 26 | 4 | 37 | 62 | 0.60 | 78 | 0.47 | 49 | 0.76 | 40 | 0.93 | R | | A | | A | | 35 | 1.10 | 37 | 1.00 |
| mean | 7.2 | 19 | 35.8 | 0.64 | 31 | 0.69 | 28.3 | 0.76 | 24.4 | 0.80 | 99.2 | 0.23 | 49.8 | 0.52 | 21.8 | 0.77 | 22.8 | 0.86 | 21.2 | 0.92 |
| SD | 2.5 | 7.2 | 24 | 0.19 | 20.4 | 0.16 | 14.6 | 0.19 | 10.2 | 0.17 | 53.1 | 0.19 | 57.9 | 0.27 | 6.3 | 0.17 | 9.1 | 0.19 | 8.9 | 0.18 |
| n | 10 | 10 | 10 | 10 | 10 | 10 | 9 | 9 | 10 | 10 | 5 | 5 | 7 | 7 | 8 | 8 | 10 | 10 | 10 | 10 |
| min | 4 | 12 | 13 | 0.30 | 15 | 0.47 | 14 | 0.45 | 14 | 0.48 | 38 | 0.11 | 22 | 0.12 | 14 | 0.50 | 12 | 0.44 | 11 | 0.71 |
| max | 11 | 37 | 84 | 0.92 | 78 | 0.94 | 49 | 1.10 | 44 | 1.10 | 171 | 0.55 | 180 | 0.88 | 30 | 1.10 | 40 | 1.1 | 37 | 1.36 |

**APPENDIX C 14: Post box completion time and completion time ratios in the midazolam group from Jones et al (1993 c & d).**

**PBT** = post box toy, **CT** = completion time, **A** = asleep, **R** = refused the toy.

| Patient number | Age (yr) | Fastest CT (sec) | Preoperative data after premedication | | | | | | | | Postoperative performance | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 30 min | | 60 min | | 90 min | | 120 min | | Awakening | | 60 min | | 120 min | | 180 min | | 240 min | |
| | | | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio |
| **2** | 8.5 | 14 | 25 | 0.56 | 19 | 0.74 | 22 | 0.64 | 19 | 0.74 | 44 | 0.32 | 25 | 0.56 | 31 | 0.45 | 21 | 0.67 | 18 | 0.78 |
| **5** | 11 | 12 | 15 | 0.80 | 19 | 0.63 | 15 | 0.80 | 18 | 0.67 | 80 | 0.15 | 17 | 0.71 | 18 | 0.67 | 15 | 0.8 | 13 | 0.92 |
| **6** | 9 | 13 | 36 | 0.36 | 23 | 0.57 | 18 | 0.72 | 18 | 0.72 | R | | 19 | 0.68 | 22 | 0.59 | 17 | 0.77 | 18 | 0.72 |
| **13** | 6 | 16 | 26 | 0.62 | 25 | 0.64 | 22 | 0.73 | 21 | 0.76 | 36 | 0.44 | 17 | 0.94 | 24 | 0.67 | 20 | 0.80 | 18 | 0.89 |
| **16** | 6 | 24 | 26 | 0.92 | 29 | 0.83 | 29 | 0.83 | 32 | 0.75 | 65 | 0.37 | 35 | 0.69 | 20 | 1.20 | 19 | 1.26 | 22 | 1.10 |
| **17** | 5 | 20 | 29 | 0.69 | 39 | 0.51 | 32 | 0.63 | 34 | 0.59 | 38 | 0.53 | 27 | 0.74 | 28 | 0.71 | 23 | 0.87 | 28 | 0.71 |
| **18** | 6 | 20 | 24 | 0.83 | 22 | 0.91 | 23 | 0.87 | 35 | 0.57 | 40 | 0.50 | 24 | 0.83 | 22 | 0.91 | 24 | 0.83 | 19 | 1.10 |
| **22** | 9 | 14 | 20 | 0.70 | 22 | 0.64 | 23 | 0.61 | 18 | 0.78 | 122 | 0.12 | 42 | 0.33 | 28 | 0.50 | 24 | 0.58 | 22 | 0.64 |
| **25** | 8 | 13 | 28 | 0.46 | 22 | 0.59 | 17 | 0.77 | 21 | 0.62 | 17 | 0.77 | 11 | 1.18 | R | | 10 | 1.30 | 13 | 1.00 |
| **30** | 5 | 22 | 31 | 0.71 | 30 | 0.73 | 31 | 0.71 | 25 | 0.88 | 40 | 0.55 | 25 | 0.88 | 26 | 0.85 | 23 | 0.96 | 23 | 0.96 |
| **mean** | 7.4 | 16.8 | 26 | 0.67 | 25 | 0.68 | 23.2 | 0.73 | 24.1 | 0.71 | 53.6 | 0.42 | 24.2 | 0.76 | 24.3 | 0.73 | 19.6 | 0.88 | 19.4 | 0.88 |
| **SD** | 2.0 | 4.3 | 5.8 | 0.17 | 6.2 | 0.12 | 5.9 | 0.09 | 7.0 | 0.10 | 31.4 | 0.20 | 9.1 | 0.23 | 4.2 | 0.23 | 4.5 | 0.23 | 4.6 | 0.16 |
| **n** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 9 | 9 | 10 | 10 | 9 | 9 | 10 | 10 | 10 | 10 |
| **min** | 5 | 12 | 15 | 0.36 | 19 | 0.51 | 15 | 0.61 | 18 | 0.57 | 17 | 0.12 | 11 | 0.33 | 18 | 0.45 | 10 | 0.58 | 13 | 0.64 |
| **max** | 11 | 24 | 36 | 0.92 | 39 | 0.91 | 32 | 0.87 | 35 | 0.88 | 122 | 0.77 | 42 | 1.18 | 31 | 1.2 | 24 | 1.30 | 28 | 1.10 |

**APPENDIX C 15:** **Post box toy completion time and completion time ratios in the propofol group from Jones et al (1993 c & d).**
**PBT** = post box toy, **CT** = completion time, **R** = refused the toy.

| Patient number | Age (yr) | fastest CT (sec) | Preoperative data after premedication | | | | | | | | Postoperative performance | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 30 min | | 60 min | | 90 min | | 120 min | | Awakening | | 60 min | | 120 min | | 180 min | | 240 min | |
| | | | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio | CT (sec) | PBT ratio |
| 1 | 6 | 22 | 42 | 0.52 | 48 | 0.46 | 41 | 0.54 | 43 | 0.51 | 62 | 0.36 | A | | 36 | 0.61 | 24 | 0.92 | 31 | 0.71 |
| 3 | 10 | 11 | 14 | 0.79 | 14 | 0.79 | 15 | 0.73 | 15 | 0.73 | 31 | 0.36 | 20 | 0.55 | 17 | 0.65 | 14 | 0.79 | 18 | 0.61 |
| 8 | 7 | 16 | 21 | 0.76 | 22 | 0.73 | 22 | 0.73 | 27 | 0.59 | 33 | 0.49 | 20 | 0.80 | 22 | 0.73 | 19 | 0.84 | 22 | 0.73 |
| 10 | 6 | 20 | 63 | 0.32 | 32 | 0.63 | 31 | 0.65 | 24 | 0.83 | R | | 30 | 0.67 | 23 | 0.87 | 35 | 0.57 | 40 | 0.67 |
| 15 | 12 | 13 | 19 | 0.68 | 17 | 0.77 | 13 | 1.00 | 16 | 0.81 | 66 | 0.20 | 25 | 0.52 | 13 | 1.00 | 15 | 0.87 | 13 | 1.00 |
| 21 | 5 | 23 | A | | A | | 53 | 0.43 | 45 | 0.51 | 78 | 0.30 | 70 | 0.33 | 27 | 0.85 | 26 | 0.89 | 27 | 0.85 |
| 24 | 8 | 13 | 16 | 0.81 | 14 | 0.93 | 15 | 0.87 | 16 | 0.81 | 33 | 0.39 | 30 | 0.43 | 15 | 0.87 | 15 | 0.87 | 15 | 0.87 |
| 27 | 8.5 | 16 | 23 | 0.70 | 45 | 0.36 | 29 | 0.55 | 23 | 0.70 | 34 | 0.47 | A | | 20 | 0.80 | 27 | 0.59 | 17 | 0.94 |
| 28 | 5 | 29 | 30 | 0.97 | 33 | 0.88 | 34 | 0.85 | | | 30 | 0.97 | A | | 42 | 0.69 | 34 | 0.85 | 25 | 1.16 |
| 29 | 6 | 21 | 27 | 0.78 | 24 | 0.88 | 22 | 0.96 | 19 | 1.11 | 49 | 0.43 | 27 | 0.78 | 17 | 1.24 | 26 | 0.81 | 20 | 1.05 |
| mean | 7.35 | 18.4 | 28.3 | 0.70 | 27.7 | 0.71 | 27.5 | 0.73 | 25.3 | 0.73 | 46.2 | 0.44 | 31.7 | 0.58 | 23.2 | 0.83 | 23.5 | 0.80 | 21.8 | 0.86 |
| SD | 2.3 | 5.6 | 15.5 | 0.19 | 12.7 | 0.20 | 12.8 | 0.19 | 11.4 | 0.19 | 18.2 | 0.22 | 17.4 | 0.18 | 9.4 | 0.19 | 7.6 | 0.12 | 6.3 | 0.18 |
| n | 10 | 10 | 9 | 9 | 9 | 9 | 10 | 10 | 9 | 9 | 9 | 9 | 7 | 7 | 10 | 10 | 10 | 10 | 10 | 10 |
| min | 5 | 11 | 14 | 0.32 | 14 | 0.36 | 13 | 0.43 | 15 | 0.51 | 30 | 0.20 | 20 | 0.33 | 13 | 0.61 | 14 | 0.57 | 13 | 0.61 |
| max | 12 | 29 | 63 | 0.97 | 48 | 0.93 | 53 | 1 | 45 | 1.10 | 78 | 0.97 | 70 | 0.80 | 42 | 1.24 | 35 | 0.92 | 31 | 1.16 |

**APPENDIX C 16: Post box toy completion time and completion time ratios in the thiopentone group from Jones et al (1993 c & d).**

**PBT** = post box toy, **CT** = completion time, **A** = asleep, **R** = refused the toy.

| Patient number | Age (yr.m day) | Highest code score | Preoperative WISC-R performance after premedication | | | | | | | | Postoperative WISC-R coding performance | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 30 min | | 60 min | | 90 min | | 120 min | | Awake | | 60 min | | 120 min | | 180 min | | 240 min | |
| | | | score | scale | score | scale | score | scale | score | scale | score | scale | score | scale | score | scale | score | scale | score | scale |
| 4 | 5.4,24 | 48 | 42 | 18 | 47 | 19 | 45 | 18 | 45 | 18 | 9 | 4 | 38 | 16 | 48 | 19 | 49 | 19 | 45 | 18 |
| 7 | 9.0,15 | 85 | 63 | 17 | 64 | 18 | 46 | 11 | 49 | 12 | R | 1 | R | 1 | 29 | 5 | 52 | 14 | 68 | 18 |
| 9 | 5.9,18 | 49 | 45 | 18 | 48 | 19 | 47 | 18 | 46 | 18 | R | 1 | 25 | 10 | 45 | 18 | 46 | 18 | 49 | 19 |
| 11 | 8.0,5 | 85 | 71 | 19 | 65 | 19 | 74 | 19 | 81 | 19 | R | 1 | 69 | 19 | 80 | 19 | 85 | 19 | 78 | 19 |
| 12 | 4.9,23 | 20 | 14 | | 17 | | 24 | | 31 | | A | | A | | R | | 38 | | 32 | |
| 14 | 6.2,21 | 48 | 46 | 18 | 46 | 18 | 48 | 18 | 47 | 18 | 6 | 3 | 46 | 18 | 49 | 19 | 50 | 19 | 50 | 19 |
| 19 | 9.2,13 | 74 | 48 | 12 | 65 | 18 | 53 | 14 | 61 | 17 | 4 | 1 | 23 | 4 | 52 | 14 | 77 | 19 | 77 | 19 |
| 20 | 9.11,8 | 74 | 84 | 19 | 61 | 15 | | | 86 | 19 | 15 | 1 | 46 | 10 | 66 | 17 | 59 | 15 | 78 | 19 |
| 23 | 11.5,4 | 75 | 38 | 5 | 67 | 14 | 71 | 15 | 71 | 15 | 14 | 1 | 41 | 6 | 67 | 14 | 80 | 18 | 66 | 13 |
| 26 | 4.5,15 | 45 | 15 | | 15 | | 18 | | 17 | | R | | A | | A | | 19 | | R | |
| mean | | 57.6 | 46.6 | 15.8 | 49.5 | 17.5 | 47.3 | 16.1 | 53.4 | 17.0 | 9.6 | 1.6 | 41.1 | 10.5 | 54.5 | 15.6 | 59.6 | 17.6 | 60.3 | 18.0 |
| SD | | 19.5 | 22.2 | 4.9 | 19.4 | 1.9 | 18.4 | 2.9 | 21.6 | 2.4 | 4.8 | 1.2 | 15.4 | 6.7 | 15.8 | 4.8 | 16.9 | 2.0 | 16.8 | 2.1 |
| n | | 10 | 10 | 8 | 10 | 8 | 9 | 7 | 10 | 8 | 5 | 8 | 7 | 8 | 8 | 8 | 10 | 8 | 9 | 8 |
| min | | 20 | 14 | 5 | 15 | 14 | 18 | 11 | 17 | 12 | 4 | 1 | 23 | 1 | 29 | 5 | 38 | 14 | 32 | 13 |
| max | | 85 | 84 | 19 | 67 | 19 | 74 | 19 | 86 | 19 | 15 | 4 | 69 | 19 | 80 | 19 | 85 | 19 | 87 | 19 |

**APPENDIX C 17: Perioperative Wechsler intelligence scale coding performance in the midazolam group from Jones et al (1993 c &d)**

**A** = asleep, **R** = refused the toy.

| Patient number | Age (yr.m. day) | Highest code score | Preoperative WISC-R performance after premedication | | | | | | | | Postoperative WISC-R coding performance | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 30 min | | 60 min | | 90 min | | 120 min | | Awake | | 60 min | | 120 min | | 180 min | | 240 min | |
| | | | score | scale | score | scale | score | scale | score | scale | score | scale | score | scale | score | scale | score | scale | score | scal |
| 2 | 8.6,17 | 50 | 46 | 13 | 53 | 16 | 60 | 18 | 52 | 16 | 31 | 7 | 41 | 11 | 58 | 17 | 66 | 19 | 71 | 19 |
| 5 | 11.0,25 | 73 | 84 | 19 | 49 | 9 | 73 | 16 | 75 | 17 | 13 | 1 | 68 | 15 | 89 | 19 | 87 | 19 | 88 | 19 |
| 6 | 9.2,19 | 60 | 39 | 9 | 46 | 11 | 56 | 15 | 54 | 15 | R | 1 | 59 | 16 | 67 | 18 | 56 | 15 | 70 | 19 |
| 13 | 6.3,14 | 50 | 48 | 18 | 49 | 19 | 50 | 19 | 50 | 19 | 48 | 18 | 50 | 19 | 50 | 19 | 50 | 19 | 50 | 19 |
| 16 | 6.1,13 | 49 | 49 | 19 | 47 | 18 | 48 | 18 | 49 | 19 | 30 | 11 | 46 | 18 | 50 | 19 | 50 | 19 | 49 | 19 |
| 17 | 5.7,1 | 47 | 42 | 18 | 45 | 18 | 46 | 18 | 46 | 18 | 30 | 3 | 44 | 18 | 47 | 19 | 46 | 18 | 47 | 19 |
| 18 | 6.2,1 | 50 | 48 | 18 | 48 | 18 | 48 | 18 | 47 | 18 | 45 | 17 | 46 | 18 | 49 | 19 | 48 | 18 | 44 | 17 |
| 22 | 9.0,15 | 50 | 47 | 12 | 34 | 7 | 37 | 8 | 32 | 6 | 3 | 1 | 15 | 1 | 29 | 5 | 40 | 9 | 50 | 13 |
| 25 | 8.2,10 | 55 | 14 | 1 | 20 | 4 | 47 | 14 | 9 | 1 | 51 | 16 | R | 1 | R | 1 | 82 | 19 | 65 | 19 |
| 30 | 5.2,16 | 30 | 18 | 8 | 23 | 10 | 25 | 11 | 21 | 9 | 15 | 6 | 25 | 11 | 34 | 15 | 33 | 14 | 30 | 13 |
| mean | | 51.4 | 43.5 | 13.5 | 41.4 | 13.0 | 49.0 | 15.5 | 43.5 | 13.8 | 29.6 | 8.1 | 43.8 | 12.8 | 52.6 | 15.1 | 55.8 | 17.0 | 56.4 | 17.( |
| SD | | 10.8 | 19.1 | 6.1 | 11.6 | 5.4 | 12.8 | 3.6 | 18.5 | 6.3 | 16.7 | 6.9 | 16.0 | 6.8 | 17.8 | 6.6 | 17.5 | 3.4 | 16.8 | 2.5 |
| n | | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 9 | 10 | 9 | 10 | 9 | 10 | 10 | 10 | 10 | 10 |
| min | | 30 | 14 | 1 | 20 | 4 | 25 | 8 | 9 | 1 | 3 | 1 | 15 | 1 | 29 | 1 | 33 | 9 | 30 | 13 |
| max | | 73 | 84 | 19 | 53 | 19 | 73 | 19 | 75 | 19 | 51 | 18 | 68 | 19 | 89 | 19 | 87 | 19 | 88 | 19 |

**APPENDIX C 18: Perioperative Wechsler intelligence scale coding performance in the propofol group from Jones et al (1993 c & d).**

R = refused the toy.

| Patient number | Age (yr.m. day) | Highest code score | Preoperative WISC-R performance after premedication | | | | | | | | Postoperative WISC-R coding performance | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 30 min | | 60 min | | 90 min | | 120 min | | Awake | | 60 min | | 120 min | | 180 min | | 240 min | |
| | | | score | scale | score | scale | score | scale | score | scale | score | scale | score | scale | score | scale | score | scale | score | scale |
| 1 | 6.5,3 | 32 | 27 | 9 | 31 | 11 | 32 | 11 | 34 | 12 | 8 | 2 | R | 1 | 44 | 16 | 49 | 18 | 49 | 18 |
| 3 | 8.8,9 | 75 | 88 | 19 | 75 | 19 | 52 | 15 | 69 | 19 | 41 | 10 | 44 | 11 | 69 | 19 | 93 | 19 | 93 | 19 |
| 8 | 7.0,10 | 50 | 50 | | 50 | | 50 | | 50 | | 41 | | 49 | | 49 | | 50 | | 50 | |
| 10 | 5.7,1 | 48 | 48 | 19 | 46 | 18 | 48 | 19 | 48 | 19 | 33 | 14 | 45 | 18 | 46 | 18 | 50 | 19 | 49 | 19 |
| 15 | 12.8,12 | 78 | 52 | 8 | 62 | 10 | 68 | 12 | 75 | 14 | 29 | 4 | 77 | 14 | 73 | 13 | 85 | 17 | 81 | 16 |
| 21 | 4.11,2 | 41 | A | 1 | A | 1 | 25 | 11 | 44 | 19 | 14 | 6 | 26 | 12 | 49 | 19 | 49 | 19 | 49 | 19 |
| 24 | 7.10,11 | 52 | 32 | 9 | 44 | 14 | 44 | 14 | 48 | 15 | 14 | 2 | 35 | 10 | 40 | 12 | 51 | 16 | 51 | 16 |
| 27 | 8.8,8 | 48 | 52 | 15 | 10 | 1 | 18 | 3 | 33 | 7 | 18 | 3 | A | 1 | 43 | 11 | 43 | 11 | 54 | 15 |
| 28 | 5.3,19 | 47 | 49 | 19 | 48 | 19 | 47 | 19 | | 1 | 22 | 10 | A | 1 | 48 | 19 | 49 | 19 | 50 | 19 |
| 29 | 5.7,14 | 48 | 45 | 18 | 48 | 19 | 50 | 19 | 49 | 19 | 28 | 12 | 47 | 19 | 49 | 19 | 47 | 19 | 48 | 19 |
| mean | | 51.9 | 49.2 | 13.0 | 46.0 | 12.4 | 43.4 | 13.7 | 50.0 | 13.9 | 24.8 | 7.0 | 46.1 | 9.7 | 51.0 | 16.2 | 56.6 | 17.4 | 57.4 | 17.8 |
| SD | | 14.2 | 17.1 | 6.5 | 18.2 | 7.4 | 14.6 | 5.2 | 14.0 | 6.4 | 11.5 | 4.6 | 15.8 | 7.1 | 11.0 | 3.4 | 17.3 | 2.7 | 15.9 | 1.6 |
| n | | 10 | 10 | 9 | 10 | 9 | 10 | 9 | 9 | 8 | 10 | 9 | 7 | 9 | 10 | 9 | 10 | 9 | 10 | 9 |
| min | | 32 | 27 | 1 | 10 | 1 | 18 | 3 | 33 | 7 | 8 | 2 | 26 | 1 | 40 | 11 | 43 | 11 | 48 | 15 |
| max | | 78 | 88 | 19 | 75 | 19 | 68 | 19 | 75 | 19 | 41 | 14 | 77 | 19 | 73 | 19 | 93 | 19 | 93 | 19 |

**APPENDIX C 19: Perioperative Wechsler intelligence scale coding performance in the thiopentone group from Jones et al (1993 c &d)**

**A** = asleep, **R** = refuse the toy.

# APPENDIX D

## Pharmacodynamic data

## Preoperative night - RAW data, $F_IO_2$ 0.21

| | | | | | | | Time in saturation range (% total time) | | | | | Number of episodes (>15 sec) in saturation range | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pt. No. premed (P/M) | sex | age (yr) | weight (kg) | Satmaster time discounted (hr,min,sec) | mean $SpO_2$ (%) | lowest $SpO_2$ (%) | 90-95 (%) | 85-90 (%) | 80-85 (%) | 75-80 (%) | <75 (%) | 90-95 (%) | 85-90 (%) | 80-85 (%) | 75-80 (%) | <75 (%) |
| 1 M | M | 6 | 15 | 0:03:33 | 99 | 79 | 3:51(1) | 1:51(0) | 0:46(0) | 0:11(0) | - | 21 | 6 | 5 | 1 | - |
| 2 M | F | 4 | 16 | 0:07:56 | 100 | 90 | 2:37(0) | 0:05(0) | - | - | - | 14 | 1 | - | - | - |
| 3 M | F | 1.5 | 11.5 | 0:20:43 | 99 | 69 | 1:55(0) | 0:42(0) | 0:10(0) | 1:16(0) | 0:13(0) | 8 | 3 | 2 | 4 | 2 |
| 4 M | M | 5 | 20 | 4:29:54 | 98 | 93 | 3:33(1) | - | - | - | - | 7 | - | - | - | - |
| 5 M | M | 7 | 17.5 | 0:07:51 | 96 | 61 | 3:19(1) | 0:47(0) | 3:35(1) | 20:00(3) | 46:22(7) | 16 | 5 | 5 | 13 | 49 |
| 6 M | M | 2.5 | 14.5 | 0:02:47 | 97 | 63 | 79:17(13) | 5:39(1) | 2:30(0) | 0.08(0) | 0.07(0) | 179 | 15 | 10 | 3 | 3 |
| 7 M | M | 4.5 | 15 | 0:01:23 | 97 | 73 | 74:00(9) | 43:29(5) | 26:50(3) | 2:43(0) | 0.09(0) | 132 | 96 | 69 | 21 | 1 |
| 8 M | F | 10 | 18 | 4:43:48 | 98 | 92 | 10:47(2) | - | - | - | - | 47 | - | - | - | - |
| 9 M | M | 2.5 | 16 | 0:00:18 | 98 | 91 | 4:31(1) | - | - | - | - | 12 | - | - | - | - |
| 10 M | M | 2.5 | 16.5 | 2:58:31 | 99 | 88 | 6:18(1) | 0:25(0) | - | - | - | 25 | 2 | - | - | - |
| 1 P | M | 5.5 | 16 | 0:01:29 | 99 | 85 | 5:38(1) | 2:06(0) | 0.16(0) | - | - | 22 | 4 | 2 | - | - |
| 2 P | F | 2.5 | 10.5 | 0:10:19 | 99 | 92 | 2:46(0) | - | - | - | - | 16 | - | - | - | - |
| 3 P | M | 3.5 | 15 | 0:02:54 | 99 | 85 | 3:45(1) | 0:39(0) | 0:26(0) | - | - | 17 | 2 | 1 | - | - |
| 4 P | M | 1.8 | 10.8 | 0:05:23 | 99 | 96 | - | - | - | - | - | - | - | - | - | - |
| 5 P | F | 5.5 | 20 | 0:05:09 | 98 | 84 | 10:41(2) | 1:02(0) | 0:13(0) | - | - | 46 | 6 | 1 | - | - |
| 6 P | F | 7.5 | 30 | 0:05:09 | 99 | 88 | 5:45(1) | 0:19(0) | - | - | - | 25 | 4 | - | - | - |
| 7 P | M | 2.7 | 14.5 | 0:16:35 | 100 | 94 | 0:26(0) | - | - | - | - | 1 | - | - | - | - |
| 8 P | M | 3 | 13.3 | 0:00:15 | 99 | 88 | 2:46(0) | 0:19(0) | - | - | - | 10 | 1 | - | - | - |
| 9 P | M | 2.5 | 14 | 3:22:35 | 97 | 73 | 54:59(6) | 18:04(2) | 12:16(1) | 4:44(1) | 0:42(0) | 126 | 65 | 35 | 13 | 4 |
| 10 P | M | 3.5 | 19 | 1:09:54 | 98 | 37 | 21:55(3) | 6:43(1) | 5:33(1) | 1:58(0) | 14:30(2) | 93 | 33 | 19 | 13 | 25 |

**APPENDIX D 1: Patient details and preoperative raw oximetric data from Jones et al (1993b).**

**M** = midazolam premedication **P** = pethidine premedication.

## Preoperative night - EVALUATED data, $F_IO_2$ 0.21

| | | | | | Time in saturation range (% total time) | | | | | Number of episodes (>15 sec) in saturation range | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pt. No. premed (P/M) | Operator time discounted (hr,min,sec) | total valid time (hr,min,sec) | mean $SpO_2$ (%) | lowest $SpO_2$ (%) | 90-95 (%) | 85-90 (%) | 80-85 (%) | 75-80 (%) | <75 (%) | 90-95 (%) | 85-90 (%) | 80-85 (%) | 75-80 (%) | <75 (%) |
| 1 M | 0:05:12 | 10:44:23 | 99 | 85 | 1:09(0) | 0.23(0) | 0.07(0) | - | - | 1 | 1 | - | - | - |
| 2 M | 0:01:42 | 8:50:36 | 100 | 92 | 0:51(0) | - | - | - | - | 1 | - | - | - | - |
| 3 M | 0:00:55 | 10:49:19 | 99 | 92 | 1:37(0) | - | - | - | - | 3 | - | - | - | - |
| 4 M | 4:22:56 | 9:53:57 | 98 | 94 | 5:48(1) | - | - | - | - | 7 | - | - | - | - |
| 5 M | 1:19:26 | 9:21:12 | 99 | 95 | 0:43(0) | - | - | - | - | - | - | - | - | - |
| 6 M | 1:12:50 | 8:47:57 | 98 | 94 | 33:01(6) | - | - | - | - | 22 | - | - | - | - |
| 7 M | 2:56:26 | 10:23:47 | 99 | 93 | 6:03(1) | - | - | - | - | 10 | - | - | - | - |
| 8 M | 0:06:10 | 8:27:54 | 98 | 92 | 8:10(2) | - | - | - | - | 8 | - | - | - | - |
| 9 M | 0:06:05 | 9:48:50 | 98 | 94 | 2:09(0) | - | - | - | - | 2 | - | - | - | - |
| 10 M | 0:04:38 | 9:04:46 | 99 | 88 | 3:26(1) | 0:25(0) | - | - | - | 6 | - | - | - | - |
| 1 P | 0:06:44 | 12:07:32 | 99 | 92 | 3:37(0) | - | - | - | - | 5 | - | - | - | - |
| 2 P | 0:00:54 | 10:16:45 | 99 | 93 | 1:25(0) | - | - | - | - | 1 | - | - | - | - |
| 3 P | 0:05:22 | 11:30:56 | 99 | 91 | 2:23(0) | - | - | - | - | 5 | - | - | - | - |
| 4 P | 0:30:00 | 9:01:01 | 99 | 96 | - | - | - | - | - | - | - | - | - | - |
| 5 P | 0:11:44 | 10:11:11 | 98 | 94 | 2:25(0) | - | - | - | - | 2 | - | - | - | - |
| 6 P | 0:07:40 | 11:04:33 | 99 | 94 | 0:39(0) | - | - | - | - | 1 | - | - | - | - |
| 7 P | 0:00:52 | 10:24:53 | 100 | 94 | 0:28(0) | - | - | - | - | 1 | - | - | - | - |
| 8 P | 0:02:18 | 10:47:17 | 99 | 93 | 0:56(0) | - | - | - | - | 1 | - | - | - | - |
| 9 P | 1:26:50 | 14:13:24 | 98 | 73 | 19:26(2) | 3:25(0) | 1:29(0) | 0:15(0) | - | 17 | 7 | 4 | - | - |
| 10 P | 1:22:42 | 11:36:23 | 99 | 91 | 0:55(0) | - | - | - | - | 1 | - | - | - | - |

**APPENDIX D 2: Preoperative oximetric data are after template evaluation from Jones et al (1993b).**

## Post premedication - RAW data, $F_IO_2$ 0.21

| Pt. No. premed (P/M) | Satmaster time discounted (hr,min,sec) | mean $SpO_2$ (%) | lowest $SpO_2$ (%) | Time in saturation range (% total time) | | | | | Number of episodes (>15 sec) in saturation range | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 90-95 (%) | 85-90 (%) | 80-85 (%) | 75-80 (%) | <75 (%) | 90-95 (%) | 85-90 (%) | 80-85 (%) | 75-80 (%) | <75 (%) |
| 1 M | 0:00:00 | 99 | 92 | 1:41(1) | - | - | - | - | 4 | - | - | - | - |
| 2 M | 0:00:14 | 100 | 94 | 0:12(0) | - | - | - | - | 1 | - | - | - | - |
| 3 M | 0:15:53 | 97 | 64 | 4:31(4) | 1:10(1) | 3:45(4) | 2:36(3) | 1:00(1) | 17 | 4 | 4 | 9 | 10 |
| 4 M | 0:00:04 | 100 | 96 | - | - | - | - | - | - | - | - | - | - |
| 5 M | 0:07:53 | 95 | 62 | 27:05(23) | 15:21(13) | 4:09(4) | 1:20(1) | 0:27(0) | 61 | 43 | 19 | 8 | 3 |
| 6 M | 0:02:49 | 97 | 82 | 14:58(12) | 4:28(4) | 1:21(1) | - | - | 39 | 8 | 5 | | |
| 7 M | 0:01:25 | 98 | 91 | 4:15(4) | - | - | - | - | 22 | - | - | - | - |
| 8 M | 0:00:00 | 97 | 84 | 7:57(1) | 1:15(1) | 0.08(0) | - | - | 22 | 6 | 2 | - | - |
| 9 M | 0:02:00 | 98 | 91 | 1:08(1) | - | - | - | - | 3 | - | - | - | - |
| 10 M | 0:00:25 | 99 | 95 | 0:04(0) | - | - | - | - | 1 | - | - | - | - |
| 1 P | 0:00:00 | 99 | 94 | 2:32(4) | - | - | - | - | 8 | - | - | - | - |
| 2 P | 0:00:00 | 100 | 96 | 0:56(1) | - | - | - | - | 2 | - | - | - | - |
| 3 P | 0:00:00 | 99 | 93 | 0:13(0) | - | - | - | - | 2 | - | - | - | - |
| 4 P | 0:02:00 | 99 | 97 | - | - | - | - | - | - | - | - | - | - |
| 5 P | 0:00:00 | 98 | 95 | 0:20(0) | - | - | - | - | 4 | - | - | - | - |
| 6 P | 0:02:41 | 99 | 90 | 1:44(2) | 0:02(0) | - | - | - | 6 | 1 | - | - | - |
| 7 P | 0:00:07 | 100 | 96 | - | - | - | - | - | - | - | - | - | - |
| 8 P | 0:00:00 | 98 | 94 | 0:25(0) | - | - | - | - | 3 | - | - | - | - |
| 9 P | 0:00:00 | 98 | 77 | 1:54(3) | 0:47(1) | 0:06(0) | - | - | 4 | 3 | 2 | - | - |
| 10 P | 0:03:16 | 96 | 69 | 13:26(19) | 6:00(8) | 3:22(5) | 1:41(2) | 0:16(0) | 48 | 26 | 13 | 8 | 4 |

**APPENDIX D 3: Post premedication raw oximetric data from Jones et al (1993b).**

## Post premedication - EVALUATED data, $F_IO_2$ 0.21

| | | | | | Time in saturation range (% total time) | | | | | Number of episodes (>15 sec) in saturation range | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pt. No. premed (P/M) | Operator time discounted (hr,min,sec) | total valid time (hr,min,sec) | mean $SpO_2$ (%) | lowest $SpO_2$ (%) | 90-95 (%) | 85-90 (%) | 80-85 (%) | 75-80 (%) | <75 (%) | 90-95 (%) | 85-90 (%) | 80-85 (%) | 75-80 (%) | <75 (%) |
| 1 M | 0:01:48 | 1:55:16 | 99 | 95 | 0:02(0) | - | - | - | - | - | - | - | - | - |
| 2 M | 0:00:20 | 1:52:58 | 100 | 96 | - | - | - | - | - | - | - | - | - | - |
| 3 M | 0:12:28 | 1:29:28 | 99 | 92 | 1:11(1) | - | - | - | - | 1 | - | - | - | - |
| 4 M | 0:00:00 | 2:14:27 | 100 | 96 | - | - | - | - | - | - | - | - | - | - |
| 5 M | 0:47:27 | 1:11:01 | 98 | 87 | 9:55(14) | 1:15(2) | - | - | - | 11 | 2 | - | - | - |
| 6 M | 0:21:04 | 1:46:23 | 98 | 91 | 6:34(6) | - | - | - | - | 7 | - | - | - | - |
| 7 M | 0:05:18 | 1:36:27 | 99 | 95 | 1:00(1) | - | - | - | - | - | - | - | - | - |
| 8 M | 0:07:24 | 1:52:03 | 97 | 92 | 3:34(3) | - | - | - | - | 4 | - | - | - | - |
| 9 M | 0:00:00 | 2:10:50 | 98 | 91 | 1:08(1) | - | - | - | - | 1 | - | - | - | - |
| 10 M | 0:00:00 | 1:50:57 | 99 | 95 | 0:04(0) | - | - | - | - | - | - | - | - | - |
| 1 P | 1:06:02 | 1:01:54 | 97 | 92 | 2:29(4) | - | - | - | - | 3 | - | - | - | - |
| 2 P | 0:13:06 | 1:23:45 | 99 | 94 | 0:56(1) | - | - | - | - | 1 | - | - | - | - |
| 3 P | 0:00:28 | 1:30:14 | 99 | 95 | 0:05(0) | - | - | - | - | - | - | - | - | - |
| 4 P | 0:30:00 | 1:51:07 | 99 | 97 | - | - | - | - | - | - | - | - | - | - |
| 5 P | 0:01:03 | 1:19:48 | 98 | 95 | 0:07(0) | - | - | - | - | - | - | - | - | - |
| 6 P | 0:02:49 | 1:22:28 | 99 | 96 | - | - | - | - | - | - | - | - | - | - |
| 7 P | 0:00:00 | 1:27:33 | 100 | 96 | - | - | - | - | - | - | - | - | - | - |
| 8 P | 0:00:14 | 1:27:13 | 98 | 95 | 0:14(0) | - | - | - | - | - | - | - | - | - |
| 9 P | 0:01:38 | 0:56:23 | 98 | 85 | 1:08(2) | 0:16(0) | 0:02(0) | - | - | 2 | - | - | - | - |
| 10 P | 0:35:03 | 0:37:33 | 99 | 91 | 3:21(9) | - | - | - | - | 5 | - | - | - | - |

**APPENDIX D 4: Post premedication oximetric data after templated evaluation from Jones et al (1993b).**

## Recovery room - RAW data, $F_IO_2$ 0.28 - 0.35

| | | | | Time in saturation range (% total time) | | | | | Number of episodes (>15 sec) in saturation range | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pt. No. premed (P/M) | Satmaster time discounted (hr,min,sec) | mean $SpO_2$ (%) | lowest $SpO_2$ (%) | 90-95 (%) | 85-90 (%) | 80-85 (%) | 75-80 (%) | <75 (%) | 90-95 (%) | 85-90 (%) | 80-85 (%) | 75-80 (%) | <75 (%) |
| 1 M | 0:00:29 | 99 | 82 | 0:26(1) | 2:26(6) | 0:28(1) | - | - | 2 | 4 | 2 | - | - |
| 2 M | 0:00:00 | 100 | 99 | - | - | - | - | - | - | - | - | - | - |
| 3 M | 0:00:00 | 100 | 98 | - | - | - | - | - | - | - | - | - | - |
| 4 M | 0:00:00 | 100 | 99 | - | - | - | - | - | - | - | - | - | - |
| 5 M | 0:01:14 | 100 | 93 | 0:31(2) | - | - | - | - | 3 | - | - | - | - |
| 6 M | 0:00:07 | 96 | 82 | 2:29(25) | 0:48(8) | 0:06(1) | - | - | 7 | 3 | 1 | - | - |
| 7 M | 0:00:00 | 99 | 90 | 1:31(8) | 0:03(0) | - | - | - | 3 | 1 | - | - | - |
| 8 M | 0:00:00 | 96 | 82 | 8:00(40) | 0:10(1) | 0:50(4) | - | - | 5 | 1 | 1 | - | - |
| 9 M | 0:00:00 | 99 | 91 | 1:10(6) | 0:05(0) | - | - | - | 4 | 1 | - | - | - |
| 10 M | 0:01:13 | 100 | 88 | 0:11(1) | 0:06(0) | 0:06(0) | 0:07(0) | - | 1 | 1 | 1 | 1 | - |
| 1 P | 0:00:00 | 99 | 80 | 0:19(1) | 0:09(1) | 0:15(1) | 0:13(1) | - | 2 | 1 | 1 | 1 | - |
| 2 P | 0:00:00 | 100 | 98 | - | - | - | - | - | - | - | - | - | - |
| 3 P | 0:00:00 | 98 | 92 | 1:44(5) | - | - | - | - | 4 | - | - | - | - |
| 4 P | 0:00:00 | 98 | 91 | 0:28(8) | - | - | - | - | 1 | - | - | - | - |
| 5 P | 0:00:00 | 99 | 89 | 1:16(7) | 0:07(1) | - | - | - | 5 | 1 | - | - | - |
| 6 P | 0:01:09 | 100 | 100 | - | - | - | - | - | - | - | - | - | - |
| 7 P | 0:00:00 | 100 | 97 | - | - | - | - | - | - | - | - | - | - |
| 8 P | 0:00:00 | 100 | 99 | - | - | - | - | - | - | - | - | - | - |
| 9 P | 0:00:00 | 98 | 88 | 0:27(3) | 0:29(3) | - | - | - | 1 | 3 | - | - | - |
| 10 P | 0:00:21 | 100 | 94 | 0:21(2) | - | - | - | - | 2 | - | - | - | - |

**APPENDIX D 5: Recovery room raw oximetric data from Jones et al (1993b).**

## Recovery room - EVALUATED data, $F_IO_2$ 0.28 - 0.35

| | | | | | Time in saturation range (% total time) | | | | | Number of episodes (>15 sec) in saturation range | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pt. No. premed (P/M) | Operator time discounted (hr,min,sec) | total valid time (hr,min,sec) | mean $SpO_2$ (%) | lowest $SpO_2$ (%) | 90-95 (%) | 85-90 (%) | 80-85 (%) | 75-80 (%) | <75 (%) | 90-95 (%) | 85-90 (%) | 80-85 (%) | 75-80 (%) | <75 (%) |
| 1 M | 0:00:10 | 0:37:51 | 99 | 80 | 0:18(1) | 2:26(6) | 0:49(2) | 0:01(0) | - | 1 | 2 | 1 | - | - |
| 2 M | 0:00:00 | 0:11:54 | 100 | 99 | - | - | - | - | - | - | - | - | - | - |
| 3 M | 0:00:00 | 0:41:31 | 100 | 98 | - | - | - | - | - | - | - | - | - | - |
| 4 M | 0:00:00 | 0:14:14 | 100 | 99 | - | - | - | - | - | - | - | - | - | - |
| 5 M | 0:03:52 | 0:29:52 | 100 | 98 | - | - | - | - | - | - | - | - | - | - |
| 6 M | 0:03:58 | 0:06:06 | 97 | 82 | 0:12(3) | - | 0:02(1) | - | - | - | - | - | - | - |
| 7 M | 0:02:32 | 0:15:26 | 99 | 96 | - | - | - | - | - | - | - | - | - | - |
| 8 M | 0:02:56 | 0:16:57 | 97 | 85 | 6:39(39) | - | 0:01(0) | - | - | 2 | - | - | - | - |
| 9 M | 0:32:57 | 0:17:45 | 99 | 95 | 0:50(5) | - | - | - | - | 1 | - | - | - | - |
| 10 M | 0:25:31 | 0:23:05 | 100 | 97 | - | - | - | - | - | - | - | - | - | - |
| 1 P | 0:00:00 | 0:21:50 | 99 | 80 | 0:19(1) | 0:09(1) | 0:15(1) | 0:13(1) | - | 1 | 1 | 1 | 1 | - |
| 2 P | 0:00:00 | 0:05:17 | 100 | 98 | - | - | - | - | - | - | - | - | - | - |
| 3 P | 0:02:15 | 0:30:31 | 98 | 92 | 0:25(1) | - | - | - | - | - | - | - | - | - |
| 4 P | 0:01:00 | 0:04:32 | 99 | 97 | - | - | - | - | - | - | - | - | - | - |
| 5 P | 0:01:40 | 0:16:48 | 99 | 95 | 0:09(1) | - | - | - | - | - | - | - | - | - |
| 6 P | 0:09:07 | 0:09:31 | 100 | 98 | - | - | - | - | - | - | - | - | - | - |
| 7 P | 0:12:34 | 0:20:30 | 100 | 100 | - | - | - | - | - | - | - | - | - | - |
| 8 P | 0:00:00 | 0:21:05 | 100 | 99 | - | - | - | - | - | - | - | - | - | - |
| 9 P | 0:00:58 | 0:12:54 | 99 | 96 | - | - | - | - | - | - | - | - | - | - |
| 10 P | 0:00:49 | 0:21:59 | 100 | 97 | - | - | - | - | - | - | - | - | - | - |

**APPENDIX D 6: Recovery room oximetric data after template evaluation from Jones et al (1993b).**

## Post operative ward - RAW data, $F_IO_2$ 0.21

| | | | | Time in saturation range (% total time) | | | | | Number of episodes (>15 sec) in saturation range | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pt. No. premed (P/M) | Satmaster time discounted (hr,min,sec) | mean $SpO_2$ (%) | lowest $SpO_2$ (%) | 90-95 (%) | 85-90 (%) | 80-85 (%) | 75-80 (%) | <75 (%) | 90-95 (%) | 85-90 (%) | 80-85 (%) | 75-80 (%) | <75 (%) |
| 1 M | 0:00:05 | 99 | 97 | - | - | - | - | - | - | - | - | - | - |
| 2 M | 0:04:35 | 99 | 85 | 8:26(2) | 1:19(0) | 0:02(0) | - | - | 31 | 4 | - | - | - |
| 3 M | 0:00:05 | 98 | 79 | 24:54(4) | 2:54(1) | 0:17(0) | 0:12(0) | - | 57 | 11 | 1 | 1 | - |
| 4 M | 0:00:11 | 99 | 87 | 6:11(1) | 1:28(0) | - | - | - | 18 | 1 | - | - | - |
| 5 M | 0:00:45 | 99 | 88 | 2:26(1) | 0:12(0) | - | - | - | 12 | 1 | - | - | - |
| 6 M | 0:42:06 | 97 | 81 | 28:19(12) | 4:44(2) | 1:43(1) | - | - | 14 | 2 | - | - | - |
| 7 M | 0:00:00 | 98 | 92 | 6:03(2) | - | - | - | - | 14 | - | - | - | - |
| 8 M | 0:00:00 | 97 | 89 | 13:05(4) | 0:41(0) | - | - | - | 38 | 4 | - | - | - |
| 9 M | 0:00:00 | 98 | 95 | 0:25(0) | - | - | - | - | 3 | - | - | - | - |
| 10 M | 0:00:00 | 98 | 88 | 2:35(1) | 0:08(0) | - | - | - | 12 | 1 | - | - | - |
| 1 P | 0:00:58 | 98 | 78 | 11:31(3) | 1:10(0) | 0:19(0) | 0:07(0) | - | 44 | 7 | 1 | 1 | - |
| 2 P | 0:22:17 | 99 | 92 | 1:17(0) | - | - | - | - | 8 | - | - | - | - |
| 3 P | 0:01:14 | 98 | 93 | 5:51(2) | - | - | - | - | 18 | - | - | - | - |
| 4 P | 0:07:54 | 100 | 88 | 15:57(3) | 4:09(1) | 2:18(0) | 0:30(0) | - | 54 | 18 | 5 | 4 | - |
| 5 P | 0:00:00 | 98 | 96 | - | - | - | - | - | - | - | - | - | - |
| 6 P | 0:05:46 | 99 | 84 | 55:32(15) | 20:29(4) | 6:24(1) | 0:41(0) | 0:09(0) | 168 | 52 | 22 | 3 | 1 |
| 7 P | 0:00:04 | 99 | 80 | 1:19(0) | 0:12(0) | 0:06(0) | 0:06(0) | - | 6 | 2 | 1 | 1 | - |
| 8 P | 0:00:00 | 99 | 84 | 7:07(1) | 0:37(0) | 0:05(0) | - | - | 20 | 5 | 1 | - | - |
| 9 P | 0:00:00 | 98 | 90 | 1:11(0) | 0:03(0) | - | - | - | 4 | 1 | - | - | - |
| 10 P | 0:11:06 | 98 | 72 | 8:25(2) | 1:17(1) | 0:38(0) | 0:19(0) | 0:07(0) | 25 | 2 | 1 | 1 | 1 |

**APPENDIX D 7: General postoperative ward raw oximetric data from Jones et al (1993b).**

## Post operative ward - EVALUATED data, $F_IO_2$ 0.21

| | | | | | Time in saturation range (% total time) | | | | | Number of episodes (>15 sec) in saturation range | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pt. No. premed (P/M) | Operator time discounted (hr,min,sec) | total valid time (hr,min,sec) | mean $SpO_2$ (%) | lowest $SpO_2$ (%) | 90-95 (%) | 85-90 (%) | 80-85 (%) | 75-80 (%) | <75 (%) | 90-95 (%) | 85-90 (%) | 80-85 (%) | 75-80 (%) | <75 (%) |
| 1 M | 0:01:42 | 8:34:06 | 99 | 97 | - | - | - | - | - | - | - | - | - | - |
| 2 M | 0:05:02 | 5:39:38 | 100 | 87 | 3:20(1) | 0:52(0) | - | - | - | 5 | 1 | - | - | - |
| 3 M | 0:13:14 | 9:12:20 | 98 | 79 | 12:30(2) | 2:13(0) | 0:17(0) | 0:12(0) | - | 17 | 4 | 1 | - | - |
| 4 M | 0:06:08 | 6:51:01 | 99 | 91 | 1:37(0) | - | - | - | - | 2 | - | - | - | - |
| 5 M | 0:08:04 | 7:15:48 | 99 | 95 | 0:22(0) | - | - | - | - | - | - | - | - | - |
| 6 M | 0:36:30 | 3:24:17 | 98 | 87 | 5:33(3) | 0:12(0) | - | - | - | 6 | - | - | - | - |
| 7 M | 0:18:16 | 3:48:39 | 98 | 95 | 0:19(0) | - | - | - | - | - | - | - | - | - |
| 8 M | 0:00:34 | 5:10:40 | 97 | 89 | 12:35(4) | 0:41(0) | - | - | - | 16 | - | - | - | - |
| 9 M | 0:00:00 | 7:17:28 | 98 | 95 | 0:25(0) | - | - | - | - | - | - | - | - | - |
| 10 M | 0:00:00 | 7:59:34 | 98 | 88 | 2:35(1) | 0:08(0) | - | - | - | 3 | - | - | - | - |
| 1 P | 0:10:08 | 5:34:18 | 98 | 90 | 6:16(2) | 0:29(0) | - | - | - | 5 | 1 | - | - | - |
| 2 P | 0:00:52 | 6:45:42 | 99 | 93 | 0:53(0) | - | - | - | - | 1 | - | - | - | - |
| 3 P | 0:04:36 | 7:12:13 | 98 | 93 | 3:39(1) | - | - | - | - | 4 | - | - | - | - |
| 4 P | 0:30:46 | 7:35:29 | 100 | 94 | 1:50(0) | - | - | - | - | 2 | | - | - | - |
| 5 P | 0:00:00 | 7:51:10 | 98 | 96 | - | - | - | - | - | - | - | - | - | - |
| 6 P | 1:27:12 | 6:26:00 | 98 | 90 | 15:43(4) | 0:08(0) | - | - | - | 15 | - | - | - | - |
| 7 P | 0:01:44 | 7:16:48 | 99 | 95 | 0:20(0) | - | - | - | - | - | - | - | - | - |
| 8 P | 0:03:12 | 8:51:32 | 99 | 84 | 5:07(1) | 0:11(0) | 0:05(0) | - | - | 8 | 1 | - | - | - |
| 9 P | 0:00:52 | 5:23:54 | 98 | 95 | 0:24(0) | - | - | - | - | 1 | - | - | - | - |
| 10 P | 0:12:54 | 7:33:06 | 98 | 94 | 2:10(0) | - | - | - | - | 2 | - | - | - | - |

**APPENDIX D 8: General ward oximetric data after template evaluation from Jones et al (1993b).**

| Patient number | Body weight (kg) | Age (yr) | Mood on arrival in theatre (*) | Heart rate (beats min$^{-1}$) after midazolam induction (min) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 0 | 2 | 4 | 6 | 8 | 10 | 15 | 20 | 30 |
| 1 | 18.70 | 6.0 | B | 77 | 106 | 111 | 116 | 114 | 113 | 115 | 113 | 104 |
| 2 | 16.00 | 5.0 | B | 154 | 110 | 126 | 107 | 108 | 110 | 108 | 107 | 101 |
| 3 | 20.00 | 6.0 | B | 92 | 107 | 138 | 129 | 120 | 120 | 147 | 141 | 122 |
| 4 | 20.00 | 6.0 | B | 99 | 117 | 129 | 122 | 128 | 132 | 132 | 99 | 88 |
| 5 | 32.00 | 8.5 | B | 90 | 93 | 148 | 130 | 100 | 96 | 99 | 102 | 79 |
| 6 | 38.50 | 9.0 | B | 124 | 93 | 134 | 112 | 108 | 111 | 104 | 113 | 92 |
| 7 | 14.00 | 5.0 | B | 122 | 131 | 156 | 125 | 110 | 108 | 129 | 104 | 101 |
| 8 | 24.00 | 7.0 | B | 97 | 120 | 113 | 107 | 102 | 96 | 84 | 76 | 79 |
| 9 | 20.00 | 8.0 | B | 113 | 110 | 115 | 113 | 107 | 108 | 105 | 105 | 104 |
| 10 | 17.00 | 5.0 | B | 109 | 94 | 88 | 79 | 81 | 72 | 77 | 75 | 88 |
| 11 | 25.00 | 7.5 | B | 81 | 94 | 109 | 100 | 98 | 101 | 105 | 78 | 87 |
| 12 | 19.00 | 5.0 | B | 79 | 112 | 119 | 118 | 111 | 109 | 112 | 101 | 101 |

**APPENDIX D 9: Heart rate data after midazolam induction from Jones et al (1993).**

(*) **A:** agitated, crying **B:** aware, apparently anxiety free **C:** drowsy **D:** asleep, responds to commands

| | Systolic Blood Pressure (mm Hg) after induction (min) | | | | | | | | | Diastolic Blood Pressure (mm Hg) after induction (min) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient number | 0 | 2 | 4 | 6 | 8 | 10 | 15 | 20 | 30 | 0 | 2 | 4 | 6 | 8 | 10 | 15 | 20 | 30 |
| 1 | 109 | 102 | 115 | 99 | 98 | 76 | 109 | 107 | 101 | 47 | 57 | 48 | 37 | 36 | 48 | 43 | 39 | 39 |
| 2 | 127 | 141 | 109 | 100 | 96 | 110 | 102 | 70 | 95 | 80 | 100 | 72 | 57 | 57 | 68 | 57 | 59 | 54 |
| 3 | 105 | 111 | 146 | 117 | 109 | 104 | 127 | 136 | 121 | 62 | 57 | 70 | 54 | 54 | 50 | 58 | 59 | 58 |
| 4 | 103 | 91 | 108 | 99 | 87 | 88 | 108 | 109 | 96 | 68 | 54 | 69 | 56 | 60 | 62 | 95 | 69 | 68 |
| 5 | 60 | 94 | 168 | 117 | 98 | 92 | 107 | 116 | 95 | 46 | 43 | 86 | 55 | 41 | 45 | 38 | 63 | 37 |
| 6 | 105 | 148 | 126 | 109 | 92 | 68 | 97 | 115 | 97 | 64 | 104 | 53 | 47 | 48 | 51 | 53 | 68 | 51 |
| 7 | 107 | 94 | 117 | 115 | 94 | 93 | 102 | 96 | 91 | 52 | 41 | 77 | 49 | 46 | 46 | 53 | 44 | 50 |
| 8 | 105 | 128 | 120 | 101 | 93 | 78 | 87 | 81 | 86 | 53 | 77 | 55 | 45 | 45 | 52 | 47 | 44 | 42 |
| 9 | 82 | 112 | 121 | 111 | 106 | 103 | 119 | 106 | 104 | 47 | 72 | 61 | 49 | 47 | 48 | 57 | 55 | 45 |
| 10 | 96 | 98 | 90 | 88 | 85 | 81 | 88 | 83 | 87 | 61 | 70 | 57 | 53 | 49 | 40 | 51 | 48 | 52 |
| 11 | 119 | 150 | 125 | 103 | 88 | 91 | 111 | 90 | 117 | 64 | 78 | 74 | 51 | 46 | 61 | 66 | 65 | 78 |
| 12 | 120 | 115 | 126 | 110 | 101 | 93 | 102 | 99 | 99 | 58 | 52 | 72 | 48 | 40 | 42 | 48 | 41 | 44 |

**APPENDIX D 10: Systolic and diastolic blood pressure data following midazolam induction from Jones et al (1993).**

| | Heart rate data (beats $min^{-1}$) after flumazenil (min) | | | | | | | | | Respiratory rate data (breaths $min^{-1}$) after flumazenil (min) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Patient number** | **0** | **2** | **4** | **6** | **8** | **10** | **15** | **20** | **30** | **0** | **2** | **4** | **6** | **8** | **10** | **15** | **20** | **30** |
| **1** | 81 | 113 | 113 | 108 | 93 | 90 | 72 | 75 | 82 | 24 | 24 | 24 | 24 | 24 | 20 | 20 | | |
| **2** | 97 | 114 | 114 | 124 | 106 | 78 | 92 | 92 | | 26 | 25 | 25 | 25 | 25 | 25 | 25 | | |
| **3** | 105 | 110 | 98 | | | | | | | 14 | 24 | | | | | | | |
| **4** | 88 | 104 | 90 | 65 | 68 | 66 | | | | 33 | 25 | 25 | 20 | | | | | |
| **5** | 94 | 70 | 75 | 83 | 78 | | | | | 20 | 25 | 25 | 25 | | | | | |
| **6** | 92 | 94 | 75 | 74 | 83 | 111 | 100 | 92 | | 11 | 20 | 20 | 20 | 22 | 22 | 20 | | |
| **7** | 68 | 105 | 78 | 82 | 79 | 72 | | | | 12 | 22 | 20 | 15 | | | | | |
| **8** | 79 | 79 | 79 | 79 | 79 | 79 | 82 | 79 | 77 | 9 | 9 | 9 | 9 | 9 | 9 | 18 | 18 | |
| **9** | 111 | 111 | 111 | 101 | 92 | 83 | 80 | 86 | 79 | 24 | 24 | 26 | 26 | 26 | 26 | 26 | | |
| **10** | 108 | 104 | 104 | 133 | | | | | | 24 | 24 | 24 | 24 | 24 | | | | |
| **11** | 72 | 83 | 71 | 83 | 74 | 85 | 105 | 78 | 107 | 9 | 15 | 15 | 15 | | | | | |
| **12** | 75 | 55 | 65 | 86 | 60 | 65 | 67 | 67 | 67 | 14 | 14 | 14 | 24 | 24 | 24 | | | |

**APPENDIX D 11: Heart rate and respiratory rate data during recovery room administration of flumazenil from Jones et al (1993).**

| | Systolic blood pressure (mm Hg) after flumazenil (min) | | | | | | | | | Diastolic blood pressure (mm Hg) after flumazenil (min) | | | | | | | | | Mean change from baseline values | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient number | 0 | 2 | 4 | 6 | 8 | 10 | 15 | 20 | 30 | 0 | 2 | 4 | 6 | 8 | 10 | 15 | 20 | 30 | heart rate | systolic press. | resp. rate |
| 1 | 92 | 103 | 120 | 126 | 106 | 112 | 106 | 114 | 99 | 36 | 46 | 64 | 50 | 54 | 60 | 54 | 80 | 52 | 32 | 11 | 0.0 |
| 2 | 104 | 96 | 96 | 96 | 94 | 94 | 106 | 106 | | 61 | 61 | 49 | 49 | 45 | 45 | 46 | 47 | | 17 | -8 | -1 |
| 3 | 119 | 136 | 136 | | | | | | | 61 | 75 | 62 | | | | | | | 5 | 17 | 10 |
| 4 | 96 | 149 | 132 | 112 | 120 | 107 | | | | 68 | 79 | 51 | 61 | 71 | 55 | | | | 16 | 53 | -8 |
| 5 | 106 | 113 | 125 | 100 | 118 | | | | | 78 | 62 | 81 | 79 | 73 | | | | | -24 | 7 | 5 |
| 6 | 114 | 128 | 128 | 115 | 111 | 120 | 117 | 117 | | 51 | 62 | 56 | 78 | 62 | 69 | 94 | 68 | | 2 | 14 | 9 |
| 7 | 91 | 89 | 91 | 91 | 129 | 127 | 132 | 114 | | 50 | 42 | 52 | 50 | 64 | 54 | 46 | 57 | | 37 | 38 | 10 |
| 8 | 86 | 90 | 101 | | | | | | | 42 | 49 | 48 | | | | | | | 3 | 4 | 9 |
| 9 | 111 | 111 | 108 | 106 | 109 | 106 | 122 | 123 | | 54 | 49 | 49 | 45 | 43 | 43 | 53 | 60 | | -10 | -3 | 2 |
| 10 | 94 | 98 | 98 | 111 | | | | | | 56 | 40 | 48 | 74 | | | | | | -4 | 4 | 0 |
| 11 | 123 | 129 | 131 | 114 | 128 | 116 | 107 | 136 | 95 | 56 | 64 | 59 | 52 | 56 | 71 | 67 | 47 | 63 | 11 | 6 | 6 |
| 12 | 114 | 114 | 114 | 109 | 117 | 112 | 125 | | | 43 | 47 | 43 | 66 | 47 | 44 | 45 | | | 11 | -5 | 10 |

**APPENDIX D 12: Blood pressure data following flumazenil administration from Jones et al (1993).**

| | Systolic blood pressure (mm Hg) during induction (min) | | | | | | Diastolic blood pressure (mm Hg) during induction (min) | | | | | | Heart rate (beats $min^{-1}$) during induction (min) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient number | pre-induction | 1 | 2 | 5 | 15 | 30 | pre-induction | 1 | 2 | 5 | 15 | 30 | pre-induction | 1 | 2 | 5 | 15 | 30 |
| 1 | 102 | 110 | 94 | 86 | 102 | 94 | 77 | 68 | 60 | 59 | 65 | 55 | 107 | 104 | 106 | 122 | 109 | 100 |
| 4 | 110 | 104 | 94 | 81 | 95 | | 81 | 64 | 58 | 60 | 60 | | 83 | 118 | 95 | 99 | 99 | 103 |
| 7 | 142 | 108 | 130 | 98 | 119 | 124 | 89 | 77 | 80 | 69 | 67 | 65 | 111 | 123 | 124 | 87 | 99 | 107 |
| 8 | 114 | 110 | 95 | 101 | 101 | 102 | 87 | 57 | 54 | 64 | 61 | 55 | 114 | 95 | 92 | 105 | 91 | 98 |
| 9 | 107 | 97 | 87 | 92 | 93 | 91 | 79 | 65 | 49 | 51 | 54 | 56 | 127 | 107 | 104 | 113 | 95 | 100 |
| 10 | 89 | 88 | 83 | 89 | 99 | | 66 | 58 | 52 | 59 | 66 | | 103 | 115 | 118 | 132 | 125 | |
| 14 | 105 | 102 | 93 | 87 | 88 | 87 | 60 | 72 | 55 | 54 | 55 | 52 | 107 | 126 | 109 | 112 | 106 | 106 |
| 16 | 110 | 108 | 107 | 95 | 91 | | 72 | 78 | 70 | 54 | 61 | | 81 | 90 | 112 | 89 | 87 | |
| 18 | 121 | 110 | 96 | 84 | 104 | 95 | 77 | 72 | 50 | 43 | 57 | 55 | 131 | 124 | 109 | 101 | 122 | 106 |
| 20 | 111 | 111 | 106 | 85 | 94 | 90 | 88 | 88 | 71 | 57 | 59 | 49 | 106 | 124 | 115 | 104 | 108 | 104 |
| 23 | 100 | 110 | 98 | 89 | 98 | | 71 | 82 | 60 | 53 | 60 | | 95 | 118 | 115 | 87 | 109 | |
| 24 | 96 | 92 | 92 | 73 | 106 | | 72 | 65 | 65 | 49 | 68 | | 98 | 114 | 123 | 95 | 125 | |
| 25 | 130 | 121 | 84 | 89 | 113 | 104 | 89 | 74 | 82 | 35 | 60 | 92 | 65 | 74 | 77 | 56 | 124 | 115 |
| 26 | 111 | 109 | 102 | 92 | 90 | | 65 | 65 | 67 | 60 | 60 | | 79 | 84 | 93 | 104 | 95 | |
| 29 | 116 | 111 | 105 | 77 | 100 | 96 | 56 | 65 | 50 | 38 | 49 | 49 | 125 | 123 | 122 | 74 | 84 | 88 |
| 31 | 119 | 119 | 99 | 67 | 93 | 94 | 65 | 64 | 56 | 37 | 49 | 47 | 176 | 107 | 121 | 93 | 100 | 103 |
| 33 | 124 | 94 | 125 | 92 | 88 | | 85 | 61 | 91 | 50 | 47 | | 148 | 134 | 141 | 116 | 120 | |
| 34 | 109 | 96 | 99 | 94 | 108 | 112 | 81 | 67 | 70 | 56 | 67 | 69 | 92 | 114 | 100 | 90 | 102 | 108 |
| 38 | 156 | 117 | 106 | 107 | 95 | 104 | 82 | 55 | 61 | 55 | 41 | 41 | 140 | 194 | 138 | 142 | 120 | 133 |
| 39 | 101 | 102 | 100 | 116 | 102 | 100 | 51 | 68 | 58 | 70 | 55 | 58 | 91 | 94 | 119 | 120 | 102 | 113 |

**APPENDIX D 13: Induction haemodynamic data in the flumazenil group from Jones et al (1991).**

| | Respiratory rate (breaths $min^{-1}$) during induction (min) | | | | | | End tidal carbon dioxide (mm Hg) during induction | | | | | | Maximum change in paramters during induction | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient number | pre-induction | 1 | 2 | 5 | 15 | 30 | pre-induct.ion | 1 | 2 | 5 | 15 | 30 | RR | SBP | HR | mean $E_TCO_2$ |
| 1 | 35 | 26 | 26 | 35 | 31 | 27 | | | 49 | 44 | 53 | 56 | 0 | 8 | 15 | 50 |
| 4 | 30 | | 34 | 32 | 35 | 30 | | 60 | 60 | 65 | 63 | 57 | 5 | -29 | 35 | 62 |
| 7 | 28 | 44 | 44 | 57 | 55 | 60 | | | 50 | 49 | 59 | 56 | 32 | -44 | 12 | 54 |
| 8 | 34 | 29 | 41 | 47 | 53 | 44 | | | 42 | 46 | 52 | 51 | 19 | -19 | 23 | 48 |
| 9 | | 32 | 32 | 41 | 42 | 39 | | 48 | 50 | 48 | 54 | 37 | | -20 | -27 | 47 |
| 10 | | | 29 | 58 | 49 | | | | 43 | 47 | 66 | | | 10 | 29 | 52 |
| 14 | | 20 | 28 | 32 | 35 | 32 | | | 47 | 47 | 54 | 56 | | 18 | 19 | 51 |
| 16 | 24 | 18 | 20 | 20 | 44 | | | | | 46 | 48 | | 20 | 19 | 31 | 47 |
| 18 | 24 | 32 | 29 | 29 | 36 | 35 | | 47 | 52 | 54 | 53 | 70 | 12 | -37 | 30 | 46 |
| 20 | | | | 19 | 36 | 28 | | | | 48 | 59 | 58 | | 26 | 18 | 55 |
| 23 | 28 | | >60 | >60 | >60 | >60 | | | 45 | 32 | 60 | | 32 | 10 | 23 | 46 |
| 24 | 24 | | 40 | 42 | 57 | | | | 54 | 50 | 57 | | 33 | 10 | 27 | 54 |
| 25 | | | | 37 | 38 | 40 | | | | 52 | 63 | 68 | | 46 | 59 | 61 |
| 26 | | | 39 | 46 | 34 | | | | 45 | 49 | 49 | | | 21 | 25 | 48 |
| 29 | 28 | | 24 | 31 | 30 | 34 | | | 30 | 42 | 52 | 56 | 6 | -20 | -51 | 45 |
| 31 | | 39 | 39 | 24 | 35 | 37 | | 46 | 46 | 46 | 51 | 49 | | | -83 | 48 |
| 33 | | | 43 | 21 | 39 | | | | 38 | 39 | 47 | | | 1 | -32 | 41 |
| 34 | 24 | | 32 | 37 | 35 | 31 | | | 47 | 53 | 58 | 55 | 13 | 3 | 22 | 53 |
| 38 | 36 | 29 | | 33 | 46 | 49 | | | 47 | 37 | 43 | 46 | 13 | -61 | 54 | 46 |
| 39 | 24 | 23 | 42 | 64 | 49 | 43 | | 44 | 44 | 39 | 48 | 63 | -40 | 15 | -72 | 44 |

**APPENDIX D 14: Induction respiratory data in the flumazenil group from Jones et al (1991).**

RR = respiratory rate (breaths $min^{-1}$); SBP = systolic blood pressure (mm Hg); HR = heart rate (beats $min^{-1}$); $E_TCO_2$= end-tidal carbon dioxide tension (mm Hg)

| | Respiratory rate (breaths min$^{-1}$) after flumazenil (min) | | | | | | Heart rate (beats min$^{-1}$) after flumazenil (min) | | | | | | Maximum change in parameters after flumazenil | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient number | pre-flumazenil | 2 | 5 | 10 | 30 | 60 | pre-flumazenil | 2 | 5 | 10 | 30 | 60 | RR | SBP | HR |
| 1 | 20 | | | 16 | 18 | 18 | 93 | 77 | 104 | 90 | 83 | | -4 | 20 | 11 |
| 4 | | | | | | | 97 | 92 | 94 | 107 | 98 | 100 | | 23 | 10 |
| 7 | | | | | | | 105 | 83 | 147 | 101 | 85 | 90 | | 24 | 42 |
| 8 | | | | | | | 86 | 66 | 75 | 60 | 84 | 82 | | 20 | 4 |
| 9 | | | | | | | 97 | 84 | 78 | 84 | 75 | 73 | | 15 | -25 |
| 10 | | | | | | | 138 | 125 | 120 | 94 | 113 | 120 | | 7 | -44 |
| 14 | 22 | | | 24 | 22 | | 81 | 65 | 97 | 96 | 97 | 74 | | 4 | 66 |
| 16 | | | | 24 | 24 | 22 | 72 | 65 | 64 | 70 | 64 | 60 | | 20 | 8 |
| 18 | 18 | | 24 | 24 | 24 | 24 | 94 | 113 | 113 | 102 | 108 | 108 | | 25 | 16 |
| 20 | 18 | 20 | 20 | 24 | 24 | 20 | 94 | 111 | 78 | 78 | 86 | 102 | 2 | 22 | 17 |
| 23 | | | | | | | 102 | 89 | 81 | 125 | 104 | 100 | | 11 | 21 |
| 24 | 36 | | | 30 | | | 93 | 79 | 84 | 86 | 84 | 88 | | 13 | 14 |
| 25 | | | | | | | 111 | 136 | 136 | 122 | 96 | 92 | | -7 | 25 |
| 26 | | | | | | | 92 | 68 | 150 | 72 | | 108 | | 13 | 58 |
| 29 | 28 | | | 24 | 20 | | 82 | 65 | 65 | 64 | 94 | 80 | | -3 | -17 |
| 31 | | | | | | | 98 | 88 | 61 | | | | | 35 | -37 |
| 33 | 19 | 19 | 19 | 24 | 18 | 22 | 113 | 113 | 98 | 94 | 98 | 102 | 0 | 0 | -5 |
| 34 | 24 | 20 | 20 | 24 | 20 | 18 | 97 | 82 | 73 | 100 | 89 | 90 | -4 | 7 | -24 |
| 38 | 24 | 24 | 24 | | | | 121 | 122 | 122 | 163 | | | 0 | -11 | 0 |
| 39 | 32 | | | | | | 108 | 88 | 83 | | | | | -9 | -25 |

**APPENDIX D 15: Patient cardio-respiratory data following flumazenil administration from Jones et al (1991).**

RR = respiratory rate (breaths min$^{-1}$) SBP = systolic blood pressure (mm Hg) HR = heart rate (beats min$^{-1}$)

| Patient number | Systolic blood pressure (mm Hg) after flumazenil (min) | | | | | | Diastolic blood pressure (mm Hg) after flumazenil (min) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | pre-flumazenil | 2 | 5 | 10 | 30 | 60 | pre-flumazenil | 2 | 5 | 10 | 30 | 60 |
| 1 | 88 | 82 | 108 | 99 | 101 | | 81 | 59 | 57 | 54 | 59 | |
| 4 | 98 | 94 | 99 | 107 | 121 | 110 | 65 | 65 | 76 | 82 | 84 | 80 |
| 7 | 122 | 138 | 146 | 146 | 135 | 120 | 59 | 63 | 81 | 87 | 73 | 70 |
| 8 | 103 | 108 | 123 | 114 | 110 | 110 | 65 | 67 | 90 | 69 | 70 | 70 |
| 9 | 95 | 90 | 96 | 106 | 100 | 103 | 54 | 52 | 63 | 63 | 58 | 54 |
| 10 | 88 | 84 | 95 | 92 | 85 | 90 | 51 | 56 | 68 | 76 | 68 | 70 |
| 14 | 81 | 74 | 85 | 96 | 96 | 98 | 52 | 35 | 47 | 58 | 58 | 41 |
| 16 | 110 | 111 | 130 | 124 | 116 | 100 | 73 | 82 | 73 | 92 | 82 | 60 |
| 18 | 87 | 93 | 112 | 113 | 120 | 120 | 44 | 54 | 52 | 76 | 90 | 90 |
| 20 | 87 | 109 | 94 | 94 | 108 | 110 | 51 | 71 | 59 | 59 | 62 | 72 |
| 23 | 93 | 82 | 88 | 101 | 110 | 110 | 43 | 46 | 50 | 59 | 70 | 70 |
| 24 | 95 | 82 | 86 | 106 | 110 | 104 | 49 | 47 | 58 | 76 | 86 | 76 |
| 25 | 101 | 104 | 94 | 111 | | | 44 | 48 | 60 | | | |
| 26 | 96 | 95 | 109 | 107 | | 100 | 54 | 54 | 71 | 69 | | 70 |
| 29 | 82 | 79 | 79 | 74 | 100 | 110 | 43 | 35 | 35 | 38 | 56 | 60 |
| 31 | 81 | 90 | 125 | | | | 48 | 47 | 83 | | | |
| 33 | 83 | 83 | 83 | 81 | 79 | | 35 | 35 | 38 | 32 | 41 | |
| 34 | 102 | 101 | 109 | 130 | 113 | 99 | 58 | 58 | 58 | 88 | 77 | 78 |
| 38 | 91 | 88 | 88 | 82 | | | 41 | 41 | 41 | 68 | | |
| 39 | 100 | 91 | 96 | | | | 49 | 47 | 49 | | | |

**APPENDIX D 16: Haemodynamic data after flumazenil administration from Jones et al (1991).**

| | Systolic blood pressure (mm Hg) during induction (min) | | | | | | Diastolic blood pressure (mm Hg) during induction (min) | | | | | | Heart rate (beats min$^{-1}$) during induction (min) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient number | pre-iinduction | 1 | 2 | 5 | 15 | 30 | pre-induction | 1 | 2 | 5 | 15 | 30 | pre-induction | 1 | 2 | 5 | 15 | 30 |
| 2 | 93 | 108 | 95 | 83 | 98 | | 41 | 41 | 40 | 35 | 41 | | 133 | 133 | 133 | 129 | 123 | |
| 3 | 108 | 105 | 95 | 94 | 116 | | 60 | 60 | 45 | 41 | 48 | | 97 | 104 | 91 | 117 | 133 | |
| 5 | 115 | 134 | 126 | 120 | 122 | 93 | 67 | 113 | 90 | 97 | 62 | 48 | 121 | 116 | 147 | 149 | 116 | 126 |
| 6 | 100 | 92 | 89 | 79 | 109 | 107 | 65 | 67 | 60 | 36 | 66 | 53 | 96 | 118 | 120 | 124 | 111 | 116 |
| 11 | 97 | 91 | 83 | 72 | 87 | | 58 | 61 | 55 | 44 | 58 | | 101 | 93 | 103 | 92 | 109 | |
| 12 | 102 | 109 | 129 | 71 | 96 | | 65 | 79 | 98 | 37 | 60 | | 93 | 86 | 100 | 91 | 97 | |
| 13 | 108 | 100 | 98 | 73 | 91 | | 68 | 64 | 69 | 43 | 59 | | 98 | 101 | 113 | 98 | 104 | |
| 15 | 112 | 112 | 87 | 82 | 99 | 87 | 56 | 48 | 44 | 46 | 49 | 47 | 89 | 88 | 84 | 86 | 82 | 72 |
| 17 | 102 | 109 | 101 | 91 | 92 | 91 | 77 | 77 | 57 | 50 | 65 | 59 | 136 | 148 | 110 | 122 | 125 | 130 |
| 19 | 105 | 105 | 105 | 105 | 98 | 101 | 79 | 79 | 79 | 79 | 58 | 64 | 110 | 150 | 140 | 102 | 120 | 116 |
| 21 | 104 | 90 | 90 | 90 | 90 | 93 | 66 | 65 | 54 | 54 | 58 | 52 | 114 | 103 | 130 | 111 | 124 | 141 |
| 22 | 113 | 127 | 121 | 121 | 103 | | 68 | 66 | 70 | 70 | 67 | | 80 | 96 | 89 | 78 | 81 | |
| 27 | 115 | 112 | 95 | 94 | 98 | 94 | 76 | 74 | 59 | 55 | 46 | 46 | 109 | 105 | 108 | 96 | 105 | 101 |
| 28 | 104 | 110 | 103 | 98 | 95 | 100 | 69 | 71 | 64 | 53 | 48 | 45 | 97 | 121 | 124 | 103 | 105 | 107 |
| 30 | 93 | 94 | 90 | 84 | 95 | | 57 | 65 | 53 | 55 | 60 | | 94 | 90 | 98 | 117 | 115 | |
| 32 | 106 | 111 | 105 | 94 | 91 | | 63 | 71 | 72 | 53 | 41 | | 89 | 113 | 103 | 97 | 103 | |
| 35 | 129 | 109 | 106 | 103 | 114 | | 75 | 73 | 49 | 49 | 63 | | 107 | 149 | 108 | 121 | 139 | |
| 36 | 100 | 98 | 105 | 93 | 96 | | 65 | 72 | 64 | 56 | 53 | | 85 | 102 | 119 | 89 | 108 | |
| 37 | 104 | 90 | 85 | 99 | 96 | | 57 | 37 | 40 | 52 | 56 | | 100 | 84 | 74 | 94 | 99 | |
| 40 | 130 | 122 | 113 | 82 | 111 | 113 | 91 | 80 | 47 | 49 | 69 | 63 | 141 | 137 | 141 | 126 | 125 | 129 |

**APPENDIX D 17: Induction haemodynamic data in the placebo group from Jones et al (1991).**

| | Respiratory rate (breaths $min^{-1}$) during induction (min) | | | | | | End-tidal carbon dioxide tension (mm Hg) during induction (min) | | | | | | Maximum change in parameters during induction | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient number | pre-induction | 1 | 2 | 5 | 15 | 30 | pre-induction | 1 | 2 | 5 | 15 | 30 | RR | SBP | HR | mean $E_TCO_2$ |
| 2 | | | 48 | 41 | 43 | | | | 57 | 50 | 59 | | | 15 | -10 | 55 |
| 3 | 24 | 32 | 28 | 28 | 40 | | | 48 | 50 | 52 | 50 | | 16 | 8 | 36 | 50 |
| 5 | | 28 | 33 | 33 | 43 | 41 | | 49 | 47 | 48 | 69 | 72 | | 19 | 28 | 59 |
| 6 | 30 | 39 | 35 | 37 | 48 | 47 | | 40 | 40 | 39 | 63 | 64 | 18 | 7 | 28 | 49 |
| 11 | 24 | 32 | 44 | 53 | 49 | | | | 50 | 54 | 63 | | 29 | -25 | 8 | 56 |
| 12 | | | 29 | 38 | 40 | | | | 55 | 57 | 64 | | | 27 | 4 | 59 |
| 13 | | 24 | 22 | 32 | 44 | | | 44 | 45 | 50 | 61 | | | 35 | 15 | 50 |
| 15 | 24 | 28 | 34 | 41 | 51 | | | | 42 | 49 | 51 | | 27 | 30 | 17 | 47 |
| 17 | 30 | | 39 | 48 | 44 | 42 | | | 43 | 48 | 54 | 59 | 18 | 7 | 12 | 51 |
| 19 | 20 | | | 55 | 55 | 60 | | | | 49 | 45 | 57 | 40 | | 40 | 50 |
| 21 | 24 | | 29 | 33 | 34 | 45 | | | 45 | 58 | 63 | 73 | 21 | -14 | 17 | 60 |
| 22 | 24 | | 30 | 30 | 48 | | | | 51 | 53 | 52 | | 24 | 10 | 16 | 52 |
| 27 | 24 | | 30 | 36 | 35 | 32 | | | 51 | 47 | 51 | 54 | 12 | 21 | 13 | 51 |
| 28 | | | 42 | 35 | 32 | 32 | | | 52 | 56 | 70 | 66 | | 6 | 27 | 61 |
| 30 | | | 27 | 40 | 35 | | | | 45 | 44 | 64 | | | 2 | 23 | 51 |
| 32 | 28 | | | 26 | 26 | | | | | 54 | 57 | | -2 | 5 | 24 | 56 |
| 35 | 28 | | 30 | 38 | 40 | | | | 46 | 49 | 51 | | 12 | -26 | 42 | 49 |
| 36 | 28 | | 31 | 35 | 48 | | | | 39 | 41 | 47 | | 20 | 5 | 34 | 42 |
| 37 | 32 | 27 | 28 | 28 | 35 | | | 41 | 45 | 46 | 55 | | 3 | 19 | -26 | 45 |
| 40 | 28 | 37 | 43 | 42 | 40 | 32 | | 37 | 39 | 47 | 55 | 52 | 15 | -48 | -16 | 46 |

**APPENDIX D 18: Induction respiratory data in the placebo group from Jones et al (1991).**

RR = respiratory rate (breaths $min^{-1}$); SBP = systolic blood pressure (mm Hg); HR = heart rate (beats $min^{-1}$); $E_TCO_2$= end-tidal carbon dioxide tension(mm Hg)

| | Respiratory rate (breaths min$^{-1}$) after placebo (min) | | | | | | Heart rate (beats min$^{-1}$) after placebo (min) | | | | | | Maximum change in parameters after placebo administration | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient number | pre-placebo | 2 | 5 | 10 | 30 | 60 | pre-placebo | 2 | 5 | 10 | 30 | 60 | RR | SBP | HR |
| 2 | | | 35 | 36 | 40 | | 115 | 111 | 110 | 108 | 102 | | | 4 | -13 |
| 3 | 32 | 34 | 34 | | 28 | | 101 | 92 | 91 | 88 | 87 | | 2 | -11 | -14 |
| 5 | | | | | | | 129 | 115 | 111 | 108 | 96 | 117 | | 13 | -45 |
| 6 | | | | | | | 117 | 125 | 93 | 85 | 78 | 80 | | 31 | -43 |
| 11 | | | | | | | 101 | 97 | 101 | 100 | 80 | 81 | | 4 | -4 |
| 12 | | | | | | | 92 | 101 | 89 | 86 | 87 | 68 | | 11 | 9 |
| 13 | | | | | | | 101 | 96 | 87 | 76 | 68 | 62 | | -7 | -14 |
| 15 | 28 | 28 | 28 | 28 | 26 | 24 | 63 | 66 | 65 | 74 | 83 | 78 | 0 | 6 | 3 |
| 17 | | 32 | 22 | 26 | 24 | 24 | 125 | 115 | 147 | 101 | 101 | 124 | | 24 | 22 |
| 19 | 36 | 36 | 36 | 26 | 26 | 24 | 122 | 122 | 122 | 120 | 120 | 108 | 0 | 1 | 0 |
| 21 | 24 | 24 | 24 | 28 | | 28 | 117 | 117 | 117 | 104 | 147 | 120 | 0 | | 0 |
| 22 | 28 | 24 | 24 | 24 | 24 | 24 | 73 | 79 | 79 | 70 | 72 | 70 | -4 | 3 | 6 |
| 27 | | | 24 | 24 | | 22 | 102 | 93 | 91 | 91 | 127 | 97 | | -4 | -11 |
| 28 | 24 | 24 | 24 | 24 | | | 94 | 90 | | 74 | 117 | 78 | 0 | 2 | -4 |
| 30 | 26 | | | | 20 | | 115 | 104 | 98 | 91 | 75 | 75 | | -4 | 17 |
| 32 | 26 | 26 | | | | 24 | 93 | 87 | 90 | 78 | 76 | 77 | 0 | -10 | -6 |
| 35 | 20 | 20 | 20 | 24 | 24 | 22 | 105 | 105 | 97 | 96 | 88 | 75 | 0 | -9 | -8 |
| 36 | | | | | | | 113 | 117 | 113 | 110 | 100 | | | -1 | 4 |
| 37 | | | 24 | 24 | 22 | 24 | 94 | 94 | 96 | 84 | 82 | 58 | | -7 | 2 |
| 40 | | | | | | | 129 | 120 | 128 | 120 | 102 | | | 4 | -9 |

**APPENDIX D 19: Cardio-respiratory data after placebo administration from Jones et al (1991).**

RR = respiratory rate (breaths min$^{-1}$) SBP = systolic blood pressure (mm Hg) HR = heart rate (beats min$^{-1}$)

| | Systolic blood pressure (mm Hg) after placebo (min) | | | | | | Diastolic blood pressure (mm Hg) after placebo (min) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient number | pre-placebo | 2 | 5 | 10 | 30 | 60 | pre-placebo | 2 | 5 | 10 | 30 | 60 |
| 2 | 77 | 80 | 81 | 79 | 80 | | 32 | 30 | 44 | 43 | 50 | |
| 3 | 87 | 83 | 78 | 80 | 76 | | 48 | 35 | 39 | 42 | 41 | |
| 5 | 93 | 87 | 87 | 87 | 86 | 104 | 53 | 44 | 44 | 46 | 48 | 70 |
| 6 | 86 | 117 | 105 | 103 | 103 | 95 | 35 | 47 | 51 | 49 | 53 | 64 |
| 11 | 68 | 66 | 72 | 73 | 71 | 70 | 33 | 30 | 39 | 38 | 36 | 37 |
| 12 | 93 | 98 | 104 | 83 | 109 | 88 | 48 | 59 | 59 | 61 | 66 | 44 |
| 12 | 82 | 79 | 75 | 67 | 75 | 55 | 47 | 42 | 39 | 41 | 37 | 45 |
| 15 | 93 | 95 | 99 | 98 | 101 | 88 | 43 | 47 | 43 | 41 | 49 | 42 |
| 17 | 89 | 87 | 113 | 109 | 98 | 100 | 62 | 47 | 58 | 62 | 59 | 60 |
| 19 | 81 | 82 | 81 | 85 | 125 | 120 | 31 | 33 | 35 | 35 | 71 | 76 |
| 21 | | 92 | 92 | 97 | 53 | 90 | | 51 | 51 | 62 | 46 | 50 |
| 22 | 93 | 96 | 96 | 90 | 110 | 110 | 40 | 42 | 42 | 46 | 60 | 70 |
| 27 | 87 | 81 | 83 | 83 | 142 | 112 | 51 | 42 | 41 | 41 | 63 | 72 |
| 28 | 85 | 87 | | 104 | 100 | 106 | 43 | 46 | | 49 | 51 | 43 |
| 30 | 85 | 81 | 85 | 88 | 84 | 85 | 49 | 40 | 47 | 53 | 46 | 50 |
| 32 | 81 | 77 | 81 | 86 | 85 | 112 | 31 | 33 | 35 | 58 | 33 | 69 |
| 35 | 101 | 101 | 92 | 99 | 85 | 117 | 51 | 51 | 49 | 46 | 43 | 68 |
| 36 | 83 | 82 | 82 | 76 | 82 | | 38 | 39 | 37 | 41 | 42 | |
| 37 | 88 | 88 | 81 | 87 | 84 | 85 | 47 | 47 | 54 | 55 | 58 | 58 |
| 40 | 98 | 102 | 98 | 102 | 102 | | | 44 | 45 | 45 | 45 | 45 |

**APPENDIX D 20: Haemodynamic data during placebo administration from Jones et al (1991).**

| Patient number | Induction agent | Time after induction (min) | | | | | | | | | | | Maximum change in first 6 min |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 4 | M | 128 | 109 | 106 | 105 | 106 | 106 | 90 | 110 | 115 | 115 | 121 | -38 |
| 7 | M | 105 | | 115 | 107 | 85 | 89 | 92 | 111 | 114 | 106 | 106 | -20 |
| 9 | M | 123 | 115 | 109 | 97 | 97 | 92 | 99 | 100 | 95 | 93 | 93 | -31 |
| 11 | M | 105 | 105 | 105 | 66 | 89 | 91 | 89 | 89 | 89 | 92 | 95 | -39 |
| 12 | M | 108 | 105 | 98 | 89 | 87 | 81 | | 72 | 95 | 97 | 92 | -27 |
| 14 | M | 103 | 108 | 113 | 96 | 78 | 87 | 87 | 107 | 98 | 105 | 105 | -25 |
| 19 | M | 110 | | 88 | 87 | 87 | 83 | 81 | | | | 103 | -29 |
| 20 | M | 118 | 104 | 95 | 93 | 85 | 78 | 90 | 108 | 97 | 101 | 114 | -40 |
| 23 | M | 110 | 116 | 106 | 93 | 95 | 112 | 98 | 94 | 96 | 103 | 95 | -17 |
| 26 | M | 95 | 88 | 95 | 110 | 93 | 90 | 97 | 91 | 111 | 123 | 105 | 15 |
| 2 | P | 105 | 132 | 108 | 101 | 91 | 84 | 86 | 92 | 88 | 86 | 95 | 27 |
| 5 | P | 119 | 88 | 83 | 82 | 82 | 84 | 90 | 93 | 88 | 87 | 84 | -37 |
| 6 | P | 127 | 90 | 88 | 91 | 89 | 85 | 92 | | 91 | 81 | 82 | -42 |
| 13 | P | 94 | 99 | 93 | 82 | 84 | 92 | 76 | 87 | 91 | 93 | 97 | -25 |
| 16 | P | 104 | 86 | 78 | 71 | | 68 | | 83 | 84 | 86 | 84 | -36 |
| 17 | P | 94 | | 81 | 80 | 75 | 74 | 79 | 89 | 88 | 89 | 91 | -20 |
| 18 | P | 103 | 103 | 93 | 78 | 78 | 78 | 85 | 85 | | | | -25 |
| 22 | P | 104 | 77 | 68 | 75 | 84 | 79 | 79 | 88 | 100 | 88 | 92 | -36 |
| 25 | P | 99 | 90 | 86 | 83 | 84 | 85 | 86 | | 89 | 98 | 96 | -16 |
| 30 | P | 114 | 115 | 98 | 81 | 82 | 89 | 67 | 86 | 94 | 93 | 106 | -47 |
| 1 | T | 94 | 109 | 111 | 120 | 108 | 103 | 105 | 103 | 92 | 90 | 92 | 26 |
| 3 | T | 99 | 99 | 99 | 86 | | 74 | 93 | 83 | 82 | 84 | 84 | -25 |
| 8 | T | 119 | 112 | 106 | 102 | 95 | 95 | 104 | 116 | 103 | 100 | 99 | -24 |
| 10 | T | 133 | 107 | 129 | 120 | 88 | 85 | 108 | 114 | 119 | 119 | 120 | -48 |
| 15 | T | 142 | 137 | | 116 | 103 | 86 | 101 | | 107 | 89 | 125 | -56 |
| 21 | T | 113 | 100 | 97 | 100 | 96 | 69 | 85 | 91 | 91 | 85 | 95 | -44 |
| 24 | T | 108 | 87 | 86 | 72 | 76 | 79 | | 79 | | 79 | 89 | -36 |
| 27 | T | 115 | 116 | 106 | 103 | 101 | 99 | 100 | 101 | 88 | 102 | 99 | -16 |
| 28 | T | 103 | 107 | 98 | 95 | 84 | 91 | 74 | 73 | 79 | 122 | 91 | -29 |
| 29 | T | 136 | 109 | 93 | 84 | 85 | 84 | 84 | 77 | 77 | 88 | 86 | -52 |

**APPENDIX D 21:** **Systolic blood pressure data (mm Hg) measured using the Cardiocap CM104™ during induction of anaesthesia with midazolam (M), propofol (P) and thiopentone (T) from Jones et al (1993d).**

| Patient number | Induction agent | Time after induction (min) 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Maximum change in first 6 min |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | M | 90 | 60 | 56 | 57 | 57 | 56 | 46 | 63 | 65 | 62 | 71 | -44 |
| 7 | M | 84 | | 75 | 62 | 49 | 52 | 56 | 80 | 71 | 65 | 65 | -35 |
| 9 | M | 79 | 63 | 67 | 57 | 52 | 63 | 63 | 58 | 57 | 53 | 54 | -27 |
| 11 | M | 66 | 75 | 62 | 36 | 58 | 48 | 53 | 48 | 51 | 51 | 55 | -30 |
| 12 | M | 75 | 62 | 64 | 53 | 53 | 46 | | 44 | 56 | 61 | 56 | -29 |
| 14 | M | 49 | 45 | 45 | 37 | 39 | 39 | 39 | 46 | 36 | 42 | 42 | -12 |
| 19 | M | 54 | | 49 | 43 | 48 | 34 | 36 | | | | 63 | -20 |
| 20 | M | 74 | 57 | 56 | 51 | 49 | 37 | 56 | 61 | 57 | 63 | 75 | -37 |
| 23 | M | 66 | 84 | 73 | 61 | 59 | 74 | 65 | 60 | 65 | 61 | 60 | 18 |
| 26 | M | 36 | 45 | 47 | 55 | 45 | 45 | 40 | 44 | 46 | 55 | 43 | 19 |
| 2 | P | 60 | 80 | 70 | 58 | 46 | 46 | 47 | 51 | 48 | 44 | 51 | 20 |
| 5 | P | 61 | 57 | 47 | 49 | 50 | 52 | 60 | 59 | 56 | 54 | 51 | -14 |
| 6 | P | 73 | 42 | 37 | 36 | 38 | 37 | 42 | | 37 | 36 | 37 | -37 |
| 13 | P | 55 | 45 | 42 | 40 | 39 | 38 | 53 | 42 | 43 | 39 | 43 | -17 |
| 16 | P | 70 | 41 | 38 | 41 | | 37 | | 48 | 48 | 47 | 48 | -33 |
| 17 | P | 55 | | 45 | 42 | 43 | 38 | 46 | 54 | 40 | 52 | 52 | -17 |
| 18 | P | 63 | 63 | 49 | 45 | 45 | 45 | 45 | 45 | | | | -18 |
| 22 | P | 56 | 46 | 46 | 43 | 43 | 44 | 44 | 59 | 57 | 56 | 58 | -13 |
| 25 | P | 59 | 51 | 46 | 44 | 48 | 44 | 47 | | 49 | 56 | 56 | -15 |
| 30 | P | 67 | 61 | 51 | 42 | 45 | 49 | 39 | 58 | 56 | 54 | 69 | -28 |
| 1 | T | 55 | 61 | 60 | 80 | 65 | 56 | 64 | 62 | 49 | 51 | 53 | 25 |
| 3 | T | 59 | 60 | 65 | 55 | | 39 | 48 | 50 | 47 | 48 | 51 | -20 |
| 8 | T | 81 | 72 | 67 | 61 | 54 | 55 | 93 | 100 | 62 | 60 | 61 | -27 |
| 10 | T | 78 | 41 | 72 | 63 | 45 | 38 | 58 | 52 | 54 | 52 | 57 | -40 |
| 15 | T | 58 | 52 | | 47 | 37 | 47 | 43 | | 50 | 50 | 42 | -21 |
| 21 | T | 62 | 54 | 56 | 47 | 41 | 39 | 45 | 41 | 46 | 38 | 45 | -23 |
| 24 | T | 68 | 47 | 53 | 44 | 37 | 40 | | 40 | | 40 | 48 | -28 |
| 27 | T | 73 | 72 | 64 | 56 | 54 | 55 | 76 | 58 | 55 | 52 | 59 | -19 |
| 28 | T | 76 | 56 | 49 | 48 | 51 | 42 | 38 | 37 | 41 | 90 | 48 | -38 |
| 29 | T | 68 | 61 | 55 | 47 | 42 | 45 | 44 | 46 | 47 | 34 | 50 | -26 |

**APPENDIX D 22:** **Diastolic blood pressure data (mm Hg) measured using the Cardiocap CM104™ during induction of anaesthesia with midazolam (M), propofol (P) and thiopentone (T) from Jones et al (1993d).**

| Patient number | Induction agent | Time after induction (min) | | | | | | | | | | | Maximum change in first 6 min |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 4 | M | 105 | 76 | 71 | 73 | 74 | 74 | 62 | 81 | 83 | 81 | 90 | -43 |
| 7 | M | 90 | | 85 | 75 | 60 | 62 | 63 | 93 | 84 | 77 | 77 | -30 |
| 9 | M | 94 | 80 | 81 | 70 | 67 | 73 | 75 | 72 | 70 | 66 | 67 | -27 |
| 11 | M | 79 | 85 | 76 | 46 | 68 | 62 | 65 | 62 | 64 | 65 | 68 | -33 |
| 12 | M | 85 | 75 | 75 | 65 | 63 | 57 | | 51 | 68 | 74 | 68 | -28 |
| 14 | M | 66 | 65 | 67 | 51 | 51 | 53 | 53 | 63 | 58 | 62 | 62 | -15 |
| 19 | M | 68 | | 60 | 55 | 57 | 49 | 50 | | | | 63 | -19 |
| 20 | M | 84 | 70 | 66 | 63 | 63 | 63 | 69 | 82 | 70 | 76 | 86 | -21 |
| 23 | M | 77 | 96 | 83 | 71 | 70 | 86 | 75 | 71 | 72 | 70 | 71 | 19 |
| 26 | M | 56 | 58 | 63 | 76 | 60 | 59 | 58 | 56 | 70 | 73 | 63 | 20 |
| 2 | P | 76 | 96 | 78 | 71 | 60 | 58 | 58 | 63 | 61 | 58 | 65 | 20 |
| 5 | P | 83 | 64 | 59 | 58 | 59 | 60 | 70 | 71 | 64 | 63 | 61 | -25 |
| 6 | P | 85 | 54 | 53 | 54 | 54 | 52 | 56 | | 55 | 50 | 51 | -33 |
| 13 | P | 67 | 62 | 58 | 53 | 53 | 55 | 61 | 56 | 58 | 56 | 60 | -14 |
| 16 | P | 78 | 58 | 53 | 50 | | 49 | | 61 | 61 | 61 | 61 | -29 |
| 17 | P | 66 | | 55 | 54 | 53 | 50 | 56 | 66 | 56 | 50 | 64 | -16 |
| 18 | P | 76 | 78 | 76 | 51 | 50 | 51 | 52 | 61 | | | | -26 |
| 22 | P | 71 | 53 | 51 | 50 | 54 | 53 | 53 | 65 | 69 | 64 | 67 | -21 |
| 25 | P | 69 | 61 | 56 | 55 | 57 | 58 | 57 | | 61 | 68 | 67 | -14 |
| 30 | P | 78 | 77 | 66 | 52 | 55 | 63 | 47 | 67 | 67 | 66 | 79 | -31 |
| 1 | T | 66 | 73 | 76 | 90 | 79 | 70 | 78 | 74 | 61 | 64 | 64 | 24 |
| 3 | T | 71 | 73 | 77 | 66 | | 50 | 58 | 62 | 59 | 60 | 62 | -21 |
| 8 | T | 95 | 85 | 80 | 74 | 69 | 69 | 68 | 71 | 77 | 74 | 74 | -27 |
| 10 | T | 96 | 63 | 91 | 82 | 59 | 54 | 75 | 73 | 76 | 74 | 78 | -42 |
| 15 | T | 85 | 81 | | 69 | 61 | 59 | 64 | | 68 | 62 | 74 | -26 |
| 21 | T | 73 | 65 | 65 | 62 | 57 | 48 | 58 | 55 | 58 | 57 | 59 | -25 |
| 24 | T | 77 | 58 | 63 | 50 | 47 | 55 | | 53 | | 53 | 60 | -30 |
| 27 | T | 87 | 88 | 77 | 73 | 70 | 66 | 86 | 71 | 59 | 68 | 70 | -21 |
| 28 | T | 84 | 68 | 59 | 59 | 61 | 54 | 49 | 45 | 51 | 102 | 56 | -36 |
| 29 | T | 83 | 80 | 65 | 56 | 55 | 56 | 58 | 55 | 57 | 52 | 59 | -28 |

**APPENDIX D 23:** **Mean blood pressure data (mm Hg) measured using the Cardiocap CM104™ during induction of anaesthesia with midazolam (M), propofol (P) and thiopentone (T) from Jones et al (1993d).**

| Patient number | Induction agent | Time after induction (min) | | | | | | | | | | | Maximum change in first 6 min |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| 4 | M | 123 | 112 | 90 | 95 | 94 | 95 | 93 | 110 | 111 | 109 | 117 | -33 |
| 7 | M | 94 | | 124 | 94 | 74 | 104 | 92 | 113 | 120 | 106 | 106 | 30 |
| 9 | M | 114 | 106 | 108 | 107 | 125 | 114 | 98 | 95 | 93 | 93 | 94 | -16 |
| 11 | M | 130 | 130 | 127 | 116 | 129 | 125 | 118 | 113 | 114 | 112 | 118 | -14 |
| 12 | M | 88 | 89 | 119 | 116 | 122 | 104 | | 89 | 114 | 106 | 105 | 34 |
| 14 | M | 105 | 129 | 107 | 105 | 99 | 107 | 109 | 109 | 113 | 110 | 107 | 24 |
| 19 | M | 73 | | 83 | 79 | 79 | 77 | 81 | | | | 94 | 10 |
| 20 | M | 112 | 114 | 107 | 111 | 115 | 114 | 152 | 134 | 123 | 120 | 153 | 40 |
| 23 | M | 81 | 122 | 126 | 120 | 119 | 109 | 136 | 133 | 127 | 117 | 114 | 55 |
| 26 | M | 89 | 105 | 128 | 131 | 103 | 105 | 104 | 107 | 112 | 137 | 139 | 42 |
| 2 | P | 78 | 98 | 106 | 108 | 97 | 81 | 95 | 85 | 91 | 86 | 96 | 30 |
| 5 | P | 129 | 120 | 123 | 125 | 125 | 126 | 129 | 139 | 129 | 127 | 124 | -9 |
| 6 | P | 108 | 90 | 89 | 91 | 87 | 86 | 86 | 86 | 83 | 86 | 88 | -22 |
| 13 | P | 91 | 94 | 94 | 87 | 85 | 88 | 87 | 97 | 93 | 95 | 93 | -6 |
| 16 | P | 112 | 113 | 111 | 107 | | 108 | | 104 | 104 | 105 | 103 | -5 |
| 17 | P | 87 | | 92 | 94 | 95 | 96 | 98 | 95 | 95 | 94 | 95 | 11 |
| 18 | P | 113 | 124 | 108 | 101 | 100 | 99 | 92 | 97 | | | | -21 |
| 22 | P | 93 | 87 | 89 | 81 | 78 | 69 | 81 | 85 | 84 | 78 | 89 | -24 |
| 25 | P | 75 | 96 | 89 | 87 | 82 | 85 | 85 | | 94 | 85 | 81 | 21 |
| 30 | P | 107 | 141 | 116 | 108 | 101 | 99 | 100 | 96 | 97 | 93 | 117 | 34 |
| 1 | T | 135 | 128 | 121 | 148 | 135 | 119 | 113 | 115 | 117 | 104 | 104 | -22 |
| 3 | T | 89 | 117 | 119 | 109 | 95 | 93 | 92 | 94 | 97 | 98 | 99 | 30 |
| 8 | T | 103 | 129 | 130 | 125 | 122 | 119 | 97 | 103 | 91 | 94 | 97 | 27 |
| 10 | T | 96 | 131 | 133 | 100 | 93 | 81 | 83 | 86 | 91 | 93 | 93 | 37 |
| 15 | T | 120 | 113 | 108 | 102 | 98 | 95 | 89 | | 96 | 95 | 95 | -31 |
| 21 | T | 83 | 105 | 103 | 105 | 98 | 91 | 86 | 82 | 84 | 89 | 91 | 22 |
| 24 | T | 91 | 99 | 97 | 89 | 84 | 78 | | 73 | | 78 | 80 | -13 |
| 27 | T | 110 | 129 | 113 | 99 | 86 | 82 | 83 | 78 | 83 | 83 | 81 | -28 |
| 28 | T | 106 | 113 | 119 | 121 | 115 | 109 | 99 | 87 | 88 | 92 | 92 | 15 |
| 29 | T | 166 | 140 | 111 | 97 | 89 | 93 | 98 | 121 | 101 | 118 | 106 | -77 |

**APPENDIX D 24:** **Heart rate data (beats $min^{-1}$) measured using the Cardiocap CM104™ during induction of anaesthesia with midazolam (M), propofol (P) and thiopentone (T) from Jones et al (1993d).**

## Finapres Haemodynamic Data - Midazolam Group - (n = 8)

| | SYSTOLIC BLOOD PRESSURE (mmHg) | | | DIASTOLIC BLOOD PRESSURE (mmHg) | | | MEAN BLOOD PRESSURE (mmHg) | | | HEART RATE (beats $min^{-1}$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TIME (sec) | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range |
| -120 | 102 | 40 | 35 - 164 | 72 | 25 | 29 -113 | 85 | 29 | 31 -133 | 92 | 20 | 67 - 123 |
| -110 | 101 | 41 | 34 - 167 | 69 | 27 | 29 -117 | 81 | 32 | 30 -134 | 100 | 20 | 70 - 128 |
| -100 | 105 | 29 | 71 - 148 | 72 | 20 | 52 -111 | 86 | 24 | 62 -131 | 98 | 19 | 70 - 134 |
| -90 | 109 | 32 | 62 - 169 | 74 | 22 | 53 -122 | 88 | 26 | 54 -141 | 97 | 17 | 67 - 126 |
| -80 | 106 | 33 | 62 - 168 | 74 | 22 | 55 -122 | 86 | 26 | 54 -141 | 96 | 18 | 64 - 128 |
| -70 | 113 | 33 | 74 - 180 | 78 | 21 | 56 -125 | 91 | 26 | 64 -146 | 98 | 17 | 69 - 124 |
| -60 | 114 | 27 | 87 - 168 | 81 | 17 | 55 -114 | 94 | 20 | 68 -137 | 102 | 14 | 78 - 126 |
| -50 | 113 | 28 | 85 - 166 | 80 | 17 | 59 -114 | 94 | 20 | 70 -131 | 101 | 13 | 83 - 121 |
| -40 | 117 | 26 | 89 - 169 | 82 | 18 | 54 -118 | 94 | 22 | 69 -139 | 103 | 15 | 85 - 133 |
| -30 | 116 | 27 | 90 - 171 | 81 | 18 | 55 -117 | 95 | 21 | 69 -139 | 100 | 16 | 76 - 125 |
| -20 | 116 | 26 | 92 - 165 | 79 | 18 | 55 -115 | 95 | 21 | 70 -137 | 99 | 16 | 72 - 125 |
| -10 | 118 | 24 | 93 - 164 | 82 | 17 | 61 -116 | 96 | 20 | 70 -137 | 105 | 15 | 86 - 131 |
| 0 | 115 | 19 | 89 - 146 | 83 | 16 | 60 -113 | 97 | 17 | 74 -130 | 99 | 18 | 73 - 129 |
| 10 | 116 | 28 | 84 - 170 | 83 | 20 | 60 -122 | 96 | 21 | 70 -138 | 102 | 12 | 84 - 115 |
| 20 | 120 | 39 | 63 - 192 | 82 | 27 | 38 -124 | 95 | 30 | 48 -150 | 101 | 21 | 72 - 141 |
| 30 | 104 | 23 | 63 - 132 | 73 | 21 | 38 - 94 | 88 | 23 | 47 -114 | 101 | 17 | 76 - 132 |
| 40 | 106 | 24 | 61 - 130 | 72 | 20 | 36 - 95 | 87 | 23 | 46 -118 | 101 | 11 | 87 - 117 |
| 50 | 100 | 24 | 53 - 128 | 68 | 18 | 33 - 88 | 82 | 22 | 38 -101 | 99 | 16 | 79 - 127 |
| 60 | 100 | 24 | 56 - 124 | 68 | 19 | 33 - 88 | 81 | 21 | 42 -106 | 102 | 22 | 65 - 140 |
| 70 | 106 | 32 | 55 - 162 | 72 | 23 | 33 -110 | 84 | 25 | 41 -121 | 93 | 11 | 70 - 107 |
| 80 | 101 | 21 | 57 - 122 | 71 | 19 | 34 - 92 | 80 | 18 | 42 -101 | 97 | 27 | 63 - 148 |
| 90 | 98 | 20 | 57 - 117 | 68 | 18 | 32 - 84 | 81 | 20 | 41 -101 | 102 | 21 | 70 - 133 |
| 100 | 95 | 22 | 52 - 116 | 67 | 21 | 30 - 94 | 77 | 21 | 38 -102 | 96 | 19 | 70 - 133 |
| 110 | 97 | 21 | 57 - 123 | 68 | 19 | 34 - 93 | 78 | 20 | 40 -107 | 102 | 21 | 74 - 129 |
| 120 | 102 | 12 | 83 - 115 | 73 | 14 | 53 - 94 | 85 | 16 | 64 -112 | 108 | 24 | 67 - 140 |
| 130 | 100 | 14 | 81 - 127 | 70 | 13 | 52 - 94 | 83 | 14 | 64 -111 | 108 | 21 | 75 - 142 |

| | SYSTOLIC BLOOD PRESSURE (mmHg) | | | DIASTOLIC BLOOD PRESSURE (mmHg) | | | MEAN BLOOD PRESSURE (mmHg) | | | HEART RATE (beats $min^{-1}$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TIME (sec) | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range |
| 140 | 102 | 16 | 82 - 134 | 72 | 14 | 54 -102 | 84 | 15 | 66 -117 | 108 | 25 | 60 - 143 |
| 150 | 100 | 14 | 82 - 125 | 71 | 12 | 52 - 94 | 83 | 12 | 66 -107 | 110 | 23 | 70 - 142 |
| 160 | 98 | 11 | 80 - 113 | 70 | 10 | 54 - 83 | 82 | 12 | 67 -104 | 112 | 23 | 75 - 143 |
| 170 | 96 | 12 | 80 - 113 | 69 | 11 | 50 - 83 | 80 | 10 | 63 - 93 | 112 | 21 | 85 - 144 |
| 180 | 95 | 12 | 76 - 113 | 68 | 12 | 48 - 84 | 79 | 11 | 59 - 93 | 110 | 19 | 86 - 145 |
| 190 | 96 | 17 | 74 - 131 | 70 | 17 | 47 -101 | 80 | 17 | 56 -115 | 108 | 19 | 91 - 145 |
| 200 | 98 | 19 | 72 - 135 | 70 | 17 | 46 -100 | 81 | 17 | 55 -113 | 110 | 17 | 96 - 143 |
| 210 | 100 | 24 | 71 - 153 | 74 | 23 | 46 -120 | 85 | 24 | 55 -136 | 112 | 19 | 90 - 142 |
| 220 | 98 | 21 | 69 - 142 | 73 | 19 | 46 -110 | 82 | 21 | 54 -127 | 110 | 24 | 65 - 139 |
| 230 | 94 | 14 | 68 - 112 | 70 | 13 | 47 - 90 | 80 | 13 | 54 - 96 | 114 | 15 | 96 - 137 |
| 240 | 96 | 20 | 72 - 139 | 71 | 19 | 48 -114 | 81 | 17 | 58 -117 | 115 | 19 | 95 - 141 |
| 250 | 94 | 18 | 72 - 128 | 69 | 16 | 48 -101 | 79 | 14 | 57 -107 | 112 | 20 | 86 - 145 |
| 260 | 96 | 25 | 70 - 152 | 71 | 22 | 46 -120 | 82 | 25 | 55 -139 | 109 | 19 | 82 - 138 |
| 270 | 98 | 29 | 68 - 163 | 72 | 24 | 44 -126 | 83 | 28 | 54 -147 | 110 | 16 | 92 - 136 |
| 280 | 99 | 27 | 66 - 158 | 72 | 21 | 42 -116 | 82 | 23 | 51 -132 | 110 | 18 | 84 - 132 |
| 290 | 98 | 26 | 65 - 154 | 72 | 20 | 42 -115 | 83 | 23 | 50 -131 | 111 | 16 | 88 - 132 |
| 300 | 97 | 23 | 63 - 143 | 71 | 19 | 41 -108 | 82 | 21 | 49 -124 | 109 | 17 | 88 - 133 |
| 310 | 96 | 29 | 62 - 160 | 71 | 23 | 41 -121 | 81 | 24 | 49 -134 | 107 | 19 | 76 - 136 |
| 320 | 95 | 29 | 63 - 158 | 70 | 22 | 42 -120 | 81 | 27 | 49 -141 | 107 | 18 | 77 - 134 |
| 330 | 95 | 32 | 62 - 165 | 71 | 27 | 41 -132 | 81 | 29 | 49 -146 | 108 | 20 | 75 - 132 |
| 340 | 93 | 34 | 61 - 167 | 68 | 28 | 40 -132 | 80 | 31 | 48 -151 | 106 | 17 | 80 - 133 |
| 350 | 91 | 33 | 53 - 160 | 68 | 30 | 35 -134 | 75 | 27 | 41 -130 | 98 | 16 | 70 - 127 |
| 360 | 93 | 23 | 63 - 140 | 70 | 21 | 41 -114 | 81 | 23 | 49 -131 | 108 | 17 | 82 - 129 |
| 370 | 96 | 32 | 64 - 170 | 70 | 26 | 42 -130 | 82 | 29 | 51 -149 | 105 | 18 | 74 - 125 |
| 380 | 97 | 33 | 63 - 169 | 72 | 26 | 42 -128 | 83 | 29 | 50 -147 | 103 | 18 | 74 - 126 |
| 390 | 97 | 32 | 65 - 166 | 72 | 25 | 44 -127 | 83 | 29 | 52 -146 | 100 | 18 | 68 - 122 |
| 400 | 97 | 31 | 65 - 165 | 72 | 26 | 43 -128 | 82 | 28 | 52 -144 | 105 | 18 | 75 - 127 |

| | SYSTOLIC BLOOD PRESSURE (mmHg) | | | DIASTOLIC BLOOD PRESSURE (mmHg) | | | MEAN BLOOD PRESSURE (mmHg) | | | HEART RATE (beats $min^{-1}$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TIME (sec) | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range |
| 410 | 98 | 31 | 66 - 157 | 74 | 23 | 43 -119 | 85 | 27 | 51 -136 | 103 | 20 | 71 - 125 |
| 420 | 99 | 33 | 61 - 160 | 74 | 25 | 43 -121 | 86 | 29 | 51 -140 | 102 | 20 | 65 - 127 |
| 430 | 98 | 32 | 59 - 155 | 73 | 23 | 43 -115 | 84 | 27 | 52 -133 | 104 | 20 | 67 - 133 |
| 440 | 97 | 32 | 58 - 153 | 72 | 23 | 43 -113 | 83 | 28 | 52 -133 | 103 | 22 | 66 - 136 |
| 450 | 99 | 33 | 60 - 157 | 74 | 24 | 44 -117 | 85 | 28 | 53 -136 | 105 | 21 | 70 - 138 |
| 460 | 99 | 31 | 62 - 155 | 74 | 24 | 44 -117 | 84 | 27 | 54 -134 | 106 | 22 | 69 - 138 |
| 470 | 99 | 32 | 60 - 156 | 74 | 23 | 49 -118 | 84 | 27 | 54 -135 | 108 | 19 | 72 - 136 |
| 480 | 101 | 33 | 62 - 163 | 75 | 25 | 51 -125 | 86 | 29 | 57 -143 | 108 | 19 | 73 - 136 |
| 490 | 101 | 31 | 64 - 161 | 75 | 24 | 53 -123 | 87 | 28 | 58 -142 | 108 | 19 | 72 - 135 |
| 500 | 101 | 31 | 66 - 161 | 75 | 23 | 55 -124 | 86 | 27 | 60 -141 | 109 | 19 | 72 - 135 |
| 510 | 103 | 33 | 66 - 169 | 76 | 25 | 53 -130 | 88 | 29 | 60 -148 | 107 | 20 | 70 - 135 |
| 520 | 101 | 33 | 60 - 167 | 75 | 26 | 48 -128 | 86 | 29 | 54 -147 | 107 | 20 | 69 - 134 |
| 530 | 91 | 17 | 64 - 110 | 65 | 11 | 51 - 79 | 77 | 13 | 58 - 93 | 105 | 21 | 69 - 133 |
| 540 | 104 | 38 | 64 - 183 | 75 | 30 | 51 -141 | 84 | 25 | 58 -136 | 105 | 19 | 69 - 132 |
| 550 | 99 | 33 | 61 - 165 | 73 | 25 | 49 -124 | 85 | 28 | 56 -142 | 107 | 21 | 69 - 134 |
| 560 | 99 | 31 | 62 - 160 | 71 | 24 | 46 -119 | 83 | 27 | 54 -138 | 107 | 20 | 72 - 133 |
| 570 | 100 | 31 | 67 - 164 | 73 | 24 | 49 -123 | 85 | 27 | 58 -142 | 108 | 21 | 70 - 132 |
| 580 | 100 | 29 | 69 - 161 | 72 | 22 | 51 -119 | 85 | 25 | 60 -138 | 107 | 21 | 69 - 132 |
| 590 | 102 | 28 | 71 - 158 | 73 | 21 | 52 -115 | 86 | 24 | 62 -135 | 107 | 20 | 67 - 132 |
| 600 | 102 | 29 | 71 - 159 | 72 | 21 | 52 -116 | 85 | 25 | 62 -136 | 108 | 21 | 67 - 133 |
| 610 | 102 | 29 | 71 - 159 | 73 | 21 | 52 -115 | 85 | 24 | 60 -134 | 108 | 21 | 68 - 133 |
| 620 | 102 | 27 | 72 - 153 | 73 | 20 | 52 -111 | 85 | 22 | 63 -128 | 110 | 22 | 69 - 134 |
| 630 | 102 | 27 | 74 - 156 | 73 | 20 | 53 -112 | 86 | 23 | 64 -131 | 109 | 21 | 70 - 132 |
| 640 | 101 | 26 | 73 - 153 | 72 | 20 | 53 -110 | 85 | 23 | 63 -130 | 108 | 21 | 69 - 133 |
| 650 | 101 | 25 | 73 - 149 | 72 | 19 | 52 -108 | 85 | 21 | 64 -125 | 110 | 22 | 71 - 133 |
| 660 | 102 | 27 | 75 - 155 | 73 | 21 | 52 -113 | 86 | 23 | 63 -131 | 110 | 22 | 71 - 134 |
| 670 | 102 | 28 | 75 - 157 | 73 | 22 | 51 -116 | 86 | 24 | 63 -134 | 111 | 24 | 70 - 136 |

| | SYSTOLIC BLOOD PRESSURE (mmHg) | | | DIASTOLIC BLOOD PRESSURE (mmHg) | | | MEAN BLOOD PRESSURE (mmHg) | | | HEART RATE (beats $min^{-1}$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TIME (sec) | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range |
| 680 | 102 | 29 | 71 - 158 | 73 | 23 | 50 -116 | 86 | 25 | 63 -135 | 112 | 25 | 71 - 137 |
| 690 | 103 | 30 | 72 - 160 | 73 | 23 | 50 -117 | 86 | 26 | 61 -136 | 112 | 22 | 76 - 138 |
| 700 | 103 | 27 | 75 - 156 | 74 | 21 | 50 -113 | 86 | 23 | 61 -131 | 114 | 20 | 85 - 138 |
| 710 | 102 | 24 | 75 - 147 | 74 | 20 | 50 -113 | 86 | 22 | 61 -129 | 110 | 20 | 80 - 136 |
| 720 | 104 | 27 | 75 - 156 | 74 | 21 | 49 -115 | 87 | 23 | 61 -133 | 112 | 19 | 84 - 136 |
| 730 | 105 | 27 | 75 - 156 | 74 | 20 | 49 -112 | 87 | 22 | 61 -129 | 113 | 18 | 87 - 133 |
| 740 | 105 | 26 | 75 - 155 | 74 | 19 | 49 -111 | 88 | 22 | 60 -130 | 111 | 17 | 88 - 132 |
| 750 | 103 | 25 | 75 - 151 | 73 | 18 | 49 -107 | 86 | 21 | 61 -126 | 112 | 17 | 95 - 135 |
| 760 | 103 | 26 | 77 - 154 | 73 | 19 | 51 -110 | 86 | 22 | 63 -128 | 112 | 16 | 91 - 133 |
| 770 | 103 | 25 | 74 - 151 | 73 | 19 | 51 -110 | 86 | 21 | 63 -127 | 114 | 13 | 99 - 133 |
| 780 | 104 | 25 | 79 - 155 | 75 | 19 | 53 -114 | 88 | 22 | 65 -132 | 113 | 14 | 95 - 133 |
| 790 | 105 | 26 | 80 - 158 | 74 | 21 | 54 -117 | 88 | 22 | 67 -135 | 113 | 14 | 95 - 133 |
| 800 | 103 | 27 | 76 - 158 | 74 | 20 | 55 -116 | 86 | 23 | 65 -133 | 114 | 12 | 102 - 133 |
| 810 | 104 | 28 | 77 - 162 | 74 | 22 | 55 -121 | 87 | 25 | 66 -139 | 113 | 15 | 92 - 132 |
| 820 | 104 | 28 | 77 - 162 | 74 | 22 | 54 -120 | 88 | 24 | 66 -138 | 112 | 17 | 82 - 132 |
| 830 | 105 | 28 | 82 - 164 | 74 | 23 | 52 -121 | 88 | 25 | 65 -140 | 111 | 16 | 86 - 132 |
| 840 | 104 | 27 | 81 - 162 | 73 | 22 | 52 -119 | 87 | 25 | 65 -139 | 113 | 13 | 100 - 132 |

**APPENDIX D 25: Haemodynamic data measured using the Finapres™ during induction of anaesthesia with midazolam from Jones et al (1993d)**

## Finapres Haemodynamic Data - Propofol Group - (n = 9)

| | SYSTOLIC BLOOD PRESSURE (mmHg) | | | DIASTOLIC BLOOD PRESSURE (mmHg) | | | MEAN BLOOD PRESSURE (mmHg) | | | HEART RATE (beats $min^{-1}$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TIME (sec) | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range |
| -120 | 114 | 44 | 47 -169 | 61 | 32 | 23 -105 | 78 | 37 | 26 -125 | 99 | 15 | 86 -116 |
| -110 | 119 | 37 | 71 -174 | 61 | 34 | 27 -108 | 81 | 36 | 40 -132 | 92 | 12 | 78 -108 |
| -100 | 113 | 44 | 47 -168 | 58 | 37 | 16 -107 | 75 | 42 | 26 -129 | 93 | 14 | 72 -111 |
| -90 | 118 | 29 | 83 -171 | 60 | 30 | 27 -105 | 78 | 34 | 31 -129 | 93 | 17 | 65 -114 |
| -80 | 110 | 41 | 46 -172 | 59 | 33 | 18 -106 | 76 | 37 | 29 -129 | 98 | 20 | 69 -128 |
| -70 | 120 | 29 | 89 -170 | 64 | 28 | 18 -102 | 83 | 30 | 37 -127 | 94 | 11 | 76 -105 |
| -60 | 109 | 28 | 59 -145 | 54 | 26 | 20 - 82 | 72 | 26 | 34 -101 | 94 | 10 | 78 -105 |
| -50 | 107 | 33 | 50 -150 | 54 | 28 | 16 - 89 | 71 | 31 | 26 -109 | 94 | 14 | 78 -110 |
| -40 | 110 | 29 | 60 -148 | 58 | 27 | 22 - 85 | 75 | 27 | 39 -105 | 91 | 9 | 80 -106 |
| -30 | 108 | 36 | 41 -149 | 56 | 29 | 14 - 86 | 74 | 31 | 26 -107 | 93 | 15 | 76 -110 |
| -20 | 121 | 16 | 96 -139 | 66 | 20 | 35 - 85 | 83 | 20 | 53 -105 | 99 | 16 | 78 -122 |
| -10 | 123 | 12 | 107 -139 | 69 | 18 | 34 - 85 | 87 | 18 | 54 -107 | 99 | 20 | 80 -135 |
| 0 | 115 | 21 | 80 -145 | 74 | 22 | 38 -108 | 91 | 25 | 59 -139 | 101 | 38 | 12 -133 |
| 10 | 103 | 26 | 70 -140 | 66 | 27 | 28 -107 | 82 | 28 | 49 -125 | 108 | 30 | 46 -143 |
| 20 | 96 | 36 | 56 -164 | 61 | 33 | 24 -129 | 74 | 34 | 28 -138 | 109 | 15 | 96 -140 |
| 30 | 95 | 36 | 47 -165 | 59 | 27 | 13 -107 | 72 | 31 | 24 -131 | 109 | 17 | 91 -133 |
| 40 | 94 | 35 | 42 -163 | 57 | 26 | 9 - 97 | 70 | 29 | 17 -119 | 103 | 10 | 85 -120 |
| 50 | 94 | 35 | 42 -146 | 58 | 27 | 9 - 91 | 71 | 29 | 17 -107 | 102 | 7 | 93 -114 |
| 60 | 93 | 32 | 49 -137 | 55 | 24 | 18 - 80 | 69 | 27 | 30 - 99 | 99 | 10 | 86 -114 |
| 70 | 88 | 31 | 39 -134 | 55 | 23 | 16 - 84 | 66 | 26 | 28 -103 | 98 | 10 | 82 -116 |
| 80 | 84 | 33 | 39 -131 | 56 | 27 | 16 - 88 | 66 | 29 | 22 - 99 | 104 | 10 | 86 -117 |
| 90 | 94 | 32 | 46 -136 | 61 | 28 | 15 -100 | 74 | 30 | 27 -110 | 104 | 14 | 82 -122 |
| 100 | 88 | 27 | 43 -129 | 55 | 23 | 16 - 86 | 67 | 24 | 26 - 94 | 103 | 14 | 87 -137 |
| 110 | 87 | 25 | 43 -128 | 52 | 24 | 14 - 85 | 65 | 24 | 25 - 96 | 105 | 16 | 86 -139 |
| 120 | 91 | 29 | 42 -140 | 54 | 25 | 13 - 97 | 68 | 27 | 25 -116 | 104 | 15 | 88 -135 |

| | SYSTOLIC BLOOD PRESSURE (mmHg) | | | DIASTOLIC BLOOD PRESSURE (mmHg) | | | MEAN BLOOD PRESSURE (mmHg) | | | HEART RATE (beats $min^{-1}$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TIME (sec) | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range |
| 130 | 90 | 28 | 42 -137 | 53 | 23 | 12 - 87 | 67 | 25 | 24 -107 | 100 | 9 | 90 -118 |
| 140 | 82 | 30 | 41 -135 | 50 | 23 | 11 - 84 | 62 | 27 | 21 -106 | 96 | 8 | 88 -109 |
| 150 | 89 | 25 | 40 -125 | 53 | 22 | 9 - 80 | 66 | 24 | 19 - 99 | 98 | 10 | 85 -112 |
| 160 | 87 | 24 | 40 -120 | 51 | 20 | 11 - 74 | 64 | 23 | 20 - 94 | 97 | 8 | 88 -107 |
| 170 | 87 | 24 | 38 -118 | 51 | 20 | 8 - 74 | 63 | 22 | 18 - 91 | 97 | 8 | 87 -108 |
| 180 | 85 | 24 | 39 -119 | 50 | 20 | 8 - 73 | 63 | 22 | 19 - 92 | 97 | 9 | 84 -109 |
| 190 | 82 | 24 | 38 -113 | 48 | 22 | 5 - 70 | 60 | 24 | 16 - 87 | 95 | 9 | 84 -105 |
| 200 | 82 | 22 | 34 -107 | 49 | 19 | 7 - 65 | 60 | 21 | 16 - 81 | 95 | 9 | 84 -108 |
| 210 | 80 | 22 | 31 -102 | 48 | 20 | 5 - 63 | 60 | 21 | 14 - 78 | 95 | 9 | 81 -109 |
| 220 | 80 | 19 | 38 -100 | 47 | 20 | 6 - 66 | 59 | 20 | 17 - 77 | 95 | 8 | 82 -102 |
| 230 | 79 | 18 | 39 - 98 | 46 | 19 | 7 - 66 | 58 | 19 | 19 - 76 | 94 | 7 | 82 -100 |
| 240 | 79 | 18 | 40 -100 | 47 | 19 | 7 - 65 | 58 | 19 | 20 - 76 | 94 | 7 | 81 -101 |
| 250 | 78 | 20 | 39 -101 | 47 | 21 | 4 - 66 | 58 | 21 | 17 - 76 | 93 | 8 | 79 -101 |
| 260 | 72 | 24 | 34 -101 | 43 | 23 | 4 - 68 | 53 | 23 | 16 - 77 | 90 | 10 | 73 -100 |
| 270 | 77 | 19 | 39 -100 | 44 | 23 | 3 - 68 | 56 | 22 | 16 - 79 | 93 | 7 | 79 -101 |
| 280 | 75 | 18 | 41 -101 | 43 | 23 | 4 - 67 | 56 | 21 | 20 - 78 | 93 | 8 | 78 -102 |
| 290 | 75 | 18 | 41 -102 | 43 | 22 | 4 - 67 | 55 | 21 | 20 - 78 | 92 | 9 | 77 -104 |
| 300 | 76 | 16 | 52 -101 | 46 | 17 | 20 - 68 | 57 | 18 | 26 - 78 | 91 | 10 | 69 -104 |
| 310 | 77 | 16 | 50 -101 | 46 | 19 | 16 - 70 | 57 | 18 | 30 - 80 | 91 | 10 | 72 -105 |
| 320 | 79 | 16 | 51 -102 | 48 | 20 | 14 - 68 | 60 | 19 | 30 - 80 | 93 | 11 | 75 -107 |
| 330 | 80 | 16 | 52 -104 | 48 | 21 | 13 - 68 | 60 | 19 | 28 - 80 | 93 | 9 | 76 -102 |
| 340 | 77 | 17 | 43 -103 | 49 | 19 | 19 - 66 | 60 | 19 | 27 - 79 | 93 | 9 | 77 -102 |
| 350 | 75 | 19 | 33 -104 | 48 | 17 | 20 - 67 | 58 | 17 | 25 - 79 | 80 | 28 | 10 - 97 |
| 360 | 73 | 21 | 28 - 97 | 49 | 19 | 15 - 67 | 60 | 18 | 22 - 79 | 91 | 11 | 74 -110 |
| 370 | 79 | 20 | 35 -101 | 54 | 14 | 27 - 68 | 64 | 17 | 28 - 81 | 89 | 19 | 44 -102 |
| 380 | 80 | 19 | 41 -102 | 55 | 16 | 27 - 70 | 65 | 17 | 32 - 83 | 97 | 11 | 85 -119 |
| 390 | 83 | 22 | 34 -103 | 57 | 16 | 28 - 74 | 67 | 19 | 27 - 84 | 97 | 14 | 82 -130 |

| | SYSTOLIC BLOOD PRESSURE (mmHg) | | | DIASTOLIC BLOOD PRESSURE (mmHg) | | | MEAN BLOOD PRESSURE (mmHg) | | | HEART RATE (beats $min^{-1}$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TIME (sec) | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range |
| 400 | 85 | 19 | 45 -108 | 59 | 14 | 39 - 77 | 69 | 16 | 41 - 89 | 98 | 11 | 82 -119 |
| 410 | 86 | 22 | 44 -117 | 59 | 17 | 37 - 89 | 70 | 19 | 40 -101 | 96 | 15 | 78 -126 |
| 420 | 88 | 22 | 44 -122 | 60 | 17 | 38 - 89 | 71 | 19 | 40 -103 | 97 | 15 | 78 -121 |
| 430 | 88 | 22 | 44 -122 | 60 | 17 | 38 - 91 | 71 | 19 | 40 -103 | 98 | 14 | 78 -126 |
| 440 | 92 | 24 | 44 -122 | 62 | 17 | 38 - 89 | 73 | 19 | 40 -104 | 98 | 12 | 78 -116 |
| 450 | 91 | 20 | 62 -117 | 62 | 16 | 39 - 84 | 74 | 18 | 46 - 98 | 90 | 27 | 24 -113 |
| 460 | 93 | 18 | 67 -116 | 64 | 16 | 41 - 89 | 76 | 17 | 51 -101 | 97 | 8 | 85 -111 |
| 470 | 91 | 16 | 66 -114 | 62 | 13 | 42 - 83 | 74 | 15 | 53 - 96 | 94 | 11 | 74 -115 |
| 480 | 91 | 19 | 59 -118 | 59 | 19 | 29 - 89 | 70 | 23 | 26 -103 | 99 | 8 | 85 -108 |
| 490 | 92 | 18 | 67 -117 | 60 | 17 | 40 - 87 | 73 | 17 | 52 -100 | 96 | 8 | 84 -109 |
| 500 | 92 | 17 | 66 -116 | 60 | 17 | 37 - 85 | 72 | 18 | 44 - 98 | 98 | 9 | 82 -110 |
| 510 | 96 | 13 | 79 -117 | 62 | 15 | 40 - 83 | 75 | 16 | 55 - 96 | 99 | 8 | 85 -109 |
| 520 | 95 | 12 | 78 -113 | 61 | 14 | 41 - 81 | 75 | 14 | 56 - 94 | 99 | 7 | 87 -109 |
| 530 | 95 | 13 | 73 -112 | 61 | 15 | 36 - 83 | 75 | 15 | 53 - 97 | 100 | 7 | 86 -111 |
| 540 | 96 | 14 | 72 -111 | 63 | 15 | 34 - 81 | 77 | 15 | 50 - 95 | 98 | 7 | 91 -112 |
| 550 | 94 | 14 | 74 -110 | 61 | 16 | 34 - 82 | 74 | 16 | 50 - 95 | 99 | 12 | 74 -114 |
| 560 | 94 | 13 | 75 -109 | 60 | 15 | 36 - 79 | 74 | 15 | 53 - 92 | 96 | 12 | 74 -115 |
| 570 | 94 | 14 | 74 -108 | 60 | 15 | 34 - 79 | 74 | 15 | 52 - 92 | 96 | 11 | 74 -116 |
| 580 | 93 | 15 | 70 -109 | 60 | 16 | 34 - 80 | 74 | 16 | 51 - 92 | 99 | 9 | 86 -113 |
| 590 | 94 | 13 | 75 -108 | 61 | 14 | 36 - 78 | 75 | 14 | 53 - 91 | 100 | 7 | 90 -111 |
| 600 | 97 | 13 | 73 -109 | 63 | 15 | 33 - 80 | 77 | 14 | 51 - 94 | 99 | 9 | 85 -111 |
| 610 | 96 | 13 | 72 -108 | 60 | 14 | 31 - 74 | 73 | 13 | 49 - 89 | 102 | 11 | 88 -115 |
| 620 | 93 | 12 | 71 -107 | 58 | 14 | 31 - 73 | 72 | 13 | 49 - 88 | 101 | 11 | 83 -117 |
| 630 | 92 | 12 | 72 -107 | 58 | 14 | 31 - 73 | 72 | 14 | 48 - 88 | 102 | 12 | 84 -117 |
| 640 | 92 | 12 | 71 -107 | 57 | 13 | 31 - 73 | 71 | 13 | 48 - 88 | 102 | 11 | 85 -116 |
| 650 | 92 | 12 | 73 -107 | 57 | 13 | 32 - 73 | 71 | 13 | 49 - 88 | 100 | 12 | 79 -112 |
| 660 | 91 | 12 | 73 -107 | 57 | 12 | 33 - 73 | 71 | 13 | 49 - 88 | 100 | 11 | 81 -113 |

| | SYSTOLIC BLOOD PRESSURE (mmHg) | | | DIASTOLIC BLOOD PRESSURE (mmHg) | | | MEAN BLOOD PRESSURE (mmHg) | | | HEART RATE (beats $min^{-1}$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TIME (sec) | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range |
| 670 | 89 | 17 | 64 -115 | 58 | 16 | 32 - 84 | 70 | 16 | 49 - 95 | 100 | 13 | 82 -118 |
| 680 | 96 | 15 | 71 -119 | 61 | 18 | 32 - 90 | 75 | 17 | 48 -103 | 107 | 11 | 94 -128 |
| 690 | 96 | 16 | 71 -123 | 61 | 19 | 31 - 94 | 75 | 18 | 48 -107 | 109 | 12 | 95 -132 |
| 700 | 97 | 18 | 71 -129 | 63 | 19 | 31 - 95 | 77 | 19 | 48 -111 | 110 | 10 | 100 -129 |
| 710 | 97 | 18 | 71 -127 | 63 | 20 | 31 - 95 | 77 | 19 | 48 -109 | 110 | 12 | 98 -130 |
| 720 | 100 | 18 | 72 -126 | 65 | 19 | 32 - 92 | 80 | 19 | 49 -109 | 112 | 10 | 99 -122 |
| 730 | 94 | 19 | 67 -123 | 62 | 17 | 36 - 88 | 75 | 19 | 50 -104 | 108 | 12 | 92 -125 |
| 740 | 97 | 17 | 74 -124 | 62 | 17 | 36 - 87 | 76 | 17 | 52 -104 | 108 | 10 | 97 -126 |
| 750 | 95 | 18 | 75 -121 | 62 | 18 | 37 - 85 | 75 | 19 | 51 -101 | 107 | 12 | 92 -126 |
| 760 | 95 | 18 | 73 -120 | 61 | 17 | 36 - 83 | 75 | 17 | 52 - 98 | 108 | 11 | 97 -126 |
| 770 | 94 | 16 | 73 -117 | 61 | 15 | 36 - 80 | 74 | 16 | 51 - 97 | 108 | 9 | 97 -122 |
| 780 | 95 | 15 | 75 -118 | 62 | 14 | 41 - 82 | 76 | 15 | 56 - 98 | 107 | 5 | 99 -112 |
| 790 | 92 | 16 | 72 -115 | 62 | 11 | 46 - 79 | 73 | 16 | 53 - 95 | 108 | 9 | 96 -118 |
| 800 | 97 | 13 | 82 -115 | 63 | 11 | 47 - 79 | 76 | 12 | 61 - 94 | 108 | 9 | 96 -119 |
| 810 | 96 | 12 | 83 -113 | 63 | 10 | 48 - 79 | 76 | 11 | 63 - 94 | 110 | 8 | 101 -122 |
| 820 | 94 | 15 | 83 -116 | 63 | 14 | 48 - 82 | 76 | 15 | 63 - 98 | 115 | 6 | 107 -119 |
| 830 | 95 | 14 | 84 -115 | 63 | 14 | 47 - 80 | 76 | 14 | 62 - 96 | 113 | 7 | 105 -121 |
| 840 | 95 | 14 | 84 -111 | 62 | 15 | 46 - 76 | 76 | 15 | 62 - 92 | 107 | 8 | 98 -114 |

**APPENDIX D 26: Haemodynamic data measured using the Finapres™ during induction of anaesthesia with propofol from Jones et al (1993d)**

## Finapres Haemodynamic Data - Thiopentone Group - (n = 8)

| | SYSTOLIC BLOOD PRESSURE (mmHg) | | | DIASTOLIC BLOOD PRESSURE (mmHg) | | | MEAN BLOOD PRESSURE (mmHg) | | | HEART RATE (beats $min^{-1}$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TIME (sec) | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range |
| -120 | 105 | 15 | 78 -127 | 70 | 18 | 42 - 98 | 83 | 15 | 58 -105 | 100 | 16 | 88 -131 |
| -110 | 110 | 23 | 76 -149 | 75 | 17 | 47 - 99 | 85 | 18 | 56 -115 | 103 | 20 | 72 -134 |
| -100 | 101 | 13 | 77 -119 | 67 | 16 | 49 - 87 | 81 | 15 | 59 -102 | 99 | 13 | 78 -118 |
| -90 | 102 | 18 | 75 -127 | 69 | 19 | 45 - 98 | 81 | 17 | 59 -105 | 101 | 17 | 80 -132 |
| -80 | 109 | 21 | 73 -140 | 74 | 19 | 46 -101 | 88 | 19 | 57 -115 | 104 | 16 | 84 -135 |
| -70 | 103 | 21 | 64 -129 | 68 | 23 | 36 - 96 | 81 | 22 | 48 -109 | 101 | 17 | 84 -131 |
| -60 | 110 | 16 | 86 -133 | 73 | 19 | 49 - 99 | 86 | 19 | 62 -111 | 103 | 18 | 85 -137 |
| -50 | 108 | 19 | 72 -136 | 73 | 20 | 43 -104 | 85 | 16 | 55 -101 | 99 | 18 | 79 -132 |
| -40 | 109 | 20 | 77 -141 | 73 | 19 | 43 - 99 | 87 | 18 | 58 -115 | 103 | 20 | 81 -140 |
| -30 | 111 | 24 | 69 -149 | 74 | 22 | 40 -103 | 88 | 21 | 53 -120 | 103 | 20 | 78 -132 |
| -20 | 108 | 23 | 68 -145 | 72 | 21 | 39 -103 | 86 | 19 | 55 -114 | 99 | 21 | 75 -138 |
| -10 | 105 | 19 | 69 -130 | 71 | 17 | 42 - 89 | 85 | 15 | 58 -104 | 100 | 17 | 81 -132 |
| 0 | 105 | 18 | 74 -127 | 69 | 17 | 42 - 87 | 83 | 13 | 64 - 97 | 105 | 12 | 83 -117 |
| 10 | 104 | 13 | 84 -123 | 71 | 14 | 47 - 92 | 83 | 15 | 64 -107 | 113 | 11 | 93 -130 |
| 20 | 96 | 9 | 82 -110 | 64 | 10 | 46 - 79 | 77 | 10 | 60 - 93 | 112 | 12 | 96 -129 |
| 30 | 97 | 12 | 82 -116 | 68 | 15 | 48 - 87 | 82 | 14 | 63 - 98 | 117 | 14 | 100 -135 |
| 40 | 106 | 19 | 78 -131 | 74 | 18 | 45 - 96 | 87 | 19 | 61 -114 | 113 | 13 | 92 -127 |
| 50 | 105 | 21 | 78 -140 | 74 | 20 | 41 -106 | 89 | 26 | 57 -140 | 111 | 15 | 91 -132 |
| 60 | 99 | 18 | 70 -125 | 69 | 16 | 45 - 85 | 83 | 16 | 59 -102 | 113 | 11 | 98 -130 |
| 70 | 95 | 25 | 68 -140 | 64 | 20 | 42 - 98 | 78 | 20 | 55 -115 | 110 | 16 | 91 -137 |
| 80 | 84 | 34 | 37 -132 | 57 | 25 | 16 - 86 | 67 | 31 | 13 -102 | 101 | 15 | 80 -121 |
| 90 | 93 | 27 | 58 -143 | 63 | 22 | 36 -100 | 73 | 21 | 46 -110 | 109 | 15 | 89 -133 |
| 100 | 94 | 29 | 52 -151 | 63 | 24 | 33 -108 | 75 | 24 | 45 -122 | 107 | 16 | 85 -135 |
| 110 | 92 | 28 | 54 -146 | 62 | 23 | 33 -105 | 73 | 23 | 43 -116 | 107 | 15 | 85 -132 |
| 120 | 93 | 29 | 58 -149 | 63 | 24 | 35 -107 | 74 | 25 | 44 -122 | 106 | 15 | 84 -128 |
| 130 | 93 | 26 | 57 -142 | 63 | 22 | 35 -102 | 75 | 22 | 46 -115 | 105 | 14 | 87 -123 |

| | SYSTOLIC BLOOD PRESSURE (mmHg) | | | DIASTOLIC BLOOD PRESSURE (mmHg) | | | MEAN BLOOD PRESSURE (mmHg) | | | HEART RATE (beats $min^{-1}$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TIME (sec) | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range |
| 140 | 90 | 23 | 58 -131 | 61 | 20 | 34 - 95 | 72 | 21 | 44 -107 | 103 | 17 | 77 -124 |
| 150 | 88 | 24 | 54 -130 | 59 | 21 | 31 - 94 | 69 | 23 | 34 -105 | 103 | 16 | 82 -123 |
| 160 | 87 | 23 | 54 -125 | 58 | 21 | 32 - 91 | 69 | 20 | 42 -101 | 103 | 15 | 85 -123 |
| 170 | 87 | 22 | 53 -123 | 58 | 20 | 32 - 89 | 69 | 19 | 42 - 98 | 103 | 15 | 85 -122 |
| 180 | 86 | 21 | 53 -120 | 57 | 20 | 31 - 88 | 69 | 19 | 42 - 97 | 102 | 16 | 82 -121 |
| 190 | 86 | 22 | 59 -125 | 58 | 21 | 32 - 93 | 69 | 21 | 42 -104 | 101 | 16 | 82 -120 |
| 200 | 85 | 21 | 58 -121 | 57 | 20 | 35 - 89 | 68 | 20 | 43 -101 | 99 | 19 | 70 -124 |
| 210 | 85 | 23 | 59 -127 | 58 | 21 | 36 - 96 | 68 | 21 | 47 -107 | 102 | 17 | 84 -129 |
| 220 | 85 | 22 | 60 -123 | 57 | 19 | 36 - 90 | 68 | 20 | 47 -103 | 102 | 15 | 85 -121 |
| 230 | 86 | 24 | 59 -131 | 58 | 23 | 35 -104 | 68 | 21 | 47 -108 | 103 | 18 | 85 -134 |
| 240 | 87 | 27 | 60 -144 | 59 | 25 | 36 -114 | 70 | 27 | 47 -129 | 104 | 21 | 87 -147 |
| 250 | 87 | 29 | 61 -148 | 59 | 27 | 37 -117 | 70 | 28 | 48 -133 | 104 | 22 | 87 -148 |
| 260 | 86 | 27 | 62 -142 | 58 | 24 | 37 -108 | 68 | 23 | 49 -115 | 102 | 23 | 84 -149 |
| 270 | 84 | 22 | 62 -127 | 57 | 22 | 36 -101 | 68 | 22 | 48 -113 | 101 | 22 | 82 -146 |
| 280 | 84 | 22 | 61 -124 | 58 | 21 | 36 - 99 | 69 | 22 | 48 -115 | 100 | 22 | 83 -146 |
| 290 | 84 | 24 | 60 -132 | 57 | 22 | 36 -100 | 67 | 22 | 47 -111 | 100 | 22 | 82 -144 |
| 300 | 83 | 22 | 60 -126 | 56 | 20 | 36 - 95 | 66 | 20 | 47 -108 | 99 | 20 | 80 -139 |
| 310 | 82 | 21 | 61 -125 | 55 | 19 | 37 - 93 | 65 | 19 | 48 -104 | 98 | 19 | 78 -134 |
| 320 | 83 | 20 | 61 -121 | 56 | 18 | 39 - 91 | 66 | 18 | 51 -102 | 98 | 19 | 74 -131 |
| 330 | 85 | 20 | 63 -121 | 58 | 17 | 39 - 90 | 67 | 17 | 50 -100 | 96 | 18 | 72 -125 |
| 340 | 85 | 18 | 65 -116 | 59 | 14 | 42 - 87 | 69 | 15 | 53 - 98 | 96 | 16 | 78 -122 |
| 350 | 84 | 18 | 65 -114 | 57 | 15 | 42 - 86 | 67 | 16 | 49 - 96 | 96 | 16 | 78 -124 |
| 360 | 84 | 17 | 65 -112 | 58 | 14 | 43 - 84 | 68 | 14 | 55 - 94 | 95 | 14 | 79 -120 |
| 370 | 84 | 17 | 63 -111 | 58 | 14 | 44 - 84 | 68 | 14 | 54 - 94 | 93 | 14 | 77 -117 |
| 380 | 82 | 19 | 59 -112 | 57 | 16 | 42 - 84 | 66 | 16 | 48 - 93 | 92 | 17 | 71 -115 |
| 390 | 83 | 18 | 59 -109 | 58 | 15 | 42 - 81 | 68 | 16 | 51 - 92 | 94 | 17 | 73 -123 |
| 400 | 84 | 18 | 64 -110 | 58 | 18 | 40 - 87 | 69 | 16 | 56 - 97 | 94 | 15 | 77 -118 |

| | SYSTOLIC BLOOD PRESSURE (mmHg) | | | DIASTOLIC BLOOD PRESSURE (mmHg) | | | MEAN BLOOD PRESSURE (mmHg) | | | HEART RATE (beats $min^{-1}$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TIME (sec) | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range |
| 410 | 84 | 20 | 60 -114 | 57 | 18 | 35 - 86 | 68 | 19 | 46 -100 | 94 | 14 | 70 -114 |
| 420 | 83 | 19 | 62 -110 | 57 | 16 | 40 - 81 | 67 | 17 | 48 - 93 | 94 | 18 | 70 -125 |
| 430 | 85 | 19 | 60 -114 | 59 | 15 | 44 - 82 | 69 | 16 | 52 - 95 | 95 | 20 | 63 -127 |
| 440 | 86 | 20 | 61 -115 | 60 | 17 | 40 - 88 | 71 | 18 | 51 - 98 | 98 | 20 | 67 -124 |
| 450 | 88 | 19 | 64 -115 | 61 | 17 | 37 - 89 | 72 | 17 | 53 -100 | 97 | 21 | 71 -124 |
| 460 | 86 | 20 | 61 -115 | 61 | 16 | 41 - 87 | 71 | 17 | 51 - 99 | 96 | 17 | 69 -118 |
| 470 | 86 | 19 | 60 -111 | 60 | 16 | 39 - 84 | 71 | 17 | 50 - 96 | 95 | 15 | 72 -114 |
| 480 | 86 | 18 | 60 -111 | 61 | 15 | 39 - 84 | 71 | 16 | 52 - 95 | 95 | 15 | 68 -114 |
| 490 | 86 | 17 | 58 -108 | 60 | 15 | 37 - 84 | 71 | 15 | 52 - 95 | 96 | 13 | 76 -116 |
| 500 | 86 | 18 | 57 -107 | 60 | 15 | 42 - 83 | 71 | 16 | 46 - 94 | 95 | 12 | 80 -114 |
| 510 | 88 | 16 | 65 -105 | 63 | 13 | 41 - 81 | 74 | 14 | 53 - 92 | 96 | 13 | 82 -113 |
| 520 | 89 | 15 | 67 -105 | 63 | 12 | 43 - 82 | 74 | 13 | 54 - 92 | 96 | 12 | 82 -115 |
| 530 | 89 | 15 | 68 -105 | 63 | 12 | 45 - 82 | 74 | 12 | 56 - 92 | 95 | 13 | 78 -115 |
| 540 | 89 | 16 | 63 -107 | 62 | 16 | 36 - 86 | 71 | 20 | 32 - 95 | 95 | 14 | 78 -119 |
| 550 | 92 | 14 | 74 -109 | 64 | 13 | 46 - 84 | 75 | 13 | 58 - 96 | 94 | 12 | 79 -111 |
| 560 | 91 | 14 | 74 -109 | 64 | 12 | 48 - 83 | 76 | 12 | 62 - 96 | 90 | 12 | 71 -104 |
| 570 | 91 | 14 | 72 -107 | 65 | 10 | 54 - 81 | 75 | 13 | 56 - 93 | 93 | 12 | 76 -106 |
| 580 | 91 | 14 | 72 -107 | 64 | 11 | 48 - 80 | 75 | 12 | 62 - 93 | 94 | 11 | 75 -103 |
| 590 | 92 | 13 | 73 -107 | 65 | 10 | 53 - 81 | 77 | 11 | 63 - 93 | 94 | 10 | 79 -106 |
| 600 | 93 | 13 | 74 -108 | 65 | 10 | 54 - 81 | 77 | 10 | 65 - 93 | 93 | 9 | 80 -105 |
| 610 | 92 | 12 | 75 -106 | 64 | 10 | 51 - 79 | 77 | 10 | 66 - 92 | 91 | 12 | 69 -103 |
| 620 | 92 | 12 | 78 -105 | 67 | 12 | 51 - 79 | 78 | 11 | 66 - 91 | 94 | 10 | 82 -104 |
| 630 | 91 | 13 | 76 -105 | 66 | 12 | 50 - 78 | 77 | 12 | 65 - 91 | 95 | 10 | 82 -105 |
| 640 | 91 | 14 | 77 -105 | 66 | 13 | 48 - 79 | 77 | 13 | 62 - 91 | 95 | 10 | 83 -106 |
| 650 | 90 | 13 | 77 -104 | 65 | 12 | 48 - 78 | 76 | 13 | 62 - 91 | 94 | 10 | 82 -105 |
| 660 | 90 | 14 | 75 -105 | 64 | 13 | 45 - 77 | 75 | 13 | 58 - 88 | 94 | 10 | 84 -105 |
| 670 | 91 | 14 | 75 -106 | 65 | 14 | 45 - 78 | 76 | 14 | 58 - 90 | 96 | 10 | 84 -106 |
| 680 | 90 | 14 | 74 -105 | 64 | 14 | 44 - 77 | 76 | 13 | 58 - 89 | 94 | 11 | 82 -104 |

| | SYSTOLIC BLOOD PRESSURE (mmHg) | | | DIASTOLIC BLOOD PRESSURE (mmHg) | | | MEAN BLOOD PRESSURE (mmHg) | | | HEART RATE (beats $min^{-1}$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TIME (sec) | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range | average data | standard deviation | range |
| 690 | 90 | 14 | 76 -104 | 64 | 12 | 46 - 76 | 76 | 13 | 59 - 89 | 95 | 10 | 83 -106 |
| 700 | 90 | 15 | 76 -107 | 64 | 14 | 45 - 80 | 76 | 14 | 59 - 93 | 93 | 11 | 81 -105 |
| 710 | 91 | 15 | 75 -107 | 65 | 14 | 45 - 78 | 76 | 14 | 58 - 91 | 93 | 10 | 81 -103 |
| 720 | 91 | 14 | 75 -106 | 65 | 14 | 45 - 78 | 76 | 14 | 58 - 91 | 94 | 11 | 81 -105 |
| 730 | 90 | 16 | 72 -106 | 64 | 15 | 42 - 77 | 75 | 15 | 55 - 90 | 93 | 12 | 78 -105 |
| 740 | 91 | 15 | 73 -107 | 64 | 15 | 42 - 79 | 76 | 15 | 56 - 91 | 92 | 11 | 79 -105 |
| 750 | 91 | 18 | 72 -111 | 65 | 16 | 42 - 83 | 76 | 17 | 55 - 95 | 92 | 13 | 78 -105 |
| 760 | 91 | 17 | 72 -111 | 65 | 16 | 42 - 83 | 77 | 17 | 55 - 97 | 93 | 12 | 80 -105 |
| 770 | 91 | 16 | 74 -108 | 64 | 15 | 42 - 79 | 76 | 16 | 56 - 93 | 93 | 14 | 77 -107 |
| 780 | 90 | 17 | 71 -107 | 63 | 16 | 41 - 79 | 75 | 16 | 54 - 93 | 94 | 14 | 78 -108 |
| 790 | 90 | 16 | 71 -108 | 63 | 15 | 41 - 78 | 75 | 15 | 54 - 90 | 95 | 17 | 77 -116 |
| 800 | 91 | 18 | 72 -110 | 64 | 16 | 41 - 81 | 75 | 16 | 54 - 92 | 94 | 17 | 77 -115 |
| 810 | 91 | 19 | 71 -113 | 64 | 17 | 41 - 83 | 76 | 17 | 54 - 96 | 94 | 16 | 78 -114 |
| 820 | 91 | 17 | 72 -109 | 63 | 15 | 42 - 80 | 75 | 16 | 55 - 93 | 94 | 14 | 79 -111 |
| 830 | 92 | 17 | 73 -111 | 64 | 16 | 42 - 82 | 76 | 16 | 55 - 94 | 95 | 15 | 78 -110 |
| 840 | 92 | 19 | 72 -112 | 65 | 17 | 41 - 83 | 77 | 18 | 55 - 96 | 95 | 16 | 77 -109 |

**APPENDIX D 27: Haemodynamic data measured using the Finapres™ during induction of anaesthesia with thiopentone from Jones et al (1993d)**

# APPENDIX E

## Assay methodology data

# Method evaluation data for the assay of midazolam

| | Regression parameters of calibration (4 typical curves, mean of 3 for each point) | | | |
|---|---|---|---|---|
| **Concentration (ng ml$^{-1}$)** | **1** | **2** | **3** | **4** |
| **40** | 0.094 | 0.123 | 0.089 | 0.100 |
| **100** | 0.189 | 0.128 | 0.149 | 0.158 |
| **200** | 0.286 | 0.310 | 0.373 | 0.373 |
| **500** | 0.809 | 0.910 | 0.839 | 0.830 |
| **1000** | 1.710 | 1.753 | 1.569 | 1.643 |
| **2000** | 3.855 | 3.753 | 3.454 | - |
| **Correlation** | 0.996 | 0.998 | 0.997 | 0.999 |
| **Slope** | 0.002 | 0.002 | 0.002 | 0.002 |
| **Intercept** | -0.072 | -0.037 | 0.012 | 0.026 |

**Overall summary:**

| | |
|---|---|
| Calibration range | 0 - 2000 ng ml$^{-1}$ |
| Correlation coefficient | 0.997 |
| Slope | 0.00196 |
| Intercept | - 0.01775 |
| Internal standard | 200 ng |

**Within-batch variation (n=3)**

| Amount added (ng ml$^{-1}$) | Values found (ng ml$^{-1}$) | | | mean | SD | CV (%) |
|---|---|---|---|---|---|---|
| 40 | 50.5 | 45.0 | 37.5 | 44.3 | 5.33 | 12.03 |
| 500 | 499.5 | 522.5 | 465.0 | 495.7 | 23.63 | 4.77 |

**Between-batch variation (mean of 3 for each point)**

| Concentration (ng ml$^{-1}$) | Mean midazolam/I.S. ratio (n=3) | | | mean | SD | CV (%) |
|---|---|---|---|---|---|---|
| 40 | 0.094 | 0.089 | 0.100 | 0.094 | 0.004 | 4.767 |
| 100 | 0.189 | 0.149 | 0.158 | 0.165 | 0.017 | 10.363 |
| 200 | 0.286 | 0.371 | 0.373 | 0.343 | 0.041 | 11.810 |
| 500 | 0.809 | 0.839 | 0.830 | 0.826 | 0.013 | 1.522 |
| 1000 | 1.710 | 1.569 | 1.643 | 1.641 | 0.058 | 3.510 |
| 2,000 | 3.855 | 3.454 | - | 3.655 | 0.201 | 5.486 |

# Method evaluation data for the assay of thiopentone

| | Regression parameters of calibration (5 typical curves, mean of 3 for each point) | | | | |
|---|---|---|---|---|---|
| **Concentration ($\mu g\ ml^{-1}$)** | **1** | **2** | **3** | **4** | **5** |
| **0.05** | 0.057 | 0.035 | 0.030 | 0.035 | 0.0421 |
| **0.1** | 0.096 | 0.082 | 0.059 | 0.075 | 0.0657 |
| **1** | 0.976 | 0.726 | 0.620 | 0.666 | 0.6544 |
| **5** | 4.236 | 3.350 | 2.661 | 3.482 | 2.9537 |
| **10** | 7.104 | 7.725 | 5.800 | 6.926 | 5.9462 |
| **40** | - | - | - | 23.061 | 22.9783 |
| **Correlation** | 0.991 | 0.996 | 0.998 | 0.997 | 0.999 |
| **Slope** | 0.718 | 0.762 | 0.573 | 0.574 | 0.574 |
| **Intercept** | 0.169 | -0.076 | -0.017 | -0.004 | 0.072 |

**Summary overall**:

| | |
|---|---|
| Calibration range | 0.05 - 40 $\mu g\ ml^{-1}$ |
| Correlation coefficient | 0.996 |
| Slope | 0.64 |
| Intercept | 0.016 |
| Internal standard | 20 $\mu g$ |

**Within-batch variation (n=3)**

| Amount added ($\mu g\ ml^{-1}$) | Values found ($\mu g\ ml^{-1}$) | | | mean | SD | CV(%) |
|---|---|---|---|---|---|---|
| 1 | 0.9524 | 0.9855 | 1.2578 | 1.065 | 0.137 | 12.85 |
| 10 | 11.8856 | 12.4916 | 11.6609 | 12.013 | 0.351 | 2.92 |

**Between-batch variation (mean of 3 for each point)**

| Concentration ($\mu g\ ml^{-1}$) | Mean thiopentone/I.S. ratio (n =3) | | | mean | SD | CV (%) |
|---|---|---|---|---|---|---|
| 0.05 | 0.035 | 0.035 | 0.042 | 0.037 | 0.003 | 8.957 |
| 0.1 | 0.082 | 0.075 | 0.066 | 0.074 | 0.007 | 8.994 |
| 1 | 0.726 | 0.666 | 0.654 | 0.682 | 0.031 | 4.600 |
| 5 | 3.350 | 3.482 | 2.954 | 3.262 | 0.225 | 6.882 |
| 10 | 7.725 | 6.926 | 5.946 | 6.866 | 0.727 | 10.595 |
| 40 | - | 23.061 | 22.978 | 23.020 | 0.041 | 0.180 |

# Method evaluation data for the assay of propofol

| | Regression parameters of calibration (5 typical curves, mean of 3 for each point) | | | | |
|---|---|---|---|---|---|
| **Concentration ($\mu g\ ml^{-1}$)** | **1** | **2** | **3** | **4** | **5** |
| **0.010** | 0.0230 | 0.0166 | 0.0237 | 0.0198 | 0.0244 |
| **0.025** | 0.0218 | 0.0399 | 0.0314 | 0.0398 | 0.0337 |
| **0.050** | 0.0486 | 0.0604 | 0.0523 | 0.0630 | 0.0633 |
| **0.100** | 0.1264 | 0.1499 | 0.1319 | 0.1109 | 0.1230 |
| **0.250** | 0.2921 | 0.3650 | 0.3406 | 0.2452 | 0.2724 |
| **0.500** | 0.6827 | 0.8427 | 0.6632 | 0.5133 | 0.6014 |
| **1.000** | 1.3867 | 1.5102 | 1.3215 | - | 1.1323 |
| **Correlation** | 0.9985 | 0.9964 | 0.9997 | 0.9986 | 0.9988 |
| **Slope** | 1.3867 | 1.5388 | 1.3228 | 0.9932 | 1.1324 |
| **Intercept** | -0.0159 | 0.0010 | 0.0007 | 0.0106 | 0.0085 |

**Summary overall**:

| | |
|---|---|
| Calibration range | 0.01 - 1.0 $\mu g\ ml^{-1}$ |
| Correlation coefficient | 0.998 |
| Slope | 1.185 |
| Intercept | 0.00097 |
| Internal standard | 0.12 $\mu g$ |

**Within-batch variation (n=3)**

| Amount added ($\mu g\ ml^{-1}$) | Values found ($\mu g\ ml^{-1}$) | | | mean | SD | CV (%) |
|---|---|---|---|---|---|---|
| 0.01 | 0.0147 | 0.0161 | 0.0217 | 0.0175 | 0.0022 | 12.61 |
| 0.5 | 0.4923 | 0.5114 | 0.5021 | 0.5019 | 0.0055 | 1.09 |

**Between-batch variation (mean of 3 for each point)**

| Concentration ($\mu g\ ml^{-1}$) | Mean propofol/ I.S. ratio (n = 3) | | | mean | SD | CV (%) |
|---|---|---|---|---|---|---|
| 0.01 | 0.023 | 0.024 | 0.024 | 0.0237 | 0.0004 | 1.71 |
| 0.025 | 0.022 | 0.031 | 0.034 | 0.0290 | 0.0036 | 12.58 |
| 0.050 | 0.049 | 0.052 | 0.063 | 0.0547 | 0.0044 | 0.08 |
| 0.100 | 0.126 | 0.132 | 0.123 | 0.1271 | 0.0026 | 2.04 |
| 0.250 | 0.292 | 0.341 | 0.272 | 0.3017 | 0.0203 | 6.72 |
| 0.500 | 0.683 | 0.663 | 0.601 | 0.6491 | 0.0245 | 4.08 |
| 1 | 1.377 | 1.322 | 1.132 | 1.1323 | 0.0742 | 5.81 |

# APPENDIX F

## Pharmacokinetic data

| Patient number | Time (min) 0 | 2 | 4 | 6 | 8 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 100 | 160 | 220 | 260 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 42 | 1,558 | 1,072 | 829 | 733 | 591 | 300 | 254 | 246 | 200 | 190 | 170 | 138 | 87 | 49 | 31 |
| 2 | 33 | 2,022 | 761 | 491 | 385 | 350 | 241 | 190 | 167 | 138 | 124 | 114 | 87 | 72 | 55 | 52 |
| 3 | 54 | 1,012 | 689 | 639 | 557 | 440 | 268 | 209 | 153 | 136 | 126 | 116 | 85 | 63 | 48 | 34 |
| 4 | 29 | 974 | 648 | 503 | 396 | 320 | 203 | 173 | 167 | 109 | 100 | 98 | 75 | 41 | 29 | 24 |
| 5 | 36 | 385 | 343 | 286 | 239 | 236 | 157 | 138 | 118 | 105 | 100 | 93 | 54 | 41 | 32 | 18 |
| 6 | 67 | 918 | 655 | 555 | 523 | 438 | 304 | 222 | 210 | 190 | 178 | 170 | 124 | 64 | 30 | 15 |
| 7 | 33 | 640 | 486 | 514 | 505 | 412 | 284 | 220 | 201 | 170 | 142 | 120 | 87 | 40 | 34 | 17 |
| 8 | 46 | 900 | 677 | 623 | 481 | 464 | 245 | 171 | 150 | 129 | 108 | 92 | 70 | 50 | 43 | 30 |
| 9 | 63 | 976 | 847 | 720 | 595 | 505 | 352 | 237 | 201 | 167 | 133 | 126 | 93 | 65 | 46 | 28 |
| 10 | 36 | 701 | 640 | 579 | 466 | 387 | 242 | 199 | 163 | 146 | 138 | 126 | 84 | 48 | 31 | 16 |
| 11 | 43 | 1,117 | 788 | 493 | 471 | 407 | 305 | 277 | 250 | 162 | 144 | 125 | 115 | 60 | 38 | 24 |
| 12 | 83 | 828 | 606 | 515 | 500 | 374 | 285 | 191 | 181 | 170 | 151 | 134 | 112 | 82 | 50 | 35 |
| **Mean** | 47.1 | 1,002.6 | 648.3 | 562.3 | 487.6 | 410.3 | 265.5 | 206.8 | 183.9 | 151.8 | 136.2 | 123.7 | 93.7 | 59.4 | 40.4 | 27 |
| **SD** | 15.8 | 409.7 | 173.1 | 129.2 | 115.4 | 86.7 | 49.7 | 36.8 | 37.6 | 28.6 | 26.8 | 24.5 | 23.1 | 15.2 | 8.8 | 10.1 |
| **Min.** | 29 | 385 | 343 | 286 | 239 | 236 | 157 | 138 | 118 | 105 | 100 | 92 | 54 | 40 | 29 | 15 |
| **Max.** | 83 | 2,022 | 1,072 | 829 | 733 | 591 | 352 | 277 | 250 | 200 | 190 | 170 | 138 | 87 | 55 | 52 |

**APPENDIX F 1: Midazolam concentration (ng $ml^{-1}$) with time from Jones et al (1993).**

| Patient number | Time (min) 0 | 2 | 4 | 6 | 8 | 10 | 15 | 20 | 30 | 60 | 120 | 180 | 240 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 246 | 220 | 210 | 206 | 200 | 197 | 190 | 184 | 170 | 138 | 87 | 49 | 30 |
| 2 | 173 | 167 | 154 | 152 | 140 | 138 | 136 | 124 | 114 | 87 | 72 | 55 | 52 |
| 3 | 161 | 157 | 153 | 149 | 146 | 138 | 136 | 127 | 108 | 85 | 63 | 55 | 41 |
| 4 | 167 | 154 | 113 | 109 | 107 | 105 | 104 | 100 | 98 | 75 | 41 | 29 | 24 |
| 5 | 118 | 115 | 112 | 111 | 110 | 105 | 101 | 100 | 93 | 54 | 41 | 32 | 18 |
| 6 | 198 | 196 | 190 | 186 | 183 | 180 | 178 | 173 | 168 | 124 | 64 | 30 | 15 |
| 7 | 201 | 196 | 192 | 174 | 170 | 173 | 165 | 142 | 120 | 87 | 41 | 34 | 17 |
| 8 | 108 | 97 | 94 | 92 | 90 | 83 | 81 | 72 | 70 | 52 | 47 | 38 | 23 |
| 9 | 225 | 201 | 185 | 181 | 177 | 174 | 167 | 133 | 126 | 93 | 65 | 46 | 28 |
| 10 | 172 | 166 | 163 | 160 | 151 | 148 | 146 | 138 | 126 | 84 | 48 | 31 | 17 |
| 11 | 261 | 257 | 250 | 216 | 206 | 184 | 162 | 149 | 125 | 115 | 60 | 38 | 24 |
| 12 | 170 | 165 | 159 | 151 | 146 | 141 | 134 | 127 | 120 | 103 | 82 | 50 | 35 |
| Mean | 183 | 174 | 165 | 157 | 152 | 147 | 142 | 131 | 120 | 91 | 59 | 41 | 27 |
| SD | 44.1 | 41.8 | 42.7 | 36.9 | 35.3 | 34.4 | 31.8 | 29.7 | 27.1 | 24.6 | 15.4 | 9.5 | 10.6 |
| Min. | 108 | 97 | 94 | 92 | 90 | 83 | 81 | 72 | 70 | 52 | 40 | 29 | 15 |
| Max. | 261 | 257 | 250 | 216 | 206 | 197 | 190 | 184 | 170 | 138 | 87 | 55 | 52 |

**APPENDIX F 2: Midazolam concentration (ng $ml^{-1}$) at flumazenil sampling times postoperatively from Jones et al (1993).**

| Patient number | A (ng) | B (ng) | C (ng) | alpha (min-1) | beta (min-1) | gamma (min-1) | Dose (ng) |
|---|---|---|---|---|---|---|---|
| 1 | 3,233.88 | 1,453.65 | 313.64 | 0.8228 | 0.1789 | 0.00819 | 9,350,000 |
| 2 | 3495.00 | 321.04 | 117.31 | 0.5572 | 0.0414 | 0.00319 | 8,000,000 |
| 3 | 4,764.51 | 765.02 | 174.76 | 0.4158 | 0.0956 | 0.00603 | 10,000,000 |
| 4 | 1119.60 | 233.43 | 82.30 | 0.2712 | 0.0271 | 0.00446 | 10,000,000 |
| 5 | 398.39 | 157.46 | 130.65 | 0.1850 | 0.0357 | 0.00779 | 16,000,000 |
| 6 | 1,288.12 | 312.33 | 124.19 | 0.7478 | 0.0600 | 0.01065 | 19,250,000 |
| 7 | 697.46 | 286.88 | 134.82 | 0.1275 | 0.0276 | 0.00713 | 7,000,000 |
| 8 | 960.47 | 291.25 | 113.35 | 0.1809 | 0.0440 | 0.00499 | 12,000,000 |
| 9 | 1,033.03 | 658.89 | 181.94 | 0.3722 | 0.0621 | 0.00658 | 10,000,000 |
| 10 | 824.02 | 162.08 | 150.69 | 0.1584 | 0.0274 | 0.00729 | 8,500,000 |
| 11 | 1,656.38 | 321.26 | 199.06 | 0.4914 | 0.0371 | 0.00764 | 12,500,000 |
| 12 | 948.79 | 218.84 | 211.88 | 0.2269 | 0.0576 | 0.00627 | 9,500,000 |

**APPENDIX F 3: Midazolam - 3-compartment analysis from Jones et al (1993).**

| Patient number | Wt. (kg) | Anaesthesia time (min) | $k_{12}$ ($h^{-1}$) | $k_{21}$ ($h^{-1}$) | $k_{13}$ ($h^{-1}$) | $k_{31}$ ($h^{-1}$) | $k_{10}$ ($h^{-1}$) | $k_{12}$: $k_{21}$ | $k_{31}$: $k_{10}$ | V (L) | $V_2$ (L) | $V_3$ (L) | $V_d$ (L) | $V_d$/ Wt (L $kg^{-1}$) | $V_{ss}$ (L) | $V_{ss}$ / Wt (L $kg^{-1}$) | $t_{½}^{\alpha}$ (min) | $t_{½}^{\beta}$ (min) | $t_{½}^{\gamma}$ (min) | Clearance (ml $min^{-1}$) | Clearance / Wt (ml $min^{-1}$ $kg^{-1}$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 18.7 | 31 | 1.49 | 23.67 | 14.20 | 1.84 | 5.96 | 0.06 | 0.31 | 1.9 | 1.2 | 19.6 | 22.7 | 1.21 | 21.5 | 1.15 | 0.84 | 3.9 | 84.6 | 206 | 11.02 |
| 2 | 16.0 | 33 | 16.76 | 5.53 | 8.50 | 0.61 | 4.64 | 3.01 | 0.13 | 2.0 | 6.3 | 41.0 | 49.3 | 3.08 | 45.1 | 2.82 | 1.24 | 18.0 | 189.0 | 199 | 12.44 |
| 3 | 20.0 | 39 | 5.76 | 8.57 | 8.78 | 0.85 | 7.06 | 0.67 | 0.12 | 1.8 | 1.2 | 31.3 | 34.3 | 1.72 | 36.4 | 1.82 | 1.67 | 7.3 | 115.0 | 285 | 14.25 |
| 4 | 20.0 | 35 | 8.08 | 4.64 | 2.12 | 0.55 | 2.76 | 1.74 | 0.20 | 6.9 | 12.8 | 52.0 | 71.7 | 3.59 | 41.9 | 2.10 | 2.56 | 26.0 | 105.0 | 372 | 18.60 |
| 5 | 32.0 | 43 | 3.92 | 5.55 | 1.33 | 1.13 | 1.76 | 0.71 | 0.64 | 23.3 | 18.0 | 46.7 | 88.0 | 2.75 | 93.7 | 2.93 | 3.75 | 19.0 | 89.0 | 736 | 23.00 |
| 6 | 38.5 | 40 | 24.38 | 13.52 | 4.25 | 1.37 | 5.56 | 1.80 | 0.25 | 11.5 | 21.1 | 65.0 | 97.6 | 2.54 | 47.2 | 1.23 | 0.93 | 12.0 | 65.0 | 547 | 14.21 |
| 7 | 14.0 | 31 | 2.41 | 3.74 | 0.89 | 0.75 | 1.93 | 0.65 | 0.39 | 6.3 | 4.6 | 17.5 | 28.4 | 2.03 | 21.9 | 1.56 | 5.00 | 25.0 | 97.0 | 240 | 17.14 |
| 8 | 24.0 | 58 | 3.03 | 4.81 | 2.83 | 0.75 | 2.37 | 0.63 | 0.32 | 8.8 | 5.9 | 54.7 | 69.4 | 2.89 | 58.5 | 2.44 | 3.80 | 16.0 | 139.0 | 375 | 15.63 |
| 9 | 20.0 | 31 | 7.63 | 11.77 | 3.28 | 1.01 | 2.74 | 0.65 | 0.37 | 5.3 | 3.6 | 28.1 | 37.0 | 1.85 | 30.4 | 1.52 | 1.90 | 11.0 | 105.0 | 268 | 13.40 |
| 10 | 17.0 | 31 | 3.36 | 3.49 | 1.27 | 0.91 | 2.14 | 1.08 | 0.43 | 6.5 | 9.2 | 20.0 | 35.7 | 2.10 | 27.3 | 1.61 | 4.40 | 25.0 | 95.0 | 303 | 17.82 |
| 11 | 25.0 | 29 | 16.78 | 8.30 | 2.59 | 1.06 | 3.47 | 2.02 | 0.30 | 5.7 | 12.3 | 24.9 | 42.9 | 1.72 | 35.0 | 1.40 | 1.40 | 18.0 | 90.0 | 355 | 14.20 |
| 12 | 19.0 | 48 | 4.02 | 5.98 | 3.96 | 1.49 | 1.98 | 0.67 | 0.75 | 6.9 | 4.9 | 24.4 | 36.2 | 1.91 | 34.6 | 1.82 | 3.10 | 12.0 | 110.0 | 243 | 12.79 |
| Mean | 22.0 | 37 | 8.17 | 8.30 | 4.50 | 1.03 | 3.53 | 1.14 | 0.35 | 7.2 | 8.4 | 35.4 | 51.1 | 2.20 | 41.1 | 1.87 | 2.55 | 16.1 | 107.0 | 344 | 15.37 |
| SD | 6.7 | 8 | 6.93 | 5.52 | 3.83 | 0.37 | 1.74 | 0.80 | 0.18 | 5.6 | 6.1 | 15.3 | 23.5 | 0.66 | 18.9 | 0.57 | 1.37 | 6.8 | 30.2 | 150 | 3.16 |
| Min. | 14.0 | 29 | 1.49 | 3.49 | 0.89 | 0.55 | 1.76 | 0.06 | 0.12 | 1.8 | 1.2 | 17.5 | 22.7 | 1.21 | 21.5 | 1.15 | 0.84 | 3.9 | 65.0 | 199 | 11.02 |
| Max. | 38.5 | 58 | 24.38 | 23.67 | 14.20 | 1.84 | 7.06 | 3.01 | 0.75 | 23.3 | 21.1 | 65.0 | 97.6 | 3.59 | 93.7 | 2.93 | 5.00 | 26.0 | 189.0 | 736 | 23.00 |

**APPENDIX F 4: Midazolam pharmacokinetic findings in the 12 children from Jones et al (1993).** $V_d = V + V_2 + V_3$.

| Patient number | Body weight (kg) | $t_{½}$ (min) | AUC (total) (ng min $ml^{-1}$) | Cl (ml $min^{-1}$) | Clearance / Wt (ml $min^{-1}$ $kg^{-1}$) | $V_d$(ss) (L) | $V_d$ / Wt (L $kg^{-1}$) | $V^E$ (L) | $V^E$ / Wt (L $kg^{-1}$) | MRT (min) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 18.7 | 84.6 | 45410.3 | 205.90 | 11.01 | 21.5 | 1.15 | 25.2 | 1.35 | 104.6 |
| 2 | 16.0 | 179.4 | 27871.5 | 198.70 | 12.42 | 45.1 | 2.82 | 51.5 | 3.22 | 227.1 |
| 3 | 20.0 | 105.7 | 29177.5 | 284.90 | 14.25 | 36.4 | 1.82 | 43.4 | 2.17 | 127.8 |
| 4 | 20.0 | 97.6 | 23983.5 | 371.64 | 18.58 | 42.0 | 2.10 | 52.3 | 2.62 | 112.9 |
| 5 | 32.0 | 100.3 | 19033.0 | 735.85 | 23.00 | 93.7 | 2.93 | 106.5 | 3.33 | 127.4 |
| 6 | 38.5 | 59.7 | 33877.5 | 547.11 | 14.21 | 47.2 | 1.23 | 47.1 | 1.22 | 86.3 |
| 7 | 14.0 | 77.8 | 27292.0 | 239.55 | 17.11 | 21.9 | 1.56 | 26.9 | 1.92 | 91.3 |
| 8 | 24.0 | 148.4 | 26616.0 | 374.52 | 15.61 | 58.5 | 2.44 | 80.2 | 3.34 | 156.1 |
| 9 | 20.0 | 100.5 | 33082.0 | 268.46 | 13.42 | 30.4 | 1.52 | 38.9 | 1.95 | 113.4 |
| 10 | 17.0 | 72.4 | 24979.0 | 303.46 | 17.85 | 27.3 | 1.61 | 31.7 | 1.86 | 89.8 |
| 11 | 25.0 | 82.5 | 32414.5 | 355.22 | 14.21 | 35.0 | 1.40 | 42.3 | 1.69 | 98.5 |
| 12 | 19.0 | 111.5 | 32982.5 | 242.82 | 12.78 | 35.6 | 1.87 | 39.1 | 2.06 | 142.4 |
| Mean | 22.0 | 101.7 | 29726.6 | 344.01 | 15.37 | 41.2 | 1.90 | 48.8 | 2.20 | 123.1 |
| SD | 6.7 | 31.9 | 6334.5 | 149.66 | 3.16 | 18.9 | 0.60 | 22.2 | 0.70 | 37.6 |
| Min. | 14.0 | 59.7 | 19033.0 | 198.70 | 11.01 | 21.5 | 1.10 | 25.2 | 1.20 | 86.3 |
| Max. | 38.5 | 179.4 | 45410.3 | 735.85 | 23.00 | 93.7 | 2.90 | 106.5 | 3.30 | 227.1 |

**APPENDIX F 5: Midazolam non-compartmental analysis from Jones et al (1993).**

| Patient number | Time to eyes open (sec) | Time to eyes open (min) | Midazolam concentration (ng $ml^{-1}$) | Time to self identification (sec) | Time to self identification (min) | Midazolam concentration (ng $ml^{-1}$) |
|---|---|---|---|---|---|---|
| 1 | 2760 | 46 | 215 | 2880 | 48 | 208 |
| 2 | 2520 | 42 | 160 | 2640 | 44 | 153 |
| 3 | 2880 | 48 | 138 | 3000 | 50 | 136 |
| 4 | 2640 | 44 | 154 | 2700 | 45 | 133 |
| 5 | 3180 | 53 | 103 | 3240 | 54 | 103 |
| 6 | 2940 | 49 | 193 | 2940 | 49 | 193 |
| 7 | 2460 | 41 | 198 | 2700 | 45 | 183 |
| 8 | 4140 | 69 | 93 | 4200 | 70 | 92 |
| 9 | 2400 | 40 | 201 | 2460 | 41 | 180 |
| 10 | 2400 | 40 | 164 | 2400 | 40 | 164 |
| 11 | 2280 | 38 | 259 | 2340 | 39 | 257 |
| 12 | 3480 | 58 | 159 | 3540 | 59 | 155 |
| Mean | 2840 | 47.3 | 169.8 | 2920 | 48.7 | 163.1 |
| SD | 518.1 | 8.6 | 44.9 | 510.5 | 8.5 | 43.7 |
| Min. | 2280 | 38 | 93.0 | 2340 | 39 | 92 |
| Max. | 4140 | 69 | 259.0 | 4200 | 70 | 257 |

**APPENDIX F 6: Serum midazolam concentration (ng $ml^{-1}$) on awakening from Jones et al (1993).**

| Patient number | Bulked 24 hour urine volume (ml) | α - OH Midazolam | α - OH Midazolam glucuronide | 4 - OH Midazolam | 4 - OH Midazolam glucuronide | TOTAL | Flumazenil |
|---|---|---|---|---|---|---|---|
| 1 | 950 | 0.03 | 2.09 | 0.17 | 0.20 | 2.49 | 13.25 |
| 2 | 650 | 0.23 | 13.20 | 1.12 | 1.15 | 15.70 | 13.80 |
| 3 | 1,100 | 0.00 | 4.06 | 0.05 | 0.83 | 4.94 | 10.97 |
| 4 | 900 | 0.09 | 1.74 | 0.08 | 0.01 | 1.92 | 7.06 |
| 5 | 720 | 0.08 | 1.59 | 0.05 | 0.00 | 1.72 | 6.45 |
| 6 | 1,240 | 0.03 | 0.64 | 0.04 | 0.00 | 0.71 | 8.58 |
| 7 | 650 | 0.03 | 2.88 | 0.31 | 0.23 | 3.46 | 6.33 |
| 8 | 420 | 0.04 | 1.19 | 0.03 | 0.07 | 1.33 | 5.84 |
| 9 | 550 | 0.05 | 2.12 | 0.59 | 0.11 | 2.87 | 6.45 |
| 10 | 850 | 0.03 | 1.97 | 0.51 | 0.11 | 2.62 | 11.96 |
| Total | 8,030 | 0.62 | 31.48 | 2.95 | 2.71 | | 90.69 |
| Mean | 803 | 0.06 | 3.15 | 0.30 | 0.27 | 3.78 | 9.07 |
| SD | 240.17 | 0.06 | 3.46 | 0.34 | 0.37 | 4.13 | 2.96 |
| Min. | 420 | 0.00 | 0.64 | 0.03 | 0.00 | 0.71 | 5.84 |
| Max. | 1,240 | 0.23 | 13.20 | 1.12 | 1.15 | 15.70 | 13.80 |

**APPENDIX F 7: Percentage of midazolam and flumazenil dose recovered in a bulked 24 hour urine collection from Jones et al (1993).**

| Patient number | Time (min) 2 | 4 | 6 | 8 | 10 | 15 | 20 | 30 | 60 | 120 | 180 | 240 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 18 | 32 | 62 | 93 | 97 | 35 | 33 | 30 | 23 | 16 | 0 | 0 |
| 2 | 16 | 24 | 28 | 24 | 23 | 21 | 14 | 12 | 6 | 0 | 0 | 0 |
| 3 | 25 | 45 | 39 | 37 | 33 | 31 | 27 | 21 | 13 | 4 | 0 | 0 |
| 4 | 10 | 12 | 13 | 28 | 20 | 16 | 12 | 11 | 6 | 3 | 0 | 0 |
| 5 | 17 | 23 | 28 | 33 | 30 | 18 | 15 | 12 | 9 | 0 | 0 | 0 |
| 6 | 19 | 22 | 39 | 28 | 20 | 15 | 13 | 8 | 4 | 0 | 0 | 0 |
| 7 | 27 | 39 | 48 | 56 | 50 | 44 | 42 | 38 | 23 | 16 | 0 | 0 |
| 8 | 11 | 22 | 42 | 30 | 26 | 15 | 13 | 10 | 8 | 0 | 0 | 0 |
| 9 | 13 | 25 | 36 | 33 | 30 | 23 | 22 | 15 | 8 | 3 | 0 | 0 |
| 10 | 15 | 31 | 28 | 24 | 18 | 15 | 16 | 9 | 8 | 6 | 0 | 0 |
| 11 | 14 | 15 | 19 | 16 | 14 | 11 | 8 | 7 | 3 | 0 | 0 | 0 |
| 12 | 15 | 21 | 40 | 31 | 24 | 21 | 19 | 15 | 10 | 4 | 0 | 0 |
| Mean | 16.7 | 25.9 | 35.2 | 36.1 | 32.1 | 22.1 | 19.5 | 15.7 | 10.1 | 4.3 | 0 | 0 |
| SD | 4.9 | 9.0 | 12.6 | 19.5 | 21.5 | 9.4 | 9.5 | 9.1 | 6.3 | 5.6 | 0 | 0 |
| Min. | 10 | 12 | 13 | 16 | 14 | 11 | 8 | 7 | 3 | 0 | 0 | 0 |
| Max. | 27 | 45 | 62 | 93 | 97 | 44 | 42 | 38 | 23 | 16 | 0 | 0 |

**APPENDIX F 8: Flumazenil concentration (ng $ml^{-1}$) with time from Jones et al (1993).**

| Patient number | Body weight (kg) | $t_{½}$ (min) | AUC (total) (ng min $ml^{-1}$) | Cl (ml $min^{-1}$) | Cl / Body Wt. (ml $min^{-1}$ $kg^{-1}$) | $V_d$(ss) (L) | $V_d$ / Body wt. (L $kg^{-1}$) | $V^E$ (L) | $V^E$ / Body Wt. (L $kg^{-1}$) | MRT (min) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 18.7 | 75.5 | 4513.1 | 136.27 | 7.29 | 12.7 | 0.68 | 14.8 | 0.79 | 93.4 |
| 2 | 16.0 | 24.8 | 989.0 | 465.12 | 29.07 | 17.5 | 1.09 | 16.7 | 1.04 | 38.7 |
| 3 | 20.0 | 34.8 | 2059.9 | 291.27 | 14.56 | 14.7 | 0.74 | 14.6 | 0.73 | 50.6 |
| 4 | 20.0 | 38.9 | 1087.9 | 556.14 | 27.81 | 32.7 | 1.64 | 31.2 | 1.56 | 58.7 |
| 5 | 32.0 | 29.9 | 1194.1 | 686.70 | 21.46 | 31.5 | 0.98 | 29.7 | 0.93 | 45.9 |
| 6 | 38.5 | 22.2 | 778.7 | 963.17 | 25.02 | 30.0 | 0.78 | 30.8 | 0.80 | 31.2 |
| 7 | 14.0 | 42.8 | 3477.9 | 158.14 | 11.30 | 10.3 | 0.74 | 9.8 | 0.70 | 65.2 |
| 8 | 24.0 | 25.4 | 972.4 | 575.90 | 24.00 | 23.6 | 0.98 | 21.1 | 0.88 | 40.9 |
| 9 | 20.0 | 33.3 | 1466.5 | 358.00 | 17.90 | 17.2 | 0.86 | 17.2 | 0.86 | 47.9 |
| 10 | 17.0 | 36.1 | 1102.9 | 317.35 | 18.67 | 16.8 | 0.99 | 16.5 | 0.97 | 53.1 |
| 11 | 25.0 | 21.5 | 544.5 | 771.33 | 30.85 | 24.1 | 0.96 | 23.9 | 0.96 | 31.3 |
| 12 | 19.0 | 38.7 | 1603.5 | 358.60 | 18.87 | 20.7 | 1.09 | 20.0 | 1.05 | 57.7 |
| Mean | 22.0 | 35.3 | 1648.5 | 469.83 | 20.57 | 21.0 | 1.00 | 20.5 | 0.90 | 51.2 |
| SD | 6.7 | 13.8 | 1134.8 | 239.52 | 6.92 | 7.1 | 0.20 | 6.7 | 0.20 | 16.3 |
| Min. | 14.0 | 21.5 | 544.5 | 136.27 | 7.29 | 10.3 | 0.70 | 9.8 | 0.70 | 31.2 |
| Max. | 38.5 | 75.5 | 4513.1 | 963.17 | 30.85 | 32.7 | 1.60 | 31.2 | 1.60 | 93.4 |

**APPENDIX F 9: Flumazenil non-compartmental analysis from Jones et al (1993).**

| Patient number | Time to eyes open (sec) | Time to eyes open (min) | Flumazenil concentration (ng $ml^{-1}$) | Time to self identification (sec) | Time to self identification (min) | Flumazenil concentration (ng $ml^{-1}$) |
|---|---|---|---|---|---|---|
| 1 | 240 | 4.0 | 32 | 360 | 6.0 | 62 |
| 2 | 120 | 2.0 | 24 | 240 | 4.0 | 24 |
| 3 | 120 | 2.0 | 25 | 240 | 4.0 | 45 |
| 4 | 240 | 4.0 | 12 | 300 | 5.0 | 7 |
| 5 | 240 | 4.0 | 23 | 300 | 5.0 | 14 |
| 6 | 180 | 3.0 | 20 | 180 | 3.0 | 20 |
| 7 | 180 | 3.0 | 33 | 420 | 7.0 | 52 |
| 8 | 300 | 5.0 | 32 | 360 | 6.0 | 42 |
| 9 | 150 | 2.5 | 13 | 210 | 3.5 | 25 |
| 10 | 180 | 3.0 | 23 | 180 | 3.0 | 23 |
| 11 | 60 | 1.0 | 14 | 120 | 2.0 | 14 |
| 12 | 240 | 4.0 | 21 | 300 | 5.0 | 31 |
| Mean | 187.5 | 3.1 | 22.7 | 267.5 | 4.5 | 29.9 |
| SD | 65.0 | 1.1 | 7.0 | 84.4 | 1.4 | 16.1 |
| Min. | 60.0 | 1.0 | 12.0 | 120.0 | 2.0 | 7.0 |
| Max. | 300.0 | 5.0 | 33.0 | 420.0 | 7.0 | 62.0 |

**APPENDIX F 10: Flumazenil concentration (ng $ml^{-1}$) on awakening from Jones et al (1993).**

| Sample time (hr) | Observations (n) | Mean blood propofol concentration (ng $ml^{-1}$) | Standard deviation (SD) | Standard error of mean (SEM) |
|---|---|---|---|---|
| 0.003 | 7 | 3047.55 | 1204.30 | 455.18 |
| 0.083 | 12 | 1866.47 | 676.14 | 195.18 |
| 0.167 | 12 | 944.25 | 247.84 | 71.54 |
| 0.250 | 12 | 638.54 | 147.89 | 42.69 |
| 0.333 | 10 | 437.34 | 168.23 | 53.20 |
| 0.5 | 12 | 289.23 | 122.53 | 35.37 |
| 0.75 | 10 | 246.92 | 115.64 | 36.57 |
| 1.00 | 12 | 165.34 | 77.19 | 22.28 |
| 1.5 | 12 | 96.74 | 34.60 | 9.99 |
| 2.0 | 12 | 68.85 | 35.32 | 10.20 |
| 3.0 | 12 | 67.85 | 122.82 | 35.43 |
| 4.0 | 11 | 30.10 | 17.18 | 5.18 |
| 6.0 | 10 | 23.89 | 11.54 | 3.65 |
| 8.0 | 9 | 13.38 | 12.27 | 4.09 |
| 10.0 | 5 | 10.77 | 4.92 | 2.20 |
| 12.0 | 4 | 14.38 | 7.85 | 3.93 |
| 18.0 | 3 | 7.81 | 4.36 | 2.52 |
| 24.0 | 2 | 4.79 | 1.76 | 1.25 |

**APPENDIX F 11: Mean (SEM) blood propofol concentrations for each sampling time in the 12 children from Jones et al (1990a).**

| Patient number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | mean | SEM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $K_{12}$ | 4.185 | 9.151 | 0.313 | 11.984 | 2.889 | 5.589 | 5.874 | 3.170 | 5.574 | 13.412 | 3.712 | 3.742 | 5.80 | 1.12 |
| $K_{21}$ | 3.789 | 9.959 | 9.628 | 4.757 | 2.964 | 3.532 | 3.904 | 1.310 | 8.012 | 5.192 | 2.841 | 2.368 | 4.85 | 0.82 |
| $K_{13}$ | 5.722 | 9.471 | 3.748 | 2.906 | 1.595 | 1.115 | 1.678 | 0.641 | 1.378 | 1.564 | 2.194 | 2.125 | 2.84 | 0.72 |
| $K_{31}$ | 0.342 | 0.405 | 2.700 | 0.800 | 0.255 | 0.440 | 0.207 | 0.222 | 0.179 | 0.395 | 0.215 | 0.206 | 0.55 | 0.23 |
| $K_{10}$ | 6.792 | 19.549 | 3.336 | 14.412 | 2.942 | 3.715 | 4.317 | 1.811 | 2.539 | 5.792 | 5.449 | 6.156 | 6.40 | 1.53 |
| $V^G$ | 265.12 | 172.22 | 44.63 | 63.46 | 799.10 | 468.68 | 402.10 | 307.39 | 284.11 | 268.24 | 570.11 | 260.58 | 325.47 | 61.22 |
| $V^G$/kg | 11.05 | 5.56 | 2.23 | 3.97 | 23.50 | 12.67 | 18.28 | 11.82 | 14.76 | 6.88 | 21.93 | 16.04 | 12.38 | 1.98 |
| AUC | 75.10 | 96.54 | 61.24 | 58.83 | 41.33 | 37.24 | 56.44 | 86.19 | 90.02 | 73.63 | 45.51 | 62.24 | 65.35 | 5.56 |
| $V^{ss}$ (L) | 132.79 | 61.94 | 33.70 | 20.25 | 345.40 | 204.13 | 143.60 | 157.62 | 118.56 | 103.44 | 196.68 | 82.10 | 133.34 | 25.56 |
| $V^{ss}$/kg | 5.53 | 2.00 | 1.69 | 1.27 | 10.16 | 5.52 | 6.53 | 6.06 | 6.16 | 2.65 | 7.56 | 5.05 | 5.01 | 2.66 |
| $T_{½}^{a}$ (min) | 2.32 | 1.01 | 3.78 | 1.32 | 4.67 | 3.29 | 2.94 | 6.44 | 2.69 | 1.70 | 3.33 | 3.22 | 3.06 | 0.43 |
| $T_{½}^{b}$ (min) | 15.30 | 5.87 | 5.26 | 15.36 | 26.42 | 28.77 | 24.46 | 74.99 | 19.94 | 25.31 | 23.43 | 26.86 | 24.33 | 5.13 |
| $T_{½}^{i}$ (min) | 229.98 | 153.77 | 37.88 | 64.68 | 262.50 | 131.48 | 285.97 | 282.47 | 368.29 | 140.38 | 276.65 | 276.65 | 209.22 | 29.26 |
| TBC ($Lmin^{-1}$) | 798 | 797 | 816 | 679 | 2,056 | 2,470 | 974 | 754 | 534 | 1,324 | 1,428 | 652 | 1,106 | 175 |
| TBC / kg | 33.25 | 25.70 | 40.80 | 42.43 | 60.47 | 66.75 | 44.27 | 29.00 | 27.74 | 33.94 | 39.66 | 40.12 | 40.34 | 3.60 |
| $V^c$ (L) | 7.06 | 7.45 | 14.69 | 2.83 | 41.94 | 39.90 | 13.54 | 24.99 | 12.63 | 13.72 | 15.72 | 6.36 | 16.31 | 3.77 |
| $V^c$/kg | 0.29 | 0.08 | 0.73 | 0.18 | 1.23 | 1.08 | 0.62 | 0.96 | 0.66 | 0.35 | 0.60 | 0.39 | 0.60 | 0.10 |
| Age (yr) | 9 | 12 | 5 | 4 | 7 | 12 | 8 | 8 | 7 | 11 | 7 | 5 | 7.92 | 0.77 |
| Weight (kg) | 24 | 31 | 20 | 16 | 34 | 37 | 22 | 26 | 19 | 39 | 26 | 16 | 25.83 | 2.28 |
| anaesthetic time (min) | 27 | 34 | 35 | 22 | 31 | 30 | 30 | 22 | 27 | 31 | 36 | 21 | 28.83 | 1.48 |
| eye opening time (min) |  | 30 | 38 | 36 | 28 | 21 | 34 | 28 | 15 | 61 | 11 | 33 | 30.45 | 4.00 |
| propofol dose (mg) | 60 | 77 | 50 | 40 | 85 | 92 | 55 | 65 | 48 | 98 | 65 | 41 | 64.35 | 9.70 |

**APPENDIX F 12: Demographic, awakening and propofol pharmacokinetic data in the 12 children from Jones et al (1990a).**

# APPENDIX G

## Drug blood levels

| Patient number | Age (yr) | Weight (kg) | Induction agent | Premed effect | Picture Score after sleep | Picture Score after premed | Preoperative Serum Midazolam Concentration (ng ml$^{-1}$) 30 min | 60 min | 90 min | 120 min |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 6 | 25.0 | T | 2 | 40 | 0 | 30.50 | 74.00 | 50.75 | 42.62 |
| 3 | 10 | 37.4 | T | 2 | 100 | 100 | 42.50 | 78.00 | 57.00 | 49.00 |
| 8 | 7 | 19.0 | T | 2 | 100 | 100 | 29.50 | 77.00 | 42.00 | 42.00 |
| 10 | 6 | 17.0 | T | 2 | 80 | 80 | 31.50 | 48.50 | 38.50 | 37.60 |
| 15 | 12 | 33.5 | T | 2 | 100 | 100 | 19.50 | 68.50 | 50.00 | 35.50 |
| 21 | 5 | 18.5 | T | 2 | 100 | 80 | 33.35 | 55.00 | 31.25 | 40.00 |
| 24 | 8 | 21.0 | T | 2 | 100 | 80 | 25.00 | 93.75 | 52.50 | 35.00 |
| 27 | 8.5 | 30.0 | T | 2 | 100 | 100 | 37.00 | 92.00 | 47.00 | 38.00 |
| 28 | 5 | 19.0 | T | 2 | 100 | 80 | 31.38 | 81.50 | 57.50 | 41.00 |
| 29 | 6 | 17.0 | T | 2 | 100 | 80 | 39.50 | 134.00 | 68.00 | 28.00 |
| 2 | 8.5 | 28.0 | P | 2 | 100 | 100 | 16.50 | 69.00 | 40.35 | 34.50 |
| 5 | 11 | 33.0 | P | 4 | 100 | 100 | 26.00 | 59.00 | 31.00 | 30.34 |
| 6 | 9 | 25.0 | P | 2 | 100 | 100 | 31.50 | 55.00 | 30.50 | 32.88 |
| 13 | 6 | 18.0 | P | 2 | 80 | 100 | 31.50 | 55.10 | 42.50 | 30.34 |
| 16 | 6 | 25.0 | P | 2 | 100 | 100 | 19.00 | 92.00 | 68.00 | 38.38 |
| 17 | 5 | 22.0 | P | 2 | 100 | 60 | 40.00 | 66.00 | 37.03 | 21.62 |
| 18 | 6 | 18.0 | P | 2 | 80 | 80 | 28.00 | 68.35 | 31.00 | 31.00 |
| 22 | 9 | 27.0 | P | 2 | 100 | 80 | 35.75 | 77.00 | 65.75 | 20.50 |
| 25 | 8 | 27.0 | P | 2 | 100 | 100 | 23.25 | 51.38 | 47.00 | 38.00 |
| 30 | 5 | 16.0 | P | 2 | 100 | 80 | 27.00 | 85.50 | 70.75 | 52.00 |
| 4 | 5 | 17.5 | M | 2 | 80 | 80 | 35.50 | 57.00 | 52.00 | 42.00 |
| 7 | 9 | 25.5 | M | 2 | 100 | 100 | 29.00 | 59.50 | 47.50 | 30.00 |
| 9 | 5 | 21.5 | M | 2 | 100 | 0 | 33.50 | 78.00 | 37.50 | 26.00 |
| 11 | 8 | 22.0 | M | 2 | 100 | 100 | 21.62 | 76.00 | 57.25 | 46.00 |
| 12 | 4.5 | 16.0 | M | 2 | 100 | 100 | 31.50 | 57.25 | 39.13 | 33.50 |
| 14 | 6 | 18.0 | M | 2 | 100 | 100 | 19.50 | 43.50 | 28.50 | 18.50 |
| 19 | 9 | 26.6 | M | 2 | 100 | 100 | 39.00 | 74.00 | 63.00 | 43.00 |
| 20 | 10 | 25.0 | M | 2 | 100 | 100 | 26.00 | 100.15 | | 42.00 |
| 23 | 11 | 27.0 | M | 2 | 100 | 80 | 33.35 | 88.75 | 76.66 | 38.35 |
| 26 | 4 | 15.0 | M | 2 | 100 | 0 | 26.15 | 52.00 | 44.5 | 32.00 |

**APPENDIX G 1: Patient data and preoperative serum midazolam levels from Jones et al (1993c & d).**

| Patient number | Anaesthesia duration (min) | Eye-opening time (min) | Identification time (min) | Post-operative Serum Midazolam Concentration (ng $ml^{-1}$) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | awakening | 60 (min) | 120 (min) | 180 (min) | 240 (min) |
| **4** | 32 | 24 | 26 | 151.00 | 97.50 | 59.00 | 34.00 | |
| **7** | 42 | 30 | 36 | 141.00 | 93.50 | 78.50 | 40.12 | 33.00 |
| **9** | 27 | 29 | 45 | 137.00 | 67.50 | 39.00 | 35.00 | 31.00 |
| **11** | 39 | 21 | 29 | 134.38 | 91.00 | 51.25 | 37.00 | 19.50 |
| **12** | 35 | 23 | 24 | 127.88 | 58.50 | 49.75 | 41.62 | 29.00 |
| **14** | 48 | 27 | 31 | 131.00 | 77.25 | 52.25 | 48.50 | 33.50 |
| **19** | 32 | 57 | 57 | 134.50 | 74.00 | 66.00 | 53.00 | 19.50 |
| **20** | 33 | 30 | 30 | 131.00 | 79.75 | 51.00 | | |
| **23** | 32 | 35 | 35 | 115.00 | 90.00 | 46.25 | 45.00 | 28.35 |
| **26** | 35 | 42 | 42 | 190.70 | 69.50 | 49.50 | 19.50 | 17.00 |
| **mean** | 35.5 | 31.8 | 35.5 | 139.35 | 79.85 | 54.25 | 39.30 | 26.36 |
| **SD** | 6.0 | 10.8 | 10.1 | 19.22 | 12.17 | 10.54 | 9.71 | 6.65 |
| **min** | 27 | 21 | 24 | 115.00 | 58.50 | 39.00 | 19.50 | 17.00 |
| **max** | 48 | 57 | 57 | 190.70 | 97.50 | 78.50 | 53.00 | 33.50 |

**APPENDIX G 2: Awakening data and postoperative serum midazolam levels from Jones et al (1993c & d).**

| Patient number | Anaesthesia duration (min) | Eye-opening time (min) | Identification time (min) | Post-operative Serum Thiopentone Concentration (ng ml$^{-1}$) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | awakening | 60 (min) | 120 (min) | 180 (min) | 240 (min) |
| 1 | 27 | 36 | 40 | - | 0.39 | 0.26 | 0.25 | 0.09 |
| 3 | 47 | 25 | 26 | - | 0.42 | 0.07 | 0.06 | 0.06 |
| 8 | 35 | 19 | 19 | 0.42 | 0.12 | 0.09 | 0.07 | 0.06 |
| 10 | 38 | 33 | 34 | - | 0.82 | 0.74 | 0.61 | 0.51 |
| 15 | 37 | 22 | 22 | 0.34 | 0.05 | - | - | - |
| 21 | 36 | 16 | 16 | - | 0.21 | 0.11 | 0.06 | - |
| 24 | 21 | 23 | 25 | 14.44 | 0.13 | 0.08 | - | - |
| 27 | 28 | 26 | 29 | 1.46 | 1.40 | 0.60 | 0.53 | 0.11 |
| 28 | 25 | 34 | 36 | 2.35 | 0.16 | 0.16 | 0.14 | 0.11 |
| 29 | 31 | 18 | 23 | 18.15 | 0.35 | 0.11 | 0.10 | 0.09 |
| mean | 32.5 | 25.2 | 27.0 | 6.19 | 0.41 | 0.22 | 0.18 | 0.11 |
| SD | 7.2 | 6.7 | 7.3 | 7.26 | 0.39 | 0.24 | 0.21 | 0.14 |
| min | 21 | 16 | 16 | 0.34 | 0.05 | 0.0 | 0.0 | 0.0 |
| max | 47 | 36 | 40 | 18.15 | 1.40 | 0.74 | 0.61 | 0.51 |

**APPENDIX G 3: Awakening data and postoperative serum thiopentone levels from Jones et al (1993c & d).**

| Patient number | Anaesthesia duration (min) | Eye-opening time (min) | Identification time (min) | Post-operative Blood Propofol Concentration (ng $ml^{-1}$) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | awakening | 60 (min) | 120 (min) | 180 (min) | 240 (min) |
| 2 | 30 | 21 | 22 | 463.5 | 83.7 | 44.7 | 27.4 | 24.3 |
| 5 | 39 | 23 | 23 | - | 162.7 | 102.8 | 70.8 | 70.1 |
| 6 | 33 | 24 | 25 | 438.5 | 116.3 | 80.4 | 35.8 | 35.0 |
| 13 | 25 | 10 | 10 | - | 176.8 | 150.2 | 34.0 | 29.4 |
| 16 | 25 | 33 | 34 | 379.0 | 97.7 | 85.6 | 46.9 | 37.3 |
| 17 | 28 | 30 | 34 | 323.1 | 100.2 | 58.7 | 56.1 | 49.4 |
| 18 | 30 | 18 | 22 | 286.0 | 105.5 | 80.1 | 49.3 | 25.9 |
| 22 | 35 | 11 | 11 | - | 226.0 | 215.7 | 113.1 | 104.2 |
| 25 | 27 | 29 | 29 | 941.1 | 306.1 | 141.7 | 115.9 | 69.4 |
| 30 | 27 | 20 | 20 | 439.4 | 181.1 | 91.5 | 78.7 | 65.1 |
| mean | 29.9 | 21.9 | 23 | 467.2 | 155.6 | 105.2 | 62.8 | 51.0 |
| SD | 4.3 | 7.2 | 7.8 | 82.7 | 22.2 | 16.1 | 9.9 | 8.2 |
| min | 25 | 10 | 10 | 286.0 | 83.7 | 44.7 | 27.4 | 24.3 |
| max | 39 | 33 | 34 | 941.1 | 306.1 | 215.7 | 115.9 | 104.2 |

**APPENDIX G 4: Awakening data and postoperative serum propofol levels from Jones et al (1993c & d).**

# APPENDIX H

## Data collection sheets

## PATIENT DATA PREMEDICATION / SATURATION

| NAME : HOSPITAL NO.: AGE: DATE: / / 90 WEIGHT: kg No: | | |
|---|---|---|
| Medical History \| | | PRE-MEDICATION |
| **1.** RESPIRATORY SYMPTOMS<br>RTI? N / Y Date:<br>SLEEP APNOEA N / Y SIDS SIB ?<br>TONSILLITIS N / Y<br>OBSTRUCTIVE SYMPTOMS N / Y | **2.** OTHER RELEVANT MEDICAL HISTORY | **3.** PETHIDINE/ATROPINE<br>MIDAZOLAM/ATROPINE<br>---<br>TIME (24 Hr CLOCK)<br>PRE MED :<br>INTO OR :<br>INTO RECOVERY :<br>TO IDENTIFY SELF : |
| **4.** ANAESTHESIA<br>FENTANYL Y / N DOSE Mcg | **5.**<br>TONSILLAR ENLARGEMENT<br>CORMACK & LEHANE | **6.** WARD DETAILS<br>SLEEPING ON RETURN Y / N<br>HOW LONG<br>FULLY AWAKE |

# PAEDIATRIC SATURATION STUDY

**Patient name:** **Age:** **Sex:** **P / M :** **Hosp. No.:**

| | Period 1 | | Period 2 | | Period 3 | | Period 4 | |
|---|---|---|---|---|---|---|---|---|
| Time invalidated by satmaster | | | | | | | | |
| Time invalidated by operator | | | | | | | | |
| Total time valid | | | | | | | | |
| | | | | | | | | |
| Mean $SpO_2$ | | | | | | | | |
| Time in Range: 90 - 95% | | | | | | | | |
| 85 - 90% | | | | | | | | |
| 80 - 85% | | | | | | | | |
| 75 - 80% | | | | | | | | |
| 70 - 75% | | | | | | | | |
| < 70% | | | | | | | | |
| No. of episodes 90 - 95% | | | | | | | | |
| 85 - 90% | | | | | | | | |
| 80 - 85% | | | | | | | | |
| 75 - 80% | | | | | | | | |
| 70 - 75% | | | | | | | | |
| < 70% | | | | | | | | |

## INSTRUCTIONS TO NURSING STAFF

The aim of this study is to find out what happens to the oxygen saturation of children before and after they undergo surgery.

**Do not disconnect any of the plugs from the oximeter, computer or at the wall. If the computer is disconnected, even for one second, it loses all the information and this is a disaster!!! If disconnecting the oximeter to go to toilet etc. Do not remove the micropore from the patient but disconnect at the grey / white junction.**

THANK YOU for your help and co-operation!

Any problem / question - ring 298.

Please fill in the following information below:

1. Time patient receives pre-med
2. Times oximeter disconnected and re-connected for procedures. Please keep the time disconnected to a minimum.
3. Times post-op analgesia given and dose **also** fill in overleaf if patient was awake / asleep on returning to the ward and for how long.

| Time | Event |
|---|---|

## PATIENT DATA
## MIDAZOLAM / FLUMAZENIL (ANEXATE) PHARMACOKINETICS

NAME: HOSPITAL NO: HKID:

DATE: AGE: WEIGHT: kg CODE NO:

*Condition on arrival in theatre:*

1. Agitated / Crying .....
2. Aware, apparently anxiety free .....
3. Drowsy .....
4. Asleep, responds to commands .....

1. Are you frightened? Y / N
   leaving mummy Y / N
   going to sleep Y / N
2. If Y, then what are you frightened of?
   Pain Y / N gweilos Y / N dying Y / N
   needles Y / N .....

***Induction:***

Alfentanil 5 micg/kg , then 60 sec later give Midazolam 0.5 mg/kg over 30 seconds
**Commence pharmacokinetic timing at the end of midazolam administration**
Atracurium 0.5 mg/kg

**Time of induction:** ..... hr **Time of extubation:**.....hr
Duration of anaesthesia ..... min

Induction comments: .....

***Extubation:***

Commence 6 minute timing and give reversal, 100% oxygen and extubate simultaneously.
Gently ventilate by mask until spontaneous ventilation recommences
when breathing transfer to recovery
6 minutes after reversal give the first undiluted does of flumazenil,
then wait one minute and commence the diluted flumazenil infusion.
The infusion is to continue until the child says his name.

***Recovery:***

**Actual time Flumazenil given in recovery :** ..... hr

Actual time of **spontaneous eye opening :** ..... hr

Time from Flumazenil injection to spontaneous eye opening .....sec

Actual time of giving **own name:** .....hr

Volume of **full strength** flumazenil: ..... ml **Half strength** .....ml

**Total Does of flumazenil** .....mg

Recovery comments and side effects:.....

**24 Hour URINE volume:** .....ml **10 ml urine sample collected** Y / N

| *Sample No.* | MIDAZOLAM | | | | | | | | | FLUMAZENIL | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
| Time (min) | 0 | 2 | 4 | 6 | 8 | 10 | 15 | 20 | 30 | 2 | 4 | 6 | 8 | 10 | 15 | 20 | 30 | 60 | 120 | 180 | 240 |
| Actual Time | | | | | | | | | | | | | | | | | | | | | |
| HR | | | | | | | | | | | | | | | | | | | | | |
| BP | | | | | | | | | | | | | | | | | | | | | |
| RR | | | | | | | | | | | | | | | | | | | | | |
| Does patient go back to sleep in the WARD ? | | | | | | Y / N | | **COMA SCALE** | | | | | | | | | | | | | |

**Time into recovery:**

**Time of eye opening:**

**Time of identification:**

Toy Completion Time (sec)

Childs mood on awakening

1. laughing, euphoric
2. happy, contented playful
3. calm, drowsy, asleep
4. crying but calmed or irritable
5. severe pain, screaming, inconsolable

*Actual time patient goes to sleep in the WARD:* hrs

**COMA SCALE**

CONSCIOUSNESS:

| | |
|---|---|
| Fully awake, eyes open, conversing | = 4 |
| Lightly asleep, eyes opening intermittently | = 3 |
| Eyes open on command or in response to name | = 2 |
| Responding to ear pinching | = 1 |
| Not responding | = 0 |

AIRWAY:

| | |
|---|---|
| Opening mouth or coughing or both, on command | = 3 |
| No voluntary cough, but airway clear without support | = 2 |
| Airway obstructed on neck flexion but clear without support on extension | = 1 |
| Airway obstructed without support | = 0 |

ACTIVITY:

| | |
|---|---|
| Raising one arm on command | = 2 |
| Non purposeful movement | = 1 |
| Not moving | = 0 |

Add Scores for Consciousness, Airway and Activity

**WRITE IN THE BOX ABOVE** TOTAL SCORE=======

**TOY COMPLETION**

SET UP:

Tray with Box and shapes
Box at back of tray (Red button Uppermost)

2 Rows of shapes in front in the order below:

| | | | |
|---|---|---|---|
| Cross (Orange) | Arrow (Blue) | Star (Green) | Animal (Yellow) |
| Animal (Green) | Clover (Yellow) | Animal (Blue) | Animal (Orange) |

TEST:

1. Place tray in front of child
2. Start timing
3. Finish timing on completion

| | |
|---|---|
| 1st ..... sec. | 5th ..... sec. |
| 2nd ..... sec. | 6th ..... sec. |
| 3rd ..... sec. | 7th ..... sec. |
| 4th ..... sec. | |

Pre-op. Toy Completion

**PLEASE DO NOT HELP THE CHILD** **Fastest Time .....secs.**

**PATIENT DATA** **PROPOFOL / PHARMACOKINETIC DATA**

NAME: HOSPITAL NO.: HKID:

AGE: WEIGHT: kg

*Condition on Arrival in Theatre:*

1. Agitated / Crying ..... 2. Aware, apparently anxiety free .....

3. Drowsy ..... 4. Alert, responds to commands .....

Time of Induction: Time entered recovery (finish time) :

i.e. Anaesthetic time:

*Induction Grading:*

1. Good ..... absence of side effects.

2. Adequate ..... side effects not interfering with induction.

3. Poor ..... side effects severe / protracted.

ANAESTHETISTS: SAMPLER:

Movement Grading:

1. Semi-purposeful ..... 2. Tremor / rigidity .....

3. Convulsions ..... 4. Breath holding / apnoea .....

5. Hiccup / Cough / Laryngospasm ..... 6. None .....

If Apnoea occurs, Peak $ETCO_2$ Post apnoea mmHg.

Duration of apnoea secs.

Requiring ventilation Y / N

Desaturation ( < 90% ) duration : secs.

Induction Comments: .....

.....

Recovery Comments: .....

.....

| | MINUTES | | | | | | | | | | | | HOURS | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time | 0 | 2 | 5 | 10 | 15 | 20 | 30 | 45 | 60 | 90 | 120 | 180 | 4 | 6 | 8 | 10 | 12 | 18 | 24 | |
| Actual Time | | | | | | | | | | | | | | | | | | | | |
| HR | | | | | | | | | | | | | | | | | | | | |
| BP | | | | | | | | | | | | | | | | | | | | |
| $SpO_2$ | | | | | | | | | | | | | | | | | | | | |
| $E_TCO_2$ | | | | | | | | | | | | | | | | | | | | |
| RR | | | | | | | | | | | | | | | | | | | | |
| COMA SCORE | | | | | | | | | | | | | | | | | 0 | | | |
| MOOD SCORE | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |

Time into recovery:

Times eyes open spontaneously:

Time of name identification:

**COMA SCALE**

CONSCIOUSNESS:

| | |
|---|---|
| Fully awake, eyes open, conversing | = 4 |
| Lightly asleep, eyes opening intermittently | = 3 |
| Eyes open on command or in response to name | = 2 |
| Responding to ear pinching | = 1 |
| Not responding | = 0 |

AIRWAY:

| | |
|---|---|
| Opening mouth or coughing or both, on command | = 3 |
| No voluntary cough, but airway clear without support | = 2 |
| Airway obstructed on neck flexion but clear without support on extension | = 1 |
| Airway obstructed without support | = 0 |

ACTIVITY:

| | |
|---|---|
| Raising one arm on command | = 2 |
| Non purposeful movement | = 1 |
| Not moving | = 0 |

Add Scores for Consciousness, Airway and Activity

TOTAL SCORE=

**MOOD SCORE**

1. Laughing / euphoric
2. Happy, contented, playful
3. Calm or asleep
4. Crying but calmed
5. Severe pain, screaming, inconsolable

**PATIENT DATA MIDAZOLAM / ANEXATE**

NAME: HOSPITAL NO: HKID:

DATE: AGE: WEIGHT: kg CODE NO:

*Condition on arrival in theatre:*

1. Agitated/Crying..... 2. Aware, apparently anxiety free .....

3. Drowsy ..... 4. Asleep, responds to commands .....

*Induction:*

**Time of induction:** ..... hr Time of **loss of eyelash reflex** ..... hr

Duration of any apnoeic episode $SaO_2$ < 90% ..... secs or NONE

Induction comments:.....

.....

*Recovery - Events:*

Time of arrival in recovery: ..... hr Duration of Anaes: .....min

**Actual time Trial drug given in recovery: ..... hr**

Actual time of **spontaneous eye opening:** .....hr

Time from reversal injection to spontaneous eye opening .....sec

Actual time of giving **own name:** .....hr

1st injection ..... mls 2nd injection .....mls
3rd injection ..... mls 4th injection .....mls

Total Dose ..... mls

Recovery comments and side effects: .....

.....

.....

*Evaluation by doctor:*

Examination of injection site
24 hr post op.

Efficacy of trial drug .....

.....

Tolerance of trial drug .....

**CODE: 1. Excellent 2. Good 3. Moderate 4. Poor**

| | PRE INDUCTION | Minutes Post-induction | | | | | PRE DRUG | Minutes post drug administration in Recovery & Ward | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 5 | 15 | 30 | | 2 | 5 | 10 | 30 | 60 | 2 hrs | 4 hrs | 18 hrs |
| | Actual Time | | | | | | | | | | | | | | |
| RR | | | | | | | | | | | | | | | |
| BP | | | | | | | | | | | | | | | |
| HR | | | | | | | | | | | | | | | |
| $E_TCO_2$ | | | | | | | Commence injection 3 minutes after arrival in recovery | | | | | | | | |
| **MOOD SCORE** | | | | | | Coma Scale | | | | | | | | | |
| Patient asleep, not arousable = 0<br>Patient asleep, but arousable = 1<br>Patient drowsy = 2<br>Patient awake = 3 | | | | | | Mood Score | | | | | | | | | |
| | | | | | | Toy Compl Time | | | | | | | | | |

**COMMA SCALE**

CONSCIOUSNESS:
Fully awake, eye open, conversing = 4
Lightly asleep, eyes opening intermittently = 3
Eyes open on command or in response to name = 2
Responding to ear pinching = 1
Not responding = 0

AIRWAY:
Opening mouth for coughing or both, on command = 3
No voluntary cough, but airway clear with support = 2
Airway obstructed on neck flexion but clear without support on extension = 1
Airway obstructed without support = 0

ACTIVITY:
Raising one arm on command = 2
Non purposeful movement = 1
Not moving = 0

Add Scores for Consciousness, Airway and Activity

TOTAL SCORE ==========

**TOY COMPLETION**

SET UP:

Tray with Box and shapes
Box at back of tray (Red Button Uppermost)

2 Rows of shapes in front in the order below:

| | | | |
|---|---|---|---|
| Cross (Orange) | Arrow (Blue) | Star (Green) | Animal (Yellow) |
| Animal (Green) | Clover (Yellow) | Animal (Blue) | Animal (Orange) |

TESTS:
1. Place tray in front of child
2. Start timing
3. Finish timing on completion

1st .....secs. 5th .....secs.
2nd .....secs. 6th .....secs.
3rd .....secs. 7th .....secs.
4th .....secs.

Pre-op. Toy Completion

**Fastest time .....Secs.**

**DO NOT HELP THE CHILD**

**PATIENT DATA SHEET - Propofol, Midazolam, Thiopentone induction study**

**NAME:** **HOSP No:** **STUDY No:**

**DATE:** / / 1992 **AGE:** yr. **WEIGHT:** kg

**Condition on arrival in O.T.:**

| | | | |
|---|---|---|---|
| agitated or crying | | Are you frightened? | y / n |
| aware, apparently anxiety free | | What are you frightened of ? | |
| drowsy | | leaving mummy | |
| asleep but responds to commands | | going to sleep | |
| **PICTURE CARD:** | Correct | gweilos | |
| **Features:** 1. | Y / N | | |
| 2. | | pain | |
| 3. | | | |
| 4. | | needles | |
| 5. | | | |
| **Score:** | **%** | dying | |

**INDUCTION AGENT:**

**Time of induction:** hr **Time to recovery:** hr

**Duration of anaesthesia:** min.

**Induction comments:**

.....

.....

**Time of eye opening:** hrs. **Time of identification:** hrs.

| WISC-R COMPLETION | TIME (sec) | ERRORS (n) |
|---|---|---|
| 1st | | |
| 2nd | | |
| 3rd | | |
| 4th | | |
| 5th | | |
| 6th | | |
| 7th | | |
| **fastest time with least errors** | | |

| SAMPLE NO. | 1 | 2 | 3 | 4 | O. | T. | induction | | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time of Sample | 30 | 60 | 90 | 120 | 0 | 2 | 4 | 6 | AWAKE | 1 hour | 2 hour | 3 hour | 4 hour |
| Actual Time | | | | | | | | | | | | | |
| heart rate ($min^{-1}$) | | | | | | | | | | | | | |
| systolic BP (mmHg) | | | | | | | | | | | | | |
| respiratory rate ($min^{-1}$) | | | | | | | | | | | | | |
| end tidal $CO_2$ (kPa) | | | | | | | | | | | | | |
| **Post-Box toy** (sec) | | | | | | | | | | | | | |
| **WISC-R test** (sec) | | | | | | | | | | | | | |
| **MOOD** score | | | | | | | | | | | | | |
| **COMA** score | | | | | | | | | | | | | |

If the child goes back to sleep after transfer to the ward, mark the COMA score with an **A** at the time of assessment, awaken the child & perform the test.

| **AIRWAY:** | | **CONSCIOUSNESS:** | **score** | **ACTIVITY** | **score** |
|---|---|---|---|---|---|
| opening mouth or coughing on command | **3** | fully awake, eyes open, conversing | **4** | raising one arm on command | **2** |
| no voluntary cough, clear airway without support | **2** | lightly asleep, eyes opening intermittently | **3** | non-purposeful movement | **1** |
| obstruction on neck flexion, clear without support on extension | **1** | eyes open on command or in response to name | **2** | not moving | **0** |
| airway obstructed without support | **0** | responding to ear pinching | **1** | | **1** |
| | | not responding | **0** | | |
| **Add scores for AIRWAY, CONSCIOUSNESS, ACTIVITY** | **and** | write score in coma score box above | | **COMA SCORE** | |

| **MOOD SCORE:** | | **POST-BOX TOY COMPLETION TIME:** | | | | |
|---|---|---|---|---|---|---|
| laughing, euphoric | **1** | Place the box on the left of the tray with the two rows of shapes to the right, in front of the child and | 1st | | 5th | |
| happy, playful | **2** | in this order: **CROSS** (orange) **ARROW** (blue) **STAR** (green) **ANIMAL** (yellow) | 2nd | | 6th | |
| calm, drowsy, sleepy | **3** | **ANIMAL** (green) **CLOVER** (yellow) **ANIMAL** (blue) **ANIMAL** (orange) | 3rd | | 7th | |
| irritable but calmed by mother | **4** | Record the child's completion time | 4th | | 8th | |
| screaming, inconsolable | **5** | **PLEASE DO NOT HELP THE CHILD, BUT DO GIVE ENCOURAGEMENT** | | **FASTEST TIME** | | **(sec)** |