ASPECTS OF DRUG USE IN SCHIZOPHRENIA, CARDIAC SURGERY AND PALLIATIVE CARE

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submitted in fulfilment of the requirements for the degree of Doctor of Philosophy.

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SUMMARY

The research in this thesis involved four studies of the variability in plasma concentrations and effects of a selection of drugs used in schizophrenia, cardiac surgery and palliative care.

1. Fluphenazine study

Steady-state pre-dose plasma concentrations of fluphenazine were measured using a gas chromatography/mass spectrometry assay in 24 patients with schizophrenia who were receiving continuous treatment with depot intramuscular fluphenazine decanoate. Clinical response was measured using the Andreasen Scale for positive and negative symptoms. Poorer clinical control was related to higher log transformed plasma concentrations of fluphenazine and higher fluphenazine decanoate dosage. The log transformed plasma concentrations of fluphenazine and the fluphenazine decanoate dosages were weakly related. These results indicated the useful role that plasma level monitoring can fulfil in identifying patients who are therapy-resistant despite optimal or high plasma levels.

2. CPB study

This study examined the effect of cardiopulmonary bypass (CPB) surgery on the total and unbound plasma concentrations of fentanyl and the total plasma concentrations of alcuronium in sixteen patients. Due to the large number of factors which may affect pharmacokinetics during CPB, the results were difficult to deal with mathematically. Despite marked declines in the plasma concentrations of both drugs on initiation of CPB, suitable plasma concentrations for anaesthesia were maintained throughout the procedure.

3. Subcutaneous fentanyl

This study investigated the steady-state total and unbound plasma concentrations of fentanyl during continuous subcutaneous administration in 20 palliative care patients. Infusion rates and both total and unbound plasma concentrations of fentanyl were correlated. Even with standardisation for dosage, there was an 8-fold variation in total plasma concentrations and a 3.5-fold variation in unbound plasma concentrations of fentanyl. There was considerable inter-patient variability in the pharmacokinetics of fentanyl with subcutaneous infusion in the palliative care setting, which necessitated careful titration of dosage according to individual clinical response.

4. Nebulised morphine trial

The final study involved a trial of nebulised morphine for dyspnoea in eleven palliative care patients. Due to patient attrition and the resulting small sample size, a significant improvement in respiratory function and assessment of dyspnoea could not be found overall. Individual patients, however, reported an improvement in their symptoms. More studies with increased numbers are needed to statistically prove the benefit of nebulised morphine over saline alone for the relief of dyspnoea.

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ASPECTS OF DRUG USE IN SCHIZOPHRENIA, CARDIAC SURGERY AND PALLIATIVE CARE

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GENERAL INTRODUCTION

The enormous interindividual variability in plasma concentrations of drugs in patients receiving identical doses and the great diversity of responses to a particular plasma concentration has led to a growing interest in the need to individualise dosage and indeed therapy itself (Henry *et al*, 1994).

Pharmacokinetic variables are a major source of the above-mentioned non-uniformity and may include alterations to absorption, distribution, metabolism and excretion. Distribution, metabolism and excretion can all be affected by such things as age, sex, body weight and composition, tissue perfusion, degree of plasma protein binding, genetic factors, hepatic blood flow, renal function, drug interactions and the presence of chronic disease (Rowland & Tozer, 1989).

The clinical response to a drug even given the same plasma level will also vary with age, health, presence of chronic disease, genetic factors, interactions with other drugs and social habits such as alcohol and smoking (Grasela, 1994).

Different sections of the population may be problematic to treat optimally resulting from both the chronic nature of the condition they suffer and the interindividual variability of drug handling and response among the patients (Grasela, 1994).

Schizophrenia affects 1% of the population worldwide (Ryan, 1991) and after over thirty years of neuroleptic treatment, the objective is still not to provide a cure but to restore basic functions to an adequate level and seek relief from symptoms so as to ensure a satisfying and productive life. Schizophrenic patients often do not have concomitant organic

diseases such as renal or hepatic insufficiency but variations in metabolic activity are present due to hereditary and other factors, eg cigarette smoking, alcoholism and brain damage, which can all alter required dosages (Sramek *et al*, 1988). Antipsychotics typically have a narrow therapeutic window, an absence of an easily titratable clinical response, poor response rates and troublesome side effects all of which complicate treatment and add to the enormous difficulties of working with the mentally ill.

Palliative care patients can prove difficult to study scientifically due to the fact that quality of life is the overriding concern in the clinical management of these patients (Davis & Hardy, 1994). The aim is to provide treatment that enables these patients to experience the highest quality of life possible given their condition with attention focussed on the relief of suffering and alleviation of symptoms without providing a cure. The patients are commonly suffering from a multitude of disease states and as a result there is a high prevalence of polypharmacy in palliative care. In addition, elderly and cachectic patients may have abnormal pharmacokinetics due to an altered clearance, hypoalbuminaemia, poor fat stores or muscle wasting (Regnard, 1992).

In both populations the desired treatments should minimise toxicity and maximise acceptability, especially when these patients are very likely to be taking these medications every day for the rest of their lives. Furthermore, therapeutic failures are most likely to arise if the drug in question has a low therapeutic index or large pharmacokinetic variability, or if the patient is at particular risk due to concurrent disease or multiple drug therapy.

A third group of patients, those undergoing cardiopulmonary bypass, may not be taking drugs of interest long-term, but in the perioperative

period may receive up to 20 drugs concurrently (Buylaert, 1989) making interactions and additive side effects particularly important. In addition, the extreme changes during bypass to perfusion, protein binding and hepatic blood flow lead to many potential alterations to drug disposition and tend to make pharmacokinetic studies complicated (Hall, 1991).

Given the magnitude of the alterations to many factors in the study populations, the intention to control therapy on a dosage basis alone would prove difficult. To achieve therapeutic success, the dosage must be tailored in each case to meet individual needs. This can substantially decrease the likelihood and magnitude of both the over- and underdosage which are often causes of treatment failures. Tailoring of a dosage regimen for each individual and evaluating patients with possible toxicological problems is sometimes more easily achieved with knowledge of the plasma drug concentration in the patient (Brown *et al*, 1993). However, despite the knowledge of plasma drug concentration and average pharmacokinetic and pharmacodynamic data being valuable aids in the individualisation of dosage, they should not be used as substitutes for careful monitoring of clinical response. This is important as the concentration-effect relationship is often variable between individuals and for each patient there may exist a specific threshold concentration (Brown *et al*, 1993). Ultimately, information relating to the individual patient is most important.

If one dosage form proves unsuitable (eg because a patient is unable to take oral medication) or if side effects become undesirable (eg because of a high oral dose needed for therapeutic effect), a different dosage form of the same or similar drug with an altered dosage requirement may be the answer to treat the symptoms. Examples of this practice are:

i) intramuscular fluphenazine decanoate given when oral dosages are subject to non-compliance, incomplete absorption, first-pass effect and drug interactions (e.g., antacids); ii) subcutaneous fentanyl given when the palliative care patient is no longer able to take oral medication for pain control and when morphine causes unpleasant side effects such as confusion; iii) nebulised morphine given for dyspnoea in preference to oral or subcutaneous morphine thus avoiding some of the central side effects due to a lower dosage. The need for such changes in therapy will be determined on an individual basis according to the extent of any problems with the current drug therapy.

In this thesis, four studies involving plasma level monitoring and/or therapy individualisation were undertaken as outlined below.

1. *A study of schizophrenic patients receiving chronic fluphenazine therapy aiming to examine the interpatient variability in steady-state plasma levels.*

A group of twelve patients were collected as part of the author's Honours thesis (1991), but because insufficient data did not allow any definite conclusions to be made regarding plasma fluphenazine concentrations and either side effects or clinical state, a further twelve patients were recruited and their plasma analysed. This enabled a more detailed statistical treatment of the data and conclusions to be drawn.

Using proposed therapeutic ranges for fluphenazine from other studies, the proportion of study patients within this range was determined and related to clinical control in order to examine if there is any value monitoring in this situation or whether it is just an additional piece of information to guide and assess drug therapy.

2. *A study of patients undergoing cardiopulmonary bypass (CPB) surgery designed to determine the extent to which fentanyl and alcuronium pharmacokinetics are altered in these patients including investigations of the change in plasma protein binding of fentanyl and the extent of alcuronium and fentanyl binding to the extracorporeal circuit.*

The effect of CPB on concentration of drugs has been studied (Hug *et al*, 1994; Hall *et al*, 1993; Koska *et al*, 1981) but with very different dosage regimens and in different clinical settings which produce variations in the surgical procedure itself. This made it relevant to investigate the change in plasma concentrations of two of the drugs used commonly in CPB operations at the Cardiac Unit (Royal Hobart Hospital) - fentanyl and alcuronium; the major issue being whether suitable plasma concentrations are maintained given the extreme physiological changes occurring over the bypass period.

3. *A study of palliative care patients receiving subcutaneous fentanyl intended to examine the interpatient variability in steady-state plasma concentrations and relate these concentrations to dosage, pain control and other variables.*

No studies measuring the concentration of fentanyl after subcutaneous administration have been reported so this will allow a comparison between these concentrations and those found after transdermal and intravenous administration. Previous studies involve measurements in both palliative care and postoperative pain, where minimum effective analgesic concentrations have been documented (Zech *et al*, 1992; Gourlay *et al*, 1989). The occurrence of tolerance in palliative care patients may diminish the potential for target plasma concentrations.

4. *A trial in palliative care patients to evaluate the benefits of nebulised morphine administered for the treatment of dyspnoea.*

There is currently no indication that nebulised morphine is any better than saline for dyspnoea in palliative care so these patients may generally be receiving extra drugs unnecessarily. As they were already receiving many medications it would seem better to try and minimise therapy so as to reduce the potential for drug interactions and additive side effects.

Trials involving palliative care patients tend to encounter problems with patient accrual, attrition and selection of adequate outcome measures and the resulting small sample size and great intersubject variability did not allow for much statistical analysis in this study (Rinck *et al*, 1995).

PART I

MONITORING PLASMA LEVELS OF FLUPHENAZINE DURING CHRONIC TREATMENT

CHAPTER 1 : INTRODUCTION

1.1 Antipsychotics

Fluphenazine is a phenothiazine antipsychotic used in the treatment of schizophrenia. The long-acting depot formulation of fluphenazine decanoate is widely used to promote patient compliance, minimise the fluctuations in plasma concentrations of the drug, and possibly reduce the incidence of adverse effects (Davis *et al*, 1994; Hale, 1993; Burnett *et al*, 1993).

The use of fluphenazine may give rise to a number of adverse effects, including sedation, anticholinergic effects (such as dry mouth, blurred vision, urinary retention and constipation) and extrapyramidal effects. Tardive dyskinesia, which occurs in 20-30% of all patients on long term treatment (Gunne, 1990; McCreadie *et al*, 1992), is the major problem limiting the use of antipsychotics in the maintenance treatment of schizophrenia. Tardive dyskinesia has been considered to be related to the overall duration of exposure to antipsychotics and/or to the total amount absorbed (Balant-Gorgia & Balant, 1987). Similarly, it has often been suggested that high plasma levels of the antipsychotics are associated with the development of tardive dyskinesia, although the evidence remains conflicting (McCreadie *et al*, 1992; Yesavage *et al*, 1987). It seems sensible to ensure that patients do not receive greater dosages, and have higher plasma concentrations, of antipsychotics than clinically necessary (Marder, 1994; Bollini *et al*, 1994).

There is a large inter-patient variability in the dosage requirements of antipsychotic drugs. Typical dosages of fluphenazine decanoate in clinical practice are 12.5 to 75 mg intramuscularly every two to six weeks. Part of this variability is attributable to individual differences in the pharmacokinetics of these drugs; it has been well documented that steady-state plasma levels of the antipsychotics vary substantially between patients receiving the same dosage (Balant-Gorgia & Balant, 1987; Verghese *et al*, 1987; Martensson, 1990; Balant-Gorgia *et al*, 1993).

The inter-patient variability in pharmacokinetics, the relatively high rate of exacerbation of symptoms amongst patients with schizophrenia and the possible association between plasma levels and extrapyramidal adverse effects have led to considerable research over the last 10 years examining relationships between plasma levels of antipsychotics and clinical efficacy or adverse effects. This research has resulted in the tentative identification of therapeutic plasma concentration ranges for chlorpromazine, haloperidol, fluphenazine, perphenazine, thioridazine and thiothixene (Balant-Gorgia *et al*, 1993; Van Putten *et al*, 1991; Axelsson, 1990; Dahl, 1986; Table 1.1).

Table 1.1: Tentative therapeutic range of plasma concentrations for antipsychotics

Drug	Tentative therapeutic range of plasma concentrations (ng/mL)
Chlorpromazine	30 - 100
Haloperidol	5 - 15
Fluphenazine	0.2 - 2.0
Perphenazine	0.8 - 2.4
Thiothixene	2 - 15

Consequently, the determination of plasma levels of the antipsychotics is becoming more common in clinical practice as a potential means of assessing and improving patient compliance, reducing adverse effects, and improving the antipsychotic effect. It has been suggested that plasma level monitoring should be performed at least once a year in the maintenance treatment of chronic psychotic disorders (Axelsson, 1990), to shorten the duration of patients' disability and hospital stay, lessen the relapse rate, and reduce the incidence of adverse effects (Marder, 1994; Axelsson, 1990; Simpson & Kashinath, 1985). Several studies have examined the relationship between plasma concentrations of fluphenazine and clinical response, and a therapeutic range of approximately 0.2 to 2 ng/mL has been proposed (Balant-Gorgia *et al*, 1993; Van Putten *et al*, 1991; Axelsson, 1990; Dahl, 1986; Simpson & Kashinath, 1985; Jann *et al*, 1985; Dysken *et al*, 1981; Mavroidis *et al*, 1984; Midha *et al*, 1993). Others, however, believe that there have been insufficient well-designed studies with large numbers of patients to establish a therapeutic range (Javaid *et al*, 1991; Baldessarini *et al*, 1988).

1.2 Objectives of this Study

The objectives of this study were to determine the steady-state plasma concentrations of fluphenazine in patients receiving the drug by repeat depot intramuscular injection and not previously exposed to plasma level monitoring of antipsychotic drugs, and to examine any relationships between the plasma concentrations and clinical response. Because patients were not followed prospectively from the commencement of therapy, the study was not able to assist in defining a therapeutic range, but rather provides a snapshot of depot fluphenazine therapy during chronic treatment of schizophrenia.

CHAPTER 2 : MATERIALS AND METHODS

2.1 Materials

The materials used were: pure fluphenazine hydrochloride (Bristol-Myers Squibb Pharmaceuticals, Noble Park, Australia) and trifluoperazine (SmithKline Beecham, Sydney, Australia); heptane (AR; Mallinkrodt, Kentucky, USA); isopropanol (AR; Ajax Chemicals, Auburn, Australia); hydrochloric acid (AR; May and Baker Ltd, West Footscray, Australia); and sodium hydroxide (AnalaR, BDH Chemicals, Kilsyth, Australia). All of the other reagents were also of analytical grade. All glassware had been chromic acid washed. Outdated plasma from The Red Cross Society, Hobart was used for preparing standards.

The instrument used was a Hewlett-Packard model 5890 gas chromatograph coupled to a Hewlett-Packard 5970 mass selective detector. The column was a 13 m x 0.32 mm internal diameter Hewlett-Packard crosslinked fused-silica ultraperformance capillary column coated with methyl silicone gum (0.52 μm film thickness; HP-1).

2.2 Analytical Methods

Depot injections give low concentrations of fluphenazine in plasma which present considerable problems in the development of an assay with sufficient sensitivity and specificity. An assay utilising gas chromatography/mass spectrometry (GC/MS) with selective ion monitoring was adapted from several previously published procedures (Javaid *et al*, 1981; Franklin *et al*, 1978; Rivera-Calimlim & Siracusa, 1977).

2.2.1 Extraction from Plasma

Plasma standards were spiked to give fluphenazine concentrations of 0.1, 0.5, 1.0, 2.0, 3.0, 4.0 and 5.0 ng/mL from methanol solutions; 0.5 μg/mL and 50 ng/mL. Aliquots (5 mL) of plasma (patient samples, drug-free plasma, and plasma standards as above) were pipetted into 10 mL glass, conical-tipped, stoppered, centrifuge tubes. The internal standard, 80 ng trifluoperazine in methanol (10 μL), was added; 0.5 mL of 5M NaOH was added and the mixture extracted by shaking for 20 min on a horizontal shaker with 10 mL of heptane/isopropanol (9:1 v/v). Each tube was spun for 15 min in a refrigerated centrifuge (10°C) at 2,000 rpm to separate the phases and the upper organic layer was transferred to another 10 mL glass centrifuge tube and 1 mL of 0.1M HCl was added before vortexing for 2 min, centrifuging for 10 min at 2,000 rpm and discarding the organic phase. The acid phase was alkalinized with 0.25 mL 5M NaOH and extracted with 0.5 mL heptane/isopropanol (9:1 v/v) by vortexing for 1 min. After centrifugation for 10 min at 2,000 rpm, the organic phase was transferred to a 1 mL Reacti-Vial® (Pierce Chemical Company, Rockford, USA) and dried under a gentle stream of nitrogen at room temperature.

2.2.2 Derivatisation

To each vial containing the residue of the extract from plasma, 10 μL of N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA; Pierce Chemical Company) was added and mixed. It was capped and heated to 70°C in an oven and 30 min was allowed for the reaction to go to completion. This derivatisation is said to increase the sensitivity ten-fold (Whelpton & Curry, 1976) because the TMS derivative is less polar and therefore chromatographs better.

2.2.3 Quantification by Gas Chromatography/Mass Spectrometry

The injector temperature was ambient, the detector temperature was 290°C and the oven temperature program was 35°C for 0.5 minutes then increasing at a rate of 30°C/minute to 250°C and 10°C/minute to 310°C. Ultrahigh-purity helium (Commonwealth Industial Gases Ltd, Hobart, Australia) was used as a carrier gas with a head pressure of 10 psi. The ions monitored for fluphenazine were *m/z* 280 and *m/z* 406 and for trifluoperazine were *m/z* 266 and *m/z* 407. The mass spectrometer was tuned to *m/z* 264 to optimise the sensitivity of the assay.

About 1 to 2 μL of derivatised mixture was injected using a direct on-column technique into the gas chromatograph and the ratio of the peak area of fluphenazine to the peak area of the internal standard (trifluoperazine) was calculated. The concentration of fluphenazine in the plasma sample was calculated directly from the equation of the fluphenazine/trifluoperazine standard curve prepared from a series of such ratios obtained for standards.

The reproducibility of the method was ascertained by adding a known concentration of fluphenazine (2 ng/mL) and trifluoperazine (16 ng/mL) to five aliquots of drug-free plasma (5 mL) and analysing with the described procedure on the same day. The coefficient of variation of the peak area ratio of fluphenazine/trifluoperazine was calculated from the following formula:

Coefficient of variation (%) = (standard deviation/mean) x 100

The recovery of the extraction procedure was determined by comparing the peak areas of a known fluphenazine concentration (2 ng/mL) from (i) 5 mL of plasma and (ii) heptane/isopropanol (9:1 v/v). A full standard curve was run each time samples were analysed.

2.3 Human Procedures

Ethical approval to perform the research had been obtained from both the University of Tasmania and the Tasmanian State Mental Health Ethics Committees.

Twenty four patients with schizophrenia, as specified in the DSM-III-R criteria of the American Psychiatric Association (1987), were studied. The first twelve patients were part of the author's Honours thesis entitled "Monitoring plasma levels of fluphenazine during chronic treatment-relationship to efficacy and adverse effects" submitted November 1991 at the University of Tasmania. All had given informed consent (Appendix 1). They were regular attenders at a community-based rehabilitation, support and treatment centre (Peacock Centre, Hobart, Tasmania, Australia) who were receiving long term (i.e., greater than 3 years) treatment with depot fluphenazine decanoate (Modecate®). Relevant patient data were extracted from medical records (Appendix 2). Standard biochemical tests of liver and renal function were performed by the Clinical Chemistry Department of the Royal Hobart Hospital. After at least three injections with an identical dose of depot fluphenazine decanoate, a venous blood sample of 5 to 10 mL was drawn just prior to dosing and placed into tubes containing lithium heparin as an anticoagulant. In most cases, patients had been receiving constant dosages for the past 12 months. Plasma was separated by centrifugation and frozen at -18°C until determination of the fluphenazine concentration.

The Andreasen Scale for negative and positive symptoms was used to assess the presence and relative quantity of symptoms of schizophrenia (Andreasen, 1985; Koreen *et al*, 1994; Appendix 3). The assessments were independently performed by a psychiatrist and psychiatric nurse within

two weeks of blood collection. At the end of the client interview, the scores were reviewed by the assessors. Where there was concurrence with the two scores, a single score between zero and five was recorded. In cases of nonconcurrence, a single score was agreed upon after discussion. A negative symptom score was computed from the sum of the five "Scale for Assessment of Negative Symptoms" (SANS) items (alogia, avolition, anhedonia, associality and inattention). Similarly, a positive symptom score was calculated from the sum of the four "Scale for Assessment of Positive Symptoms" (SAPS) items (hallucinations, delusions, bizarre behaviour and positive formal thought disorder). A scale of 0 to 5 was used for each item; the higher the number obtained, the more severe the schizophrenic symptoms. The global indicator of clinical control was defined as the sum of the positive and negative symptom scores. The presence of any adverse effects, specifically extrapyramidal movement disorders, was also noted.

2.4 Statistical Analysis

The data were entered into a Statview® SE + Graphics (Abacus Concepts, Palo Alto, California, USA) file on a Macintosh® computer to facilitate statistical analysis. The Spearman Rank correlation coefficient was employed to determine whether there were any statistically significant relationships between plasma concentrations of fluphenazine and variables such as fluphenazine decanoate dosage and assessment of clinical control. Mann-Whitney U-tests were used to assess relationships between the plasma concentrations and categorical variables (e.g., sex and concomitant treatment with anti-Parkinsonian agents). Plasma concentrations of fluphenazine below the sensitivity of the assay procedure (0.1 ng/mL) were treated as being zero. A 'p' value below 0.05 was considered statistically significant. The patient data file can be seen in Appendix 4.

CHAPTER 3: RESULTS

3.1 Analytical Variables

3.1.1 Retention Times of Relevant Peaks

The approximate retention times for trifluoperazine and fluphenazine were 11.4 and 14 min respectively (Figure 3.2). Using selected ion monitoring GC/MS, there were no interfering peaks at these retention times.

3.1.2 Standard Curve

The relationship between the plasma concentration of fluphenazine and the peak area ratio (fluphenazine/trifluoperazine) was essentially linear (ratio = 0.269 x concentration + 0.0068; $r^2 = 0.998$) over the concentration range of 0.1 to 5.0 ng/mL (Figure 3.1).

3.1.3 Recovery and Reproducibility

The analytical recovery of fluphenazine was found to be 56% (n = 5) and the within-day coefficient of variation for the determination of fluphenazine was 5.0%.

3.1.4 Sensitivity

The sensitivity limit of the assay for measuring fluphenazine in plasma was 0.1 ng/mL when 5 mL of plasma was used.

Figure 3.1: Fluphenazine standard curve

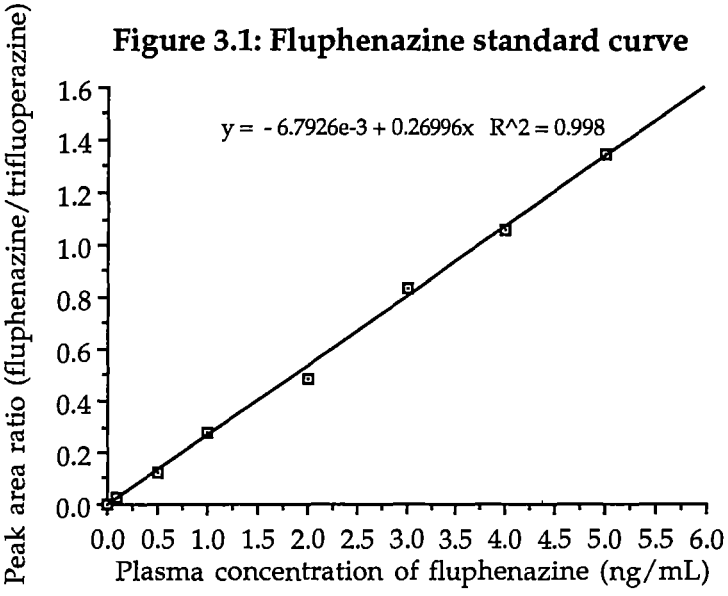
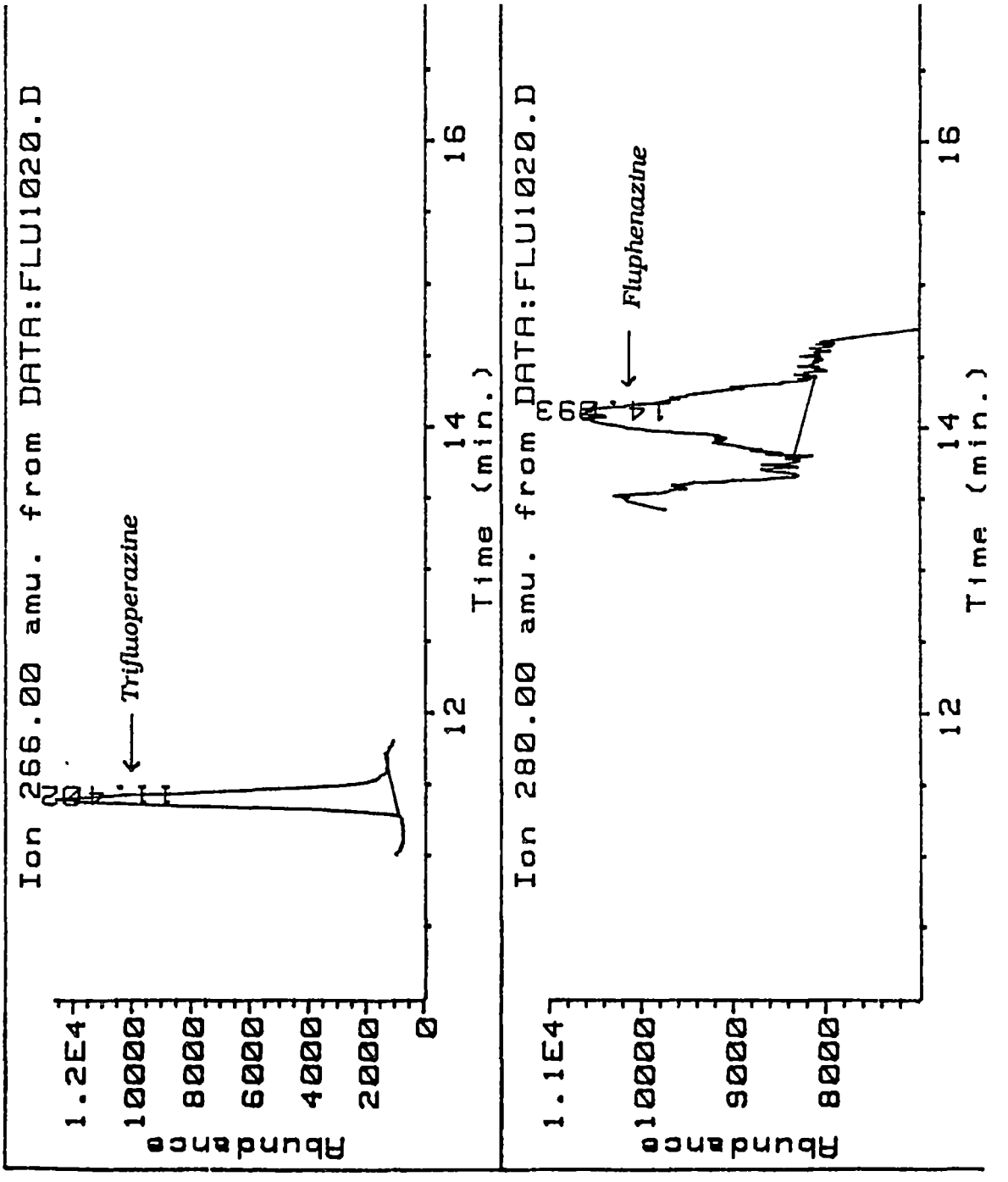


Figure 3.2: GC/MS trace of patient plasma sample (containing fluphenazine 4.3 ng/mL)



3.2 Study Results

3.2.1 Patient Characteristics

The sample of 24 patients consisted of 18 males and 6 females, ranging in age from 26 to 67 years, with a median age of 49 years. Their clinical characteristics are summarised in Table 3.1. Most patients were prescribed a number of other drugs (including other antipsychotic agents) on a long term basis, none of which have been documented as affecting the pharmacokinetics of fluphenazine (Table 3.2). None of the patients had biochemical evidence of hepatic or renal disease. One patient (number 20) had Parkinsonian signs and another (number 5) had tardive dyskinesia.

Table 3.1: Summary of the Clinical Characteristics of the Sample of Patients (n=24)

	Range	Mean	Median
Weight (kg)	50 - 113	79.2	80
Duration of condition (years)	3 - 40	21	18
Duration of FPZ therapy (years)	2 - 21	8.4	7
Current FPZ dose (mg/month)	12.5 - 150	53.6	43.8
Cumulative FPZ dose (mg/year)	213 - 2175	719.2	450

The median monthly dosage of fluphenazine decanoate was 43.8 mg, with a range of 12.5 to 150 mg (Figure 3.3).

3.2.2 Fluphenazine Concentrations in Plasma

The steady-state plasma concentrations of fluphenazine showed a marked inter-patient variability (Figure 3.4). The median concentration was 0.5 ng/mL (range < 0.1 to 27.9 ng/mL).

Table 3.2: Other drugs prescribed for the study sample (DA-antagonists highlighted)

Subject number	Other drugs
1	**haloperidol**, benztropine
2	benztropine
3	**haloperidol**, benztropine, propranolol
4	propantheline, **thioridazine**
5	benzhexol, clonazepam
6	nil
7	**haloperidol**, benztropine
8	nil
9	imipramine, alprazolam, carbemazepine
10	**thioridazine**
11	**haloperidol**, benztropine, diazepam
12	lithium
13	nil
14	**haloperidol**, benztropine, clonazepam, ketoprofen, propranolol, indapamide
15	mianserin, **thioridazine**, ranitidine
16	**thioridazine**, propantheline
17	clonazepam
18	**haloperidol**, benztropine
19	nil
20	orphenadrine
21	metformin, gliblenclamide
22	**chlorpromazine**
23	chloral hydrate, theophylline, doxycycline
24	hydrochlorothiazide/amiloride, metformin, glibenclamide

Figure 3.3: Frequency distribution of current fluphenazine decanoate dosage

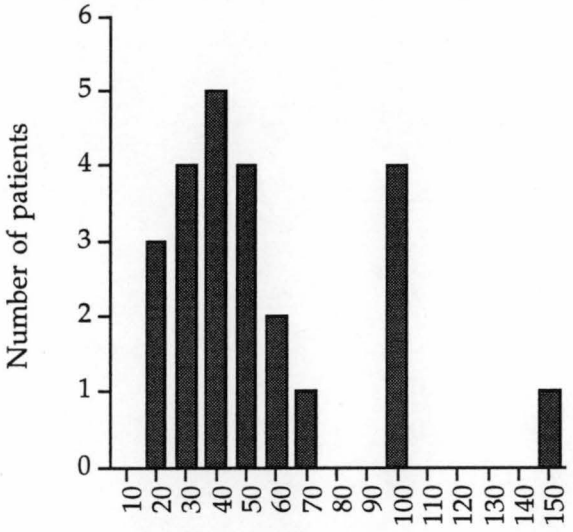
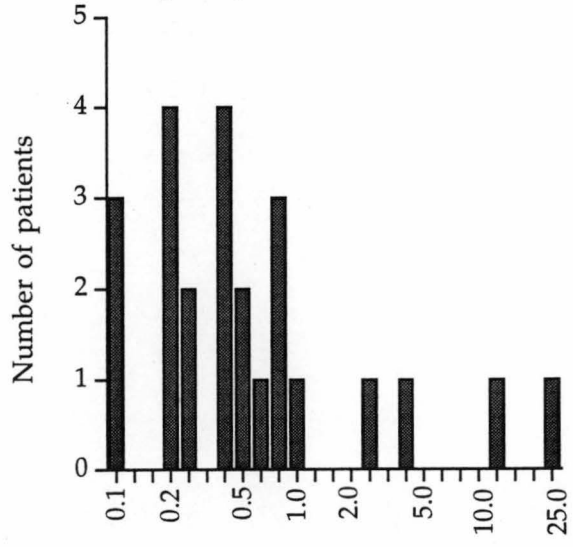


Figure 3.4: Fluphenazine plasma level frequency distribution



3.2.3 Plasma Fluphenazine Concentration in Relation to Fluphenazine Decanoate Dose

There were no significant correlations between either the fluphenazine decanoate dosage (mg/month) or fluphenazine decanoate dosage corrected for bodyweight (mg/kg/month) and the steady-state plasma concentration of fluphenazine (Spearman $\rho = 0.26$, $p > 0.20$ and Spearman $\rho = 0.33$, $p > 0.10$, respectively).

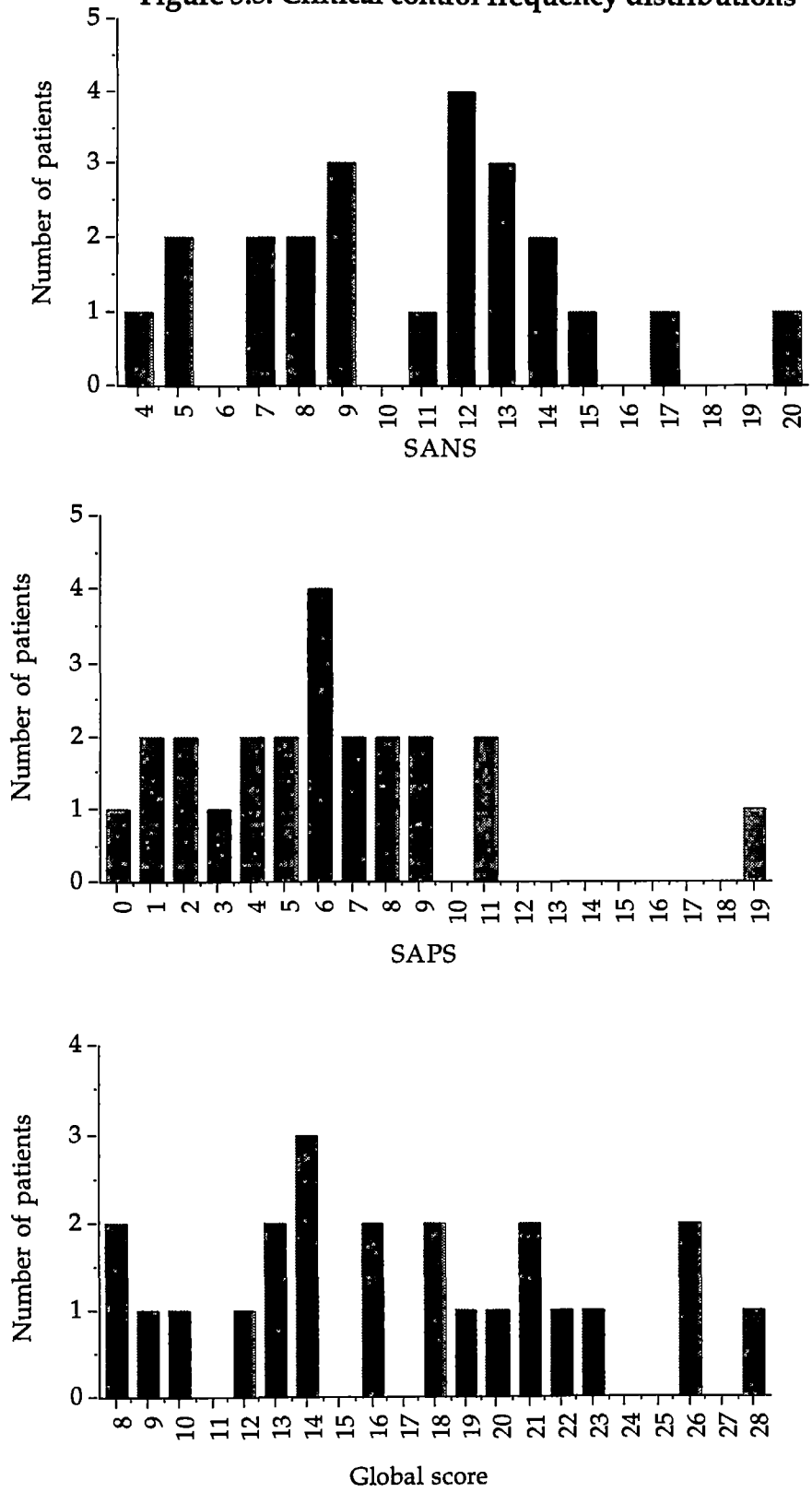
3.2.4 Relationship Between Plasma Fluphenazine Concentration and Clinical State

There was also considerable variability in clinical control, with a median value of 12 for the sum of the SANS items (range: 4 to 20), 6 for the sum of the SAPS items (range: 0 to 19), and 16 for the sum of the positive and negative symptom scores (range: 8 to 28) (Figure 3.5). The steady-state plasma concentrations of fluphenazine were not related to clinical control, expressed as the sum of the SANS items (Spearman $\rho = 0.23$, $p > 0.20$), the sum of the SAPS items (Spearman $\rho = 0.19$, $p > 0.20$), or the sum of the positive and negative symptom scores (Spearman $\rho = 0.31$, $p > 0.10$). Also, clinical control was not significantly different in patients with steady-state plasma concentrations of fluphenazine between 0.2 and 2 ng/mL compared to patients with levels above or below this tentative therapeutic range (SANS: Mann-Whitney $U = 41.5$, $z = 0.97$, $p > 0.20$; SAPS: Mann-Whitney $U = 39$, $z = 1.14$, $p > 0.20$; global: Mann-Whitney $U = 32.5$, $z = 1.57$, $p > 0.10$).

Table 3.3: Clinical Control in relation to plasma levels of fluphenazine

Plasma fluphenazine level	Global clinical control
Between 0.2 - 2.0 ng/mL (n=17)	median 15; range 8 - 26
< 0.2 or > 2.0 ng/mL (n=7)	median 20; range 14 - 28

Figure 3.5: Clinical control frequency distributions



In order to improve the normality of the distribution of plasma concentrations of fluphenazine, the values were log transformed as has been done in previous studies (Midha *et al*, 1993; Marder *et al*, 1991; Van Putten *et al*, 1991). The resulting values were significantly related to clinical control, expressed as the sum of the negative symptom scores (Spearman $\rho = 0.45$, $p < 0.05$) or the sum of the positive and negative symptom scores (Spearman $\rho = 0.47$, $p < 0.05$), but not to the sum of the positive symptoms (Spearman $\rho = 0.24$, $p > 0.20$). Hence, poorer control was related to higher log transformed plasma concentrations of fluphenazine; poorer control also tended to be associated with a higher fluphenazine decanoate dosage (e.g., Spearman $\rho = 0.38$, $p = 0.07$ for global control and monthly dosage). The log transformed plasma concentrations of fluphenazine were related to the fluphenazine decanoate dosage (mg/month; Figure 3.6) and fluphenazine decanoate dosage corrected for bodyweight (mg/kg/month; Spearman $\rho = 0.42$, $p = 0.05$ and Spearman $\rho = 0.44$, $p = 0.06$, respectively).

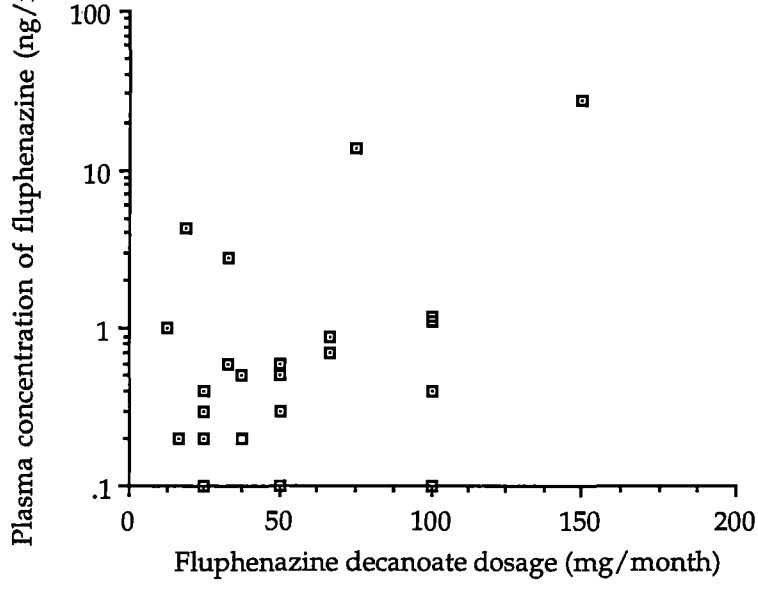
The patients receiving another antipsychotic drug in addition to fluphenazine decanoate tended to have poorer clinical control, expressed as the sum of the negative symptom scores (Mann-Whitney $U = 34$, $z = 1.93$, $p = 0.05$) or the sum of the positive and negative symptom scores (Mann-Whitney $U = 30.5$, $z = 2.15$, $p < 0.05$), but not as the sum of the positive symptoms (Mann-Whitney $U = 49.5$, $z = 0.97$, $p > 0.20$).

Table 3.4: Effect of another antipsychotic on clinical control[1]

Receiving another antipsychotic	Global clinical control	SANS	SAPS
Yes (n=11)	20 (14-28)	13 (5-20)	6 (1-19)
No (n=13)	13 (8-23)	9 (4-14)	5 (0-11)
significance	p<0.05	p=0.05	p>0.20

1. Results expressed as median (range)

Figure 3.6: Plasma fluphenazine concentration (log) versus fluphenazine decanoate dosage



These patients were also being administered higher dosages of fluphenazine decanoate (Mann-Whitney U = 38, z = 1.94, p = 0.05), but did not have significantly higher plasma concentrations (or log transformed plasma concentrations) of fluphenazine.

3.2.5 Relationship Between Plasma Fluphenazine Level and Presence of Extrapyramidal Side Effects

The steady-state plasma concentrations of fluphenazine in patients taking an anti-Parkinsonian medication were significantly higher than in patients not taking such medication (Mann-Whitney U = 34.5, z = 1.97, $p < 0.05$; Table 3.5). The fluphenazine decanoate dosage (mg/month) or fluphenazine decanoate dosage corrected for bodyweight (mg/kg/month) were not significantly different between the two groups (Mann-Whitney U = 45, z = 1.34, $p > 0.10$ and Mann-Whitney U = 39.5, z = 1.03, $p > 0.20$, respectively).

Table 3.5: Relationship between taking a concurrent anticholinergic and FPZ dosage and plasma concentration[1]

Concurrent anticholinergic	FPZ dosage (mg/month)	FPZ plasma concentration (ng/mL)
Yes (n=9)	75 (12.5-100)	1.0 (0-13.7)
No (n=15)	37.5 (16.6-150)	0.3 (0-27.9)
significance	p>0.10	p<0.05

1. Results expressed as median (range).

3.2.6 Effect of Age on Plasma Fluphenazine Levels

There were no significant associations between the age or sex of the patient or the duration of fluphenazine decanoate therapy and the dosage or steady-state plasma concentration of fluphenazine.

CHAPTER 4: DISCUSSION

Previously reported fluphenazine assay methods proved unsuitable for plasma concentration monitoring in this study due to problems with interfering peaks and limited sensitivity and reproducibility. The GC/MS procedure described here is specific for the measurement of fluphenazine and sensitive enough to measure the low plasma concentrations observed after intramuscular depot treatment with fluphenazine decanoate. The limit of detection was found to be 0.1 ng/mL when 5 mL of plasma was extracted for fluphenazine determination. This is an improvement on the sensitivity of previously published assays (Javaid *et al*, 1981 (0.5 ng/mL); Franklin *et al*, 1978 (1.0 ng/mL); Rivera-Calimlim & Siracusa, 1977 (3.0 ng/mL); Escobar *et al*, 1983 (0.2 ng/mL)).

The plasma concentrations of fluphenazine found in this study showed considerable inter-individual variability, ranging from undetectable to 27.9 ng/mL. The range was similar to that reported in other studies where fluphenazine decanoate was administered (Escobar *et al*, 1983; Furet *et al*, 1991). Using the proposed therapeutic range for fluphenazine of 0.2 to 2.0 ng/mL as a guide, about two thirds of the plasma levels fell within the range, with the remainder almost equally split above and below this optimal range. Pooling data from many studies, Axelsson (1990) found that in general about half of all patients fall within, one-quarter fall above and one-quarter fall below the optimal range.

The steady-state plasma concentration of fluphenazine was not significantly related to the fluphenazine decanoate dosage. Others have reported similar findings, indicating great variability in the pharmacokinetics of the drug (Rivera-Calimlim & Hershey, 1984; Wistedt *et al*, 1982). Log transformed plasma concentrations, however,

were moderately related to dosage. A lack of correlation between sex or age and steady-state plasma concentrations of fluphenazine was found, confirming the results of others (Dysken *et al*, 1981; Wistedt *et al*, 1982; Kane *et al*, 1982; Smith *et al*, 1979).

A significant correlation between fluphenazine dosage or plasma level and the presence of tardive dyskinesia was not revealed. Escobar *et al* (1983) reported that even though there was a trend for patients with high fluphenazine plasma levels to have higher extrapyramidal symptom scores than those with lower levels, no statistically significant relationship could be found. Other studies which had similar findings were those by Dysken *et al* (1981) and Wisdedt *et al* (1982). Levinson *et al* (1990) in a study of 53 patients claimed that severity of acute extrapyramidal symptoms was significantly correlated with oral fluphenazine dosage per kilogram. Van Putten *et al* (1991) studied 72 patients and found a significant correlation between plasma level of fluphenazine and the incidence of disabling side effects, defined as "side effects that outweigh therapeutic effects".

The steady-state plasma concentrations of fluphenazine in patients taking anti-Parkinsonian medication were significantly higher than in patients not taking such medication. It has been proposed that anticholinergic agents may decrease the amount of fluphenazine absorbed from the gastrointestinal tract by decreasing gastric motility (Dysken *et al*, 1981). This would allow more fluphenazine to pass through the gut wall and undergo extensive first-pass metabolism before reaching the systemic circulation. In addition antipsychotics including fluphenazine may be metabolised in the gut wall and as a result fluphenazine levels would be expected to decline (Dysken *et al*, 1981; Davis *et al*, 1994). However, that interaction would be significant only with orally administered phenothiazines and recent studies have shown

that concomitant anticholinergic medication does not affect plasma fluphenazine levels (Dahl, 1986; Javaid, 1994). These conflicting results have left the effect of anti-Parkinsonian medication on plasma levels of antipsychotics unclear (McCreadie *et al*, 1992).

Therefore, higher fluphenazine plasma levels are likely to be related to the presence of the adverse extrapyramidal effects rather than as a result of subsequent anticholinergic medication. In addition, although the difference was not significant, patients receiving an anticholinergic medication were generally also receiving higher dosages of fluphenazine. Supervening extrapyramidal side effects constitute a cause for dosage reduction rather than prescribing anticholinergics, as their long-term administration with an antipsychotic agent may worsen dyskinetic symptoms (Whiteford *et al*, 1987) and increase the intensity of anticholinergic side effects.

More manifest schizophrenic symptoms were associated with higher log transformed plasma concentrations of fluphenazine, probably because poor control also tended to be associated with a higher fluphenazine decanoate dosage. That is, patients with more severe clinical symptoms were generally receiving higher dosages and consequently had higher plasma levels of fluphenazine (see Table 4.1 for a summary of other studies). There was also a trend for patients with poor control to be taking another antipsychotic drug. In fact, the patient with the highest steady-state plasma concentration (27.9 ng/mL) was receiving the highest dosage of fluphenazine decanoate (150 mg monthly), along with oral thioridazine, and had the most marked global symptoms of schizophrenia. It was surprising to note that this patient showed no

Table 4.1: Summary of studies examining relationships between fluphenazine plasma levels and clinical outcome

Source	No. subjects	Route	Assay	Range of levels	Clinical Assessment	Relationship (p)
Van Putten *et al*, 1991	72	PO	RIA	*	CGI, BPRS	0.015
Dysken *et al*, 1981	29	PO	GC	0.1 - 4.2 ng/mL	NHSI	0.02
Mavroidis *et al*, 1984a	19	PO	GC	0.13 - 4.8 ng/mL	NHSI	<0.05
Escobar *et al*, 1983	14	PO, IM	GC	0.2 - 8.0 ng/mL	CGI, BPRS	NC
Fairbairn *et al*, 1983	12	IM	RIA	*	**	NC
Wisdedt *et al*, 1982	14	IM	RIA	0.4 - 2.4 ng/mL	**	NC
Dudley *et al*, 1983	5	PO, IM	GC, RIA	1.0 - 3.0 ng/mL	GAS	NC
Wiles & Gelder, 1979	36	IM	RIA	0.63 - 16.4 ng/mL	**	**
Marder *et al*, 1991	35	PO, IM	RIA	0.1 - 5.0 ng/mL	BPRS	0.001
Levinson *et al*, 1990	53	PO	**	**	BPRS, SANS, NRS	**
Javaid *et al*, 1981	18	PO	GC	0.2 - 4.4 ng/mL	**	**
Nasrallah *et al*, 1978	10	IM	GC	3 - 16 ng/mL peak	NIMH	NC

PO - oral fluphenazine
IM - depot fluphenazine decanoate
CGI - Clinical Global Impressions Scale
BPRS - Brief Psychiatric Rating Scale
NHSI - New Haven Schizophrenic Index
GAS - Global Assessment Scale
NRS - Neurological Rating Scale
NIMH - National Institute of Mental Health Inpatient Behavioural Rating Scale

* - not documented in paper
** - not investigated in particular study
NC - no significant correlations found

signs of suffering from extrapyramidal side effects. This may, in part, be explained by the fact that his Positive Symptom score was high (19 out of a possible 20), and it has been frequently noted clinically that patients with prominent positive symptoms require relatively high doses of neuroleptics to diminish their positive symptoms, and that they have remarkably few side effects (Andreasen, 1985). These results indicate the useful role that plasma level monitoring can fulfil in identifying patients who are therapy-resistant despite optimal or high plasma levels (Axelsson, 1990). These patients are generally best managed by prescribing a different antipsychotic drug, perhaps clozapine, or adding lithium (Balant-Gorgia *et al*, 1993; Farmer & Blewitt, 1993).

Overall, any lack of correlation in clinical studies involving antipsychotic control may be associated with the small sample size, considerable variation in pharmacokinetics, the confounding effect of haloperidol and other antipsychotics, clinical rating scales of varying sensitivity, indistinct and nonspecific clinical endpoints, as well as such technical problems as low steady-state levels, poor assay sensitivity, and other sources of error. Also, it highlights the enormous difficulties in working with human subjects and the additional difficulties associated with working with the mentally ill. For example, in this study we were dealing with outpatients who had to be relied upon firstly to turn up for their clinic appointment, and secondly to consent to a procedure which to someone suffering from schizophrenia may present as threatening.

Conclusions

To further elucidate the relationship between plasma concentrations of fluphenazine and clinical response, more studies with greater numbers of patients treated in monotherapy (i,e,. avoidance of other drugs) and baseline (pre-therapy) measurements of clinical status are required. Ideally, a baseline rating representing pretreatment assessment would be

measured and then steady-state clinical scores would be determined after stabilisation; the change in schizophrenic symptoms would then indicate the true clinical response to the fluphenazine treatment.

PART II

THE EFFECTS OF CARDIOPULMONARY BYPASS ON THE PHARMACOKINETICS OF DRUGS USED IN ANAESTHESIA

CHAPTER 5 : INTRODUCTION

5.1 The Bypass Procedure

5.1.1 Technical Aspects

Operations involving cardiopulmonary bypass are no longer rare with an estimated 110,000 being performed in the USA in 1980 (Holley *et al*, 1982) increasing dramatically to 480,000 by 1986 (Reves *et al*, 1987).

During cardiac surgery, including both coronary bypass graft operations and corrective surgery for heart valves, cardiac activity must be stopped, usually with the infusion of a concentrated potassium ion solution (cardioplegia) (Holley *et al*, 1982). An artificial device which both pumps and oxygenates the blood must therefore temporarily be substituted for the cardiac and pulmonary function of the patient; this is termed cardiopulmonary bypass (CPB). In addition, a number of changes occur in the normal physiological status of the patient, resulting in CPB being described as a 'controlled form of shock' (Holley *et al*, 1982).

After anaesthetisation has occurred, a median sternotomy is usually performed to gain access to the heart. A massive dose of heparin (25,000 to 35,000 U) is given to prevent blood coagulation. The blood of the patient then flows by gravity from the superior and inferior venae cavae via silicone or PVC tubing to the membrane oxygenator/heat exchanger where it is cooled to below 27°C and exposed to a mixture of oxygen and carbon dioxide to maintain $PaCO_2$. It is necessary to induce hypothermia in order to diminish the metabolic needs and oxygen requirements of

the patient; Murkin *et al* (1987) documented a 30% decrease in cerebral blood flow and oxygen consumption at 27°C during CPB. A pump is then used to return the blood to the ascending aorta and to perfuse the tissues using non-pulsatile flow. The mean arterial pressure is approximately 40 mmHg (Buylaert *et al*, 1989). There are usually filters in the pumplines to remove emboli resulting from bubbles or organic or inorganic material. Before being attached to the patient's circulation, the pump's dead space is primed with 1.5 to 2.5 L of an isotonic or slightly hypertonic electrolyte solution with buffered physiological pH (i,e,. dextrose 5% in lactated Ringer's solution) which results in haemodilution to a haematocrit of about 0.25 and an increase in plasma osmolarity. A combination of this haemodilution and the relatively low pump flow rate (1.2 to 2.4 $L/m^2/min$), may cause hypotension and alterations in perfusion to values considerably less than normal (Buylaert *et al*, 1989). Towards the end of the procedure the patient is gradually rewarmed and the effect of heparin is reversed by the administration of protamine; the heart is defibrillated if necessary. The current use of relatively inert plastics throughout the extracorporeal circuit has reduced the denaturation of plasma proteins and aggregation of platelets (Holley *et al*, 1982).

5.1.2 General Physiological Changes as a Result of Bypass

Cardiopulmonary bypass causes profound physiological changes in addition to those induced by anaesthesia and seen in 'normal surgery', because of the massive invasion of the body. These include haemodilution, hypotension and hypothermia (Buylaert *et al*, 1989).

- Haemodilution will decrease blood viscosity and occurs abruptly as bypass commences when the patient's blood is mixed with the cardiopulmonary bypass priming solution.

• Hypotension and altered regional blood flow are due to a combination of decreased systemic vascular resistance, low pump flow rate and haemodilution. Blood flow to vital organs is preserved at the expense of peripheral tissues such as muscle and fat.
• Hypothermia affects drug metabolism, distribution and effect. It also serves to promote anaesthesia.

Cardiopulmonary bypass also results in a generalised stress response which leads to the production or alteration of a large number of vasoactive substances, such as hormones, autacoids and cytokines (Downing & Edmunds, 1992). A 9 to 15 fold elevation in adrenaline and a 2 to 5 fold elevation in noradrenaline have been documented (Schwinn *et al*, 1991). The highest levels of these endogenous catecholamines usually occur towards the end of CPB and while rewarming and their clearance, which is primarily enzyme dependent, is reduced. These substances and some of the others which are released during CPB and their effects are outlined in Table 5.1. Very high doses of opioids are thought to block the stress response during surgery but are more than likely to cause post-operative respiratory depression (Reves *et al*, 1987). Administration of clonidine before CPB will reduce opioid requirements in addition to diminishing the catecholamine response by inhibiting adrenergic transmitter release (Flacke *et al*, 1987).

Table 5.1: Some of the Vasoactive Substances Released During CPB (adapted from Downing and Edmunds, 1992)

Substance	Vasoactive Effect
adrenaline	↑ HR, ↑ CO, inotrope
noradrenaline	↑ BP, ↑ SV, ↑ SVR
vasopressin	↑ sodium and water resorption
bradykinin	vasodilator
calcium	inotrope, vasoconstrictor
potassium	negative inotrope
magnesium	arrythmias
prostaglandin E_2	vasodilator
thromboxane A_2	vasoconstrictor
endothelin-1	vasoconstrictor
anaphylatoxins from complement activation	↑ vascular permeability, ↑ HR, hypotension, vasoconstrictor
histamine	↑ capillary permeability

HR=heart rate; CO=cardiac output; BP=blood pressure; SV=stroke volume; SVR=systemic vascular resistance; ↑=increased.

In vitro heparin causes increases in the levels of non-esterified fatty acids which have been shown to competitively inhibit drug binding to plasma proteins, however, the in vivo effect of heparin dosing is still uncertain (Finegan *et al*, 1992).

Finally, at the termination of bypass, the blood pressure and cardiac output will increase with the perfusion to all tissues improving; most noticeably so in peripheral tissues such as muscle and fat (Holley *et al*, 1982).

5.1.3 Drugs Commonly Administered in Bypass

Pharmacotherapy of cardiac surgery is complex with as many as 20 drugs being administered in the perioperative period (Holley *et al*, 1982). Preoperatively, long-term medication may include beta-blockers, nitrates, diuretics, digoxin and antihypertensive agents. Premedication, given about 90 minutes prior to surgery, usually consists of oral hypnosedatives such as diazepam and droperidol. On induction, a high dose of narcotic (eg fentanyl, morphine) which also provides analgesia postoperatively, a neuromuscular blocking drug to prevent movement (eg alcuronium, tubocurarine) and thiopentone to ensure hypnosis are given intravenously. Just before bypass, heparin is given to ensure anticoagulation and then as required during bypass vasodilators such as hydralazine are given to decrease peripheral resistance and increase perfusion. Protamine is given post-bypass to reverse the effect of heparin and IV cephalosporins or semisynthetic penicillins are given as antibiotic prophylaxis.

Other drugs given postoperatively may include further doses of narcotics and hypnosedatives and cardiac drugs to maintain optimum haemodynamics. The potential for drug interaction in addition to altered pharmacokinetics as a result of CPB is enormous.

5.1.4 Changes in Pharmacokinetics During Bypass

Cardiopulmonary bypass has a profound effect on the pharmacokinetic behaviour of many drugs both during and immediately after the surgery period with temperature and flow both changing at a great rate (Hall, 1991). Even in normal surgical patients, drug distribution studies are extremely complex due to the multiple effects of premedication, anaesthesia and surgery on the cardiovascular system (Mather, 1983).

Absorption would be expected to be reduced or delayed as a result of hypotension and reduced blood flow but as all drugs given during the bypass procedure are given intravenously, this is not a problem.

Distribution is expected to be affected in several ways. Firstly, the sequestration of the lungs will decrease volume of distribution with the possibility of accumulation of some substances (Buylaert *et al*, 1989) and then redistribution on restoration of pulmonary circulation. Hypotension and altered blood flow are likely to decrease the distribution to organs, however, an increase in volume of distribution may result due to a haemodilution-induced decrease in the concentration of plasma protein binding leading to redistribution of drugs from the serum to the tissues.

The elimination of drugs by the kidney will be affected (Holley *et al*, 1982). Hypotension and reduced renal blood flow will potentially decrease active tubular secretion and glomerular filtration rate. The decreased concentration of plasma binding proteins will increase free fraction and hence glomerular filtration rate, especially in highly protein bound drugs, and changes in pH and filtration volume are likely to alter the extent of tubular reabsorption. Hypothermia is expected to affect the temperature-dependent renal tubular enzymes which are involved in active secretion and reabsorption and will decrease glomerular filtration

rate. In addition, non-pulsatile flow tends to result in temporary impairment of renal function (Holley *et al*, 1982).

Hepatic elimination of most drugs will be reduced mainly due to the decreased intrinsic clearance (diminished activity of metabolic enzymes) as a result of hypothermia and severely decreased liver blood flow (Buylaert *et al*, 1989). This reduction in blood flow will also decrease the clearance of drugs with flow-dependent elimination (i,e,. high extraction drugs such as lignocaine) resulting in a prolonged effect (Buylaert *et al*, 1989). A decrease in binding protein concentration is likely to increase the clearance of low extraction drugs (restrictive elimination) as only free drug is able to be cleared (Buylaert *et al*, 1989).

In summary, plasma concentrations of most drugs may fall initially after connection to the bypass apparatus (attributed to changes in distribution), are relatively constant for a period during bypass and then increase at the termination of extracorporeal support depending on the regimen by which the drug is given. There is also a prolonged terminal half-life for most drugs during the recovery period after surgery because of reduced clearance (Mather, 1983).

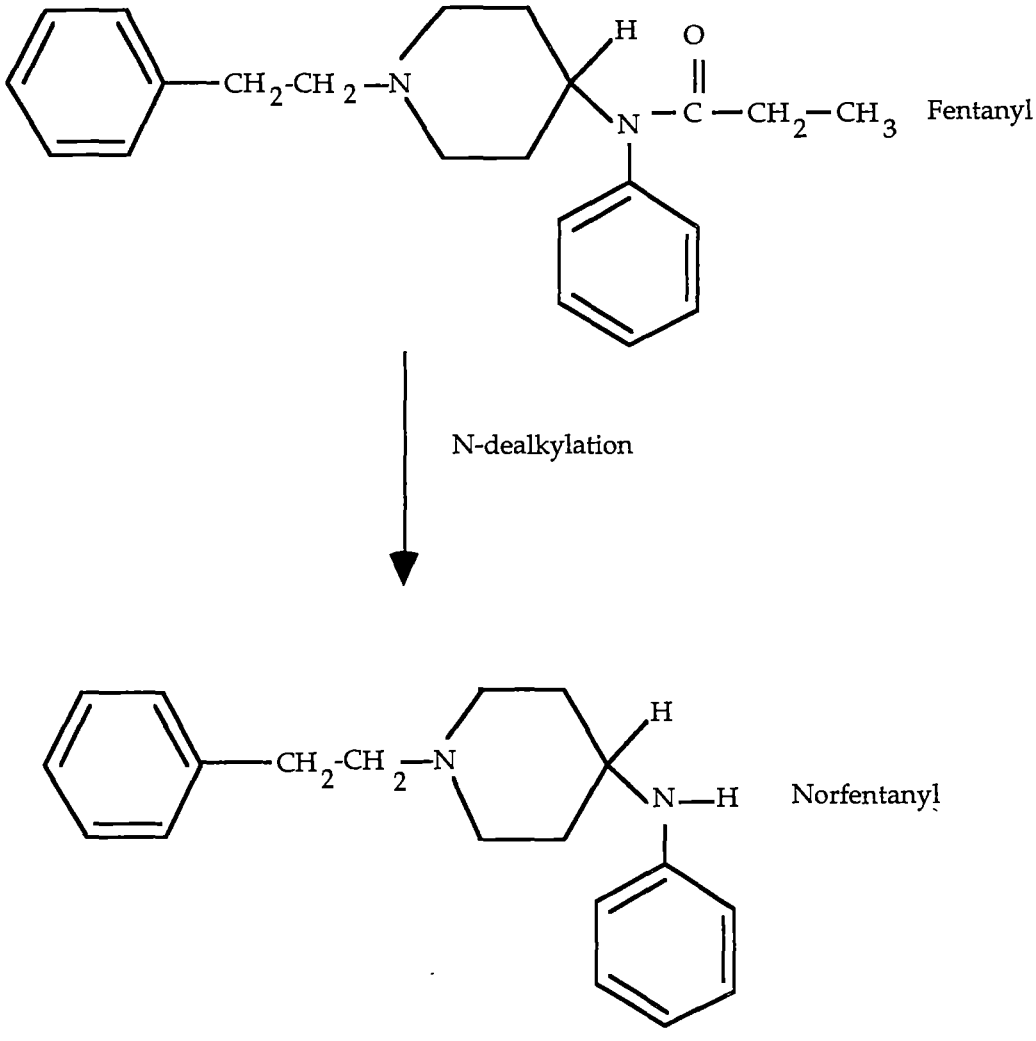
5.2 Drugs of Interest

5.2.1 Fentanyl Characteristics

Fentanyl (N-(1-phenylethyl-4-piperidyl)propionanilide) is a short-acting, highly lipophilic, synthetic narcotic analgesic with a potency 50 to 100 times that of morphine and much greater access to the brain (Mather, 1983). The structure of fentanyl contains a large hydrocarbon mass which gives it the lipophilic properties and an amide functional group and a piperidine ring tertiary amine functional group. It is made water soluble through salt formation with citric acid and does not contain a chiral centre so studies are not complicated by the presence of enantiomers (Mather & Gourlay, 1991). It was developed in 1960 after a need arose for a more potent yet less toxic opioid than morphine to be used as a primary anaesthetic agent (Clotz and Nahata, 1991). Morphine was being employed but it produced incomplete amnesia and undesirable haemodynamic responses to surgery, such as histamine release, myocardial depression, and vasodilatation (Clotz and Nahata, 1991; Holley *et al*, 1982; Robbins *et al*, 1990).

Fentanyl and its derivatives (alfentanil, sufentanil) afford excellent cardiovascular stability and have reduced or eliminated most of the disadvantages of other opioid anaesthetics (Koska *et al*, 1981). These narcotic analgesics are currently the most commonly used drugs for maintenance of anaesthesia during cardiopulmonary bypass (Kumar *et al*, 1988). Fentanyl is given intravenously and is rapid-acting, in fact because of this short duration of action after a single dose was originally thought to have a short elimination half-life (Mather & Gourlay, 1991). However, fentanyl has a long elimination half-life due to the slow return of the unchanged drug from the peripheral to the central compartment where elimination occurs (McClain & Hug, 1980). The rate-limiting step for its elimination is therefore redistribution from the

peripheral compartment. Estimates of the apparent volume of distribution of fentanyl range from 60 to 300 L, and the terminal half-life has been found to be 1.5 to 6 hours (Mather, 1983). Less than 10% of a dose of fentanyl is excreted renally as unchanged drug (Clotz & Nahata, 1991) with the remainder eliminated predominantly hepatically, by metabolism (hydrolysis of the amide) to norfentanyl.



Total body clearance ranges from 0.4 L/min to greater than 1.5 L/min and approximates liver blood flow in healthy subjects (Mather, 1983) with its hepatic extraction ratio approaching unity (Bower & Hull, 1982). Higher concentrations of fentanyl have been noted in the elderly and could be attributed to an age-related reduction in cardiac output and an age-related reduction in fat-lean body distribution (Mather & Gourlay,

1991). The maximum concentration of fentanyl occurs in fat about 30 min after intravenous injection (Mather, 1983), reflecting the drug's high affinity for lipid and the low perfusion of adipose tissue.

Protein binding of fentanyl to plasma proteins is about 80% at pH 7.4 and was found to be constant over a range of fentanyl concentrations from 0.076 to 76 ng/mL (McClain & Hug, 1980). Binding is dependent on the plasma concentration of protein and is favoured with increasing pH (Mather, 1983). The most avid binding of fentanyl occurs with α_1-acid glycoprotein and there is also some degree of binding to albumin (Mather & Gourlay, 1991).

Plasma concentrations of fentanyl are likely to reflect receptor concentrations and hence pharmacological effect, since fentanyl is highly lipophilic and rapid receptor association and dissociation has been measured in vitro (Mather & Gourlay, 1991).

5.2.2 Fentanyl and the Effects of Cardiopulmonary Bypass

The pharmacokinetic parameters (clearance, volume of distribution and half-life) in patients undergoing regular surgery (non-cardiac) have been found to be comparable with values in normal volunteers (Holley *et al*, 1982) suggesting changes during CPB are due to the bypass procedure itself rather than the effects of surgery or anaesthesia.

Fentanyl is given intravenously in CPB and its high lipid solubility results in high concentrations of drug in the well-perfused tissues such as the lungs, kidneys, heart and the brain (Mather, 1983). Skacel *et al* (1986) noted that plasma concentrations of fentanyl greater than 20 to 30 ng/mL are required to initially depress the cardiovascular response to surgery; the concentration required decreases during surgery and will also depend on other medication administered (e.g., nitrous oxide). The

redistribution of fentanyl is rapid, with 90% of an IV dose cleared from the plasma within 5 to 10 min due to uptake of the drug by well perfused tissues (Bovill & Sebel, 1980). On commencement of extracorporeal circulation, the concentration of fentanyl falls rapidly and during the bypass procedure the expected pharmacokinetics of the drug can be severely disrupted and normal methods of analysis are not suitable.

Apparent volume of distribution (V_d) may increase as a result of haemodilution which is due to the abrupt decrease in plasma drug concentration:

V_d = amount of drug in the body/plasma drug concentration

The total plasma drug concentration is reduced because, as fentanyl is a highly bound drug, the decreased concentration of binding proteins due to haemodilution will lead to an increase in the fraction of unbound drug which will favour distribution of fentanyl from plasma to tissues. The V_d may also be reduced by hypotension and the subsequent decline in peripheral perfusion which reduces blood flow to some organs; the overall change will depend on the predominance of these opposing influences. It is sometimes practice to give an additional dose of fentanyl to prevent suboptimal concentrations at the start of CPB but it is not usually necessary and can cause postoperative ventilatory depression (Hall, 1993).

Hepatic clearance of fentanyl will decrease during CPB due to an estimated reduction in liver blood flow to 70% of normal (Hall, 1991; Koska *et al*, 1981). In addition fentanyl, being a weak base, is metabolised by microsomal enzymes whose activity is reduced by hypothermia (Hall, 1991). Creatinine clearance is typically reduced by 50% during the bypass

procedure (Robbins *et al*, 1990) although this is not directly relevant for fentanyl as only negligible amounts are excreted unchanged in the urine.

The terminal half-life may be prolonged to over seven hours due to a combination of increased apparent volume of distribution and decreased clearance (Cl) (Bovill and Sebel, 1980):

$$t_{1/2} = 0.693V_d/Cl$$

After bypass, it should be possible to determine an elimination half-life as plasma fentanyl concentration/time curves would be expected to regain an apparent log-linear decay (Koska *et al*, 1981). However, statistically significant fluctuations with peaks of 1 to 2 ng/mL on top of the washout curve have been noted about 45 minutes after the completion of bypass preventing exponential curve fitting (Mather, 1983). The mobilisation of the patient on admission to the recovery room with subsequent release of fentanyl from tissue depots (eg skeletal muscle, stomach) by increased perfusion could cause these fluctuations during the elimination phase. This redistribution is important for basic drugs such as fentanyl that tend to have extensive initial distribution and even more so with the sudden increase in tissue perfusion after CPB due to spontaneous and voluntary movements as consciousness returns (McClain & Hug, 1980; Bovill & Sebel, 1980).

Repeated doses of fentanyl are given during surgery and this prolonged exposure may lead to accumulation in plasma and the CNS and an increased possibility of recurrent ventilatory depressant effects (McClain & Hug, 1980). These effects may be antagonised by noxious stimulation during surgery and on transfer of the patient to recovery, and thus may only become evident when the patient is unstimulated in the post-operative period. This respiratory depression is thought to become

insignificant at plasma levels below about 0.7 ng/mL (McClain & Hug, 1980).

The haemodilution caused by the priming solution of the CPB apparatus alters the plasma protein concentrations and may produce changes in drug-protein binding. Kumar *et al* (1988) reported the concentration of both α_1 - acid glycoprotein and albumin decreased by 50% during cardiopulmonary bypass. McClain & Hug (1980) found that a 57% reduction in protein content of plasma led to an 18% decrease in binding of fentanyl, thus increasing the free fraction. It is this free fraction which is able to equilibrate with the tissues and to initiate the pharmacological response so changes in binding may have clinical significance (Bower, 1981). For this reason, it may be necessary to monitor unbound as well as total concentrations in pharmacokinetic studies.

It is also known that plasma α_1-acid glycoprotein concentration may increase during conditions of stress as it is an acute phase reactant but this may not occur until a couple of days following surgery (Hall, 1991) so is probably unlikely to affect the pharmacokinetics of fentanyl given during CPB.

It has also been reported that under hypothermic conditions there is a reduced binding affinity of opiate receptors for certain opioids, thus conceivably reducing their potency (Hall, 1991).

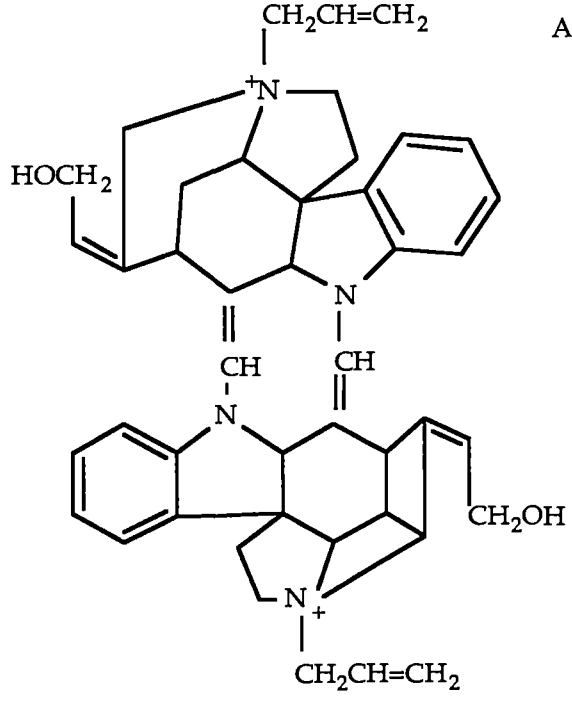
5.2.3 *Alcuronium Characteristics*

Alcuronium (diallylnortoxiferine) is a semisynthetic, water-soluble quaternary amine with a large organic structure (MW=2408) which has been in use since 1961 (Walker *et al*, 1980). It acts as a nondepolarising neuromuscular blocker and when administered as a single IV bolus dose of approximately 0.25 mg/kg at the start of cardiac surgery produces

skeletal muscle relaxation while avoiding hypertension, histamine release and tachycardia (Künzer *et al*, 1994). This absence of side effects is its main advantage over tubocurarine.

There is no evidence of any appreciable metabolism of the drug and it is eliminated almost entirely (80 to 85%) unchanged by the kidneys, predominantly due to glomerular filtration (Walker and Brown, 1983). Because it is permanently charged, alcuronium is not likely to undergo tubular reabsorption (Walker *et al*, 1983). Approximately 15 to 20% is secreted unchanged into the bile and eliminated with the faeces. The pharmacokinetic parameters for alcuronium in general surgical patients (described using a two compartment model) have been reported as 3.3 hours for elimination half-life and 90 mL/min for mean plasma clearance (Walker *et al*, 1980).

Alcuronium is not highly protein bound; only 40 % is bound to alpha-1 globulins (Hunter, 1994).



Alcuronium

5.2.4 Alcuronium and the Effects of Cardiopulmonary Bypass

Alterations in renal function as a result of cardiopulmonary bypass may alter the pharmacokinetics of alcuronium because of its high renal clearance.

It has been reported that the renal elimination of the neuromuscular blocking agents pancuronium, *d*-tubocurarine and alcuronium decreases during hypothermia of cardiopulmonary bypass (Wierda *et al*, 1990) with creatinine clearance typically reduced by 50% (Robbins *et al*, 1990). In a study involving alcuronium given as a bolus dose followed by an infusion, the concentration actually increased on CPB (Walker *et al*, 1983). However, studies involving single bolus doses of pipecuronium and metocurine concluded that the overall effect of hypothermia and bypass did not appear to influence the terminal half-lives of the drugs (Wierda *et al*, 1990; Avram *et al*, 1987). This could be explained by the fact that the patients were relatively hypovolaemic preoperatively and thus already had diminished renal perfusion. Thus, the effect of CPB on alcuronium concentrations following a single bolus dose is not well documented.

5.2.5 Drug Sequestration

The irreversible sequestration of fentanyl (through hydrophobic binding) to constituent parts of the bypass apparatus or to the lungs is documented and is expected to further complicate the pharmacokinetics of fentanyl during cardiopulmonary bypass. The membrane oxygenator has been reported as the major site of binding, whereas PVC tubing and the plastic reservoir had no binding effect on fentanyl (Koren *et al*, 1984). Hall (1991) claimed that sequestration is unlikely to have a major impact on plasma concentrations in vivo due to the large tissue reservoir of the drug. Studies indicate that the binding of fentanyl to the system appears to be a saturable process (Hynynen, 1987). This was shown when low

levels of fentanyl (20 ng/mL) used for priming totally disappeared from the system, whereas priming of the cardiopulmonary bypass solution with high levels of fentanyl (140 to 280 ng/mL) prevented the marked decrease immediately after the start of bypass and sufficient drug remained to maintain a constant low concentration (Koren *et al*, 1984). Hynynen (1987) calculated that the cardiopulmonary bypass devices were capable of adsorbing a total of 30 to 240 μg of fentanyl which represents only about 0.4 to 3% and 0.7 to 5% of the total fentanyl dose used in studies by Bentley *et al* (1983) and Bovill and Sebel (1980), respectively. Addition of plasma proteins to the priming solution did not prevent the binding of fentanyl to the bypass system (Hynynen, 1987).

High potency opioids such as fentanyl may also be sequestered in the lungs which can serve as a reservoir for drug which cannot be rapidly eliminated or distributed when the pulmonary circulation is bypassed (Bentley *et al*, 1983). Taeger *et al* (1988) reported that about 71% of an IV fentanyl dose can be extracted by the lungs over one minute. Upon termination of the extracorporeal support and resumption of blood flow to the lungs, there is a washout of a significant amount of drug back into the systemic circulation with an elevation of plasma levels. The clinical importance of this phenomenon is unknown, but as the body temperature rises back to normal, the regional blood flow, enzymatic activity, blood pressure and cardiac output will all increase, altering once again the pharmacokinetics and pharmacodynamics of fentanyl (Holley *et al*, 1982).

Sequestration of alcuronium to any parts of the extracorporeal circuit has not been documented in any studies.

5.3 Objectives of this Study

Previous studies have involved measuring total fentanyl levels after a single intravenous bolus dose (Koska *et al*, 1981; Bovill & Sebel, 1980) or after a bolus dose followed by an infusion which was discontinued on initiation of bypass (Koren *et al*, 1984) (Table 5.2).

Table 5.2: Previous studies measuring fentanyl levels

Study	No. subjects	Dose	Assay
Koska *et al* (1981)	6	0.5 mg/70 kg bolus	RIA
Bovill & Sebel (1980)	5	60 µg/kg bolus	RIA
Koren *et al* (1984)	19; children	50 µg/kg bolus + 0.3 µg/kg/min infusion	GC

RIA=radioimmunoassay; GC=gas chromatography

At the Royal Hobart Hospital, fentanyl is given in up to six bolus doses before bypass and often another dose is given on warming to maintain adequate anaesthesia resulting in pharmacokinetics which are difficult to interpret. Also, because fentanyl exists in plasma as either a protein bound or unbound (pharmacologically active) moeity it was considered important to examine unbound concentrations as well as total concentrations which have been more generally reported. This is particularly significant in cardiac surgery patients as several factors may affect the extent of plasma protein binding of fentanyl.

This study aimed to describe the plasma levels of fentanyl with this dosage regimen and plasma levels of alcuronium after a single bolus dosage in patients undergoing cardiopulmonary bypass surgery, including an investigation of the change in plasma protein binding of fentanyl throughout the procedure. An important factor is whether any of these changes that occur as a result of CPB will affect the ability of

appropriate plasma concentrations of fentanyl and alcuronium to be maintained throughout the procedure.

In addition, an in vitro study was performed to investigate the possible adsorption of fentanyl and alcuronium to extracorporeal circuits.

CHAPTER 6: MATERIALS AND METHODS

6.1 Materials and Equipment

6.1.1 Fentanyl

Fentanyl citrate and imipramine hydrochloride were donated by Janssen-Cilag Pty Ltd (Lane Cove, NSW, Australia) and Ciba Geigy (Pendle Hill, NSW, Australia), respectively. Standard solutions were prepared in methanol (Waters; Lane Cove, NSW, Australia). All other chemicals and solvents were of analytical reagent grade quality; hexane (Waters; Lane Cove, NSW, Australia), isopropanol (Ajax Chemicals; Auburn, NSW, Australia), hydrochloric acid (May and Baker Ltd; West Footscray, Victoria, Australia), and sodium hydroxide (BDH Chemicals Australia Pty Ltd; Kilsyth, Victoria, Australia). Glassware was washed in Decon® (Selby Anax, Australia) and rinsed in distilled water.

A Varian (Varian Pty Ltd; Melbourne, Australia) 3300 gas chromatograph equipped with a nitrogen phosphorus detector (NPD) was used for the analysis. The column used was an 11 m x 0.32 mm internal diameter Hewlett-Packard (Melbourne, Australia) crosslinked fused-silica ultraperformance capillary column coated with silicone gum (0.52 μm film thickness; HP-1) which was fitted to a Varian model 1093 septum-equipped programmable injector (SPI) containing a glass wool packed insert (0.8 mm internal diameter). The glass wool provided efficient transfer of the liquid sample from the syringe and trapped any contaminants present in the sample. The insert was cleaned frequently to avoid loss in sensitivity and carryover effects from adsorption. The injection-port septum (11 mm TCS, Scientific Glass Engineering Pty Ltd (SGE), Melbourne, Australia) was also changed weekly to minimise sample leakage. Chromatographic responses were recorded and integrated using a Milton-Roy CI-10B integrator (Clare, Ireland).

6.1.2 Alcuronium

The following chemicals were used for the analytical procedure: acetonitrile HPLC grade (Waters; Lane Cove, NSW, Australia), deionised water, AR grade sulphuric acid (Ajax Chemicals; Auburn, NSW, Australia), pure alcuronium dichloride (Lot 912006 Hoffman - La Roche; Basle, Switzerland), disodium sulphate (BDH Chemicals; Kilsyth, Australia), and physostigmine sulphate (BDH Chemicals; Poole, England).

The method was developed using an isocratic Waters Associates, Inc. (Milford, Massachusetts, USA) HPLC system consisting of a Solvent Delivery System model M-45, an Injector model U6K, and an Absorbance Detector model 441. Separations were performed using a 250 mm x 4.6 mm CN - 8/5 column (Scientific Glass Engineering Pty Ltd (SGE), Melbourne, Australia) with a CN guard column (SGE) attached. Chromatographic responses were recorded and integrated using a Milton-Roy CI-10B integrator (Clare, Ireland).

6.2 Development of the Assay for Fentanyl in Plasma

6.2.1 Previous Methods

In anaesthesia and palliative care, only relatively low doses of fentanyl are administered and the plasma concentration tends to fall rapidly to low levels in the ng/mL and pg/mL range. Bentley *et al* (1983) found a mean plasma concentration of fentanyl during CPB of 9.1 ± 0.8 ng/mL whereas van Lersberghe *et al* (1994) reported a minimum effective plasma concentration of fentanyl for analgesia of 0.3 to 0.7 ng/mL.

Radioimmunoassay (RIA) methods, with a lower detection limit of 2 pg/mL have been used in a number of clinical studies (Koska *et al*, 1981; Bovill & Sebel, 1980; Bower & Hull, 1982).

A gas-chromatographic assay with nitrogen phosphous detection developed by Laganière *et al* (1993) used n-butyl chloride to extract fentanyl from plasma, and sufentanyl citrate as the internal standard. Recovery was 71 ± 10% for 0.4 ng/mL and 75 ± 6% for 3.5 ng/mL and a sensitivity of 0.25 ng/mL was obtained from 2 mL plasma. Intraday coefficient of variation was found to be 5.1% and between day coefficient of variation was 6.8%; both at a fentanyl concentration of 3.5 ng/mL. Van Rooy *et al* (1981) also used gas chromatography but with a flame ionisation detector. Fentanyl was extracted using benzene with papaverine as the internal standard. The detection limit was 3.3 ng/mL with a recovery of 76 ± 6% (11 ng/mL) from 1 mL plasma. Phipps *et al* (1983) followed a similar initial extraction procedure to Van Rooy *et al* (1981) but used gas chromatography with nitrogen phosphorus detection for quantification and achieved a significantly greater sensitivity of 20 pg/mL from 1 mL plasma; recovery was 69 ± 5% at 20 pg/mL and alfentanil was used as the internal standard. Kumar *et al* (1987) used HPLC with UV detection and achieved a recovery of 90 ± 1% and a detection limit of 1.0 ng/mL.

Table 6.1: Summary of studies for detection of fentanyl

Author	Method	Recovery	Internal Standard	Detection Limit	Extraction Solvent
Koska *et al,* (1981)	RIA			*	
Bovill & Sebel (1980)	RIA			*	
Laganière *et al,* (1993)	GC (NPD)	71 ± 10%	sufentanil	0.25ng/mL	n-butyl chloride
Bower & Hull (1982)	RIA			2pg/mL	
Koren *et al,* (1984)	GC	81%	*	*	*
Skacel *et al,* (1986)	GC	93 ± 4%	alfentanil	*	*
Van Rooy *et al,* (1981)	GC (FID)	76 ± 6%	papaverine	3.3 ng/mL	benzene
Kowalski *et al,* (1987)	GC (NPD)	54 ± 12% (blood)	dextromoramide	0.25 ng/mL	heptane
Kumar & Morgan (1987)	HPLC	90 ± 1%	*	1.0 ng/mL	heptane
Phipps *et al,* (1983)	GC (NPD)	69 ± 5%	alfentanil	20 pg/mL	benzene

* Information not provided

6.2.2 *Assay Development*

A sensitive and reproducible assay is necessary to study the pharmacokinetics and pharmacodynamics as fentanyl levels frequently fall below 10 ng/mL following intravenous injection. The method was developed based on published assays and using GC with nitrogen phoshorus detection.

The first objective was to optimise the extraction of fentanyl from the plasma so that there was maximum recovery of fentanyl and minimum interference from endogenous substances. Different solvents were tried

including heptane, toluene, benzene and hexane. Hexane was found to be the most suitable solvent as it gave the best recovery and least interfering peaks. Isopropanol (0.2 mL) was added to help break up emulsions which formed on agitation of plasma/solvent mixtures.

Next, the chromatographic conditions were considered. A TSD test mixture (Varian; Australia, containing 2.00 ng/μL azobenzene, 4.00 ng/μL malathion, 4.00 μg/μL C_{17} in iso-octane, and methyl parathion in an unspecified concentration) was utilised according to the manufacturer's directions so as to achieve suitable gas flow rates through the system. These were: carrier + make up 30 mL/min, hydrogen 4.5 mL/min and air 175 mL/min. Instrumental operating conditions with regard to temperature (given later) were initially based on previous studies, and altered in order to separate peaks, improve peak shapes, or alter retention times when required.

Ultimately, the method for drug extraction from plasma was very similar to Kowalski *et al*, (1987) with imipramine, rather than dextromoramide, as the internal standard and the use of hexane, rather than heptane as the extracting solvent.

6.3 Analytical Methods-Fentanyl

6.3.1 Extraction from plasma

When blood samples were received (see Chapter 6.6), the plasma and red blood cells were separated after centrifugation at 2,000 rpm for 15 minutes (Jouan CT 1000 centrifuge). The plasma (~3.5 mL) was kept in glass miniature vials (Packard, USA) at -18°C until analysis and thawed by gently shaking in a water bath at 37°C. For preparing standard curves, outdated plasma from The Red Cross Society (Melville Street, Hobart) was used.

Plasma standards were spiked to give fentanyl concentrations of 0.25, 0.5, 0.75, 1.0, 2.0, 2.5, 4.0, 5.0, 7.5, 10.0, 12.5 and 15.0 ng/mL from methanol solutions; 0.1 ng/μL and 1.0 ng/μL. Aliquots (2 mL) of plasma (patient samples, drug-free plasma, and plasma standards as above) were pipetted into 10 mL glass, conical-tipped, stoppered, centrifuge tubes. To this was added 25 μL internal standard solution (containing 1 ng/μL imipramine in methanol), 0.4 mL 5 N sodium hydroxide, 4.5 mL hexane and 0.2 mL isopropanol. The tube was stoppered, agitated for 1 min on a vortex mixer, then centrifuged for 10 min at 2500 rpm. The organic layer was transferred via a disposable pasteur pipette to another glass centrifuge tube. Hydrochloric acid (2 mL, 0.1 N) was added to the tube, which was capped, mixed for 1 min, and centrifuged as above. The organic layer was pipetted off and discarded. To the aqueous layer was added 0.2 mL sodium hydroxide 5 N and 0.6 mL hexane. The tube was again mixed for 1 min and centrifuged at 2500 rpm for 10 min. The organic phase was then transferred to a 1.0 mL Reacti-Vial™ (Pierce Chemical Company; Rockford, USA) and evaporated, in a heating block at 60°C, to approximately 10 μL under a gentle flow of nitrogen (high purity grade; Commonwealth Industrial Gases Ltd; Hobart, Australia), which had passed through oxygen and hydrocarbon trap filters (Scientific Glass Engineering Pty Ltd, Melbourne, Australia) to remove oxygen and organic contaminants.

6.3.2 Quantification by Gas Chromatography

GC operating conditions were as follows.

Ultra high-purity helium was used as the carrier gas to produce a head pressure of 8 psi (2.5 mL/min), high-purity nitrogen (25 mL/min) as the makeup gas, and air (175 mL/min) and hydrogen (4.5 mL/min) as the detector gases. All gases were supplied by CIG (Commonwealth Industrial Gases Ltd; Hobart, Australia). The injector temperature began

at 60°C and was increased at 200°C per minute to 300°C. The column temperature was initially held at 80°C for 1 min and then increased at 30°C per min to 300°C. The detector was maintained at 300°C. The NPD was optimized for maximum sensitivity according to the manufacturer's directions, the current applied to the rubidium bead of the NPD being approximately 3.0 A. About 1 μL of the organic phase was injected into the gas chromatograph. A standard curve was constructed using the peak area ratios of fentanyl/imipramine.

The precision of the assay was assessed both within and between days. For the within-day testing, five 2 mL aliquots of a spiked plasma sample (2.5 ng/mL) were processed on the same day, while 2 mL aliquots of a single spiked plasma sample (2.5 ng/mL) were processed on five consecutive days for the between-day assessment.

The specificity of the assay was examined by analysing plasma from patients not treated with fentanyl to ensure typical drugs taken by the patients did not interfere with the assay (see Appendix 5 for a list of drugs). Plasma from six cardiac patients was obtained as single 5 mL blood samples taken immediately prior to administration of fentanyl. Plasma from ten palliative care patients was obtained from a previous study in the department (Bleasel *et al*, 1994) and had been stored frozen at -18°C until determination of the fentanyl concentration.

6.3.3 Ultrafiltration

Tritiated fentanyl (372 GBq/mmol) with a reported radiochemical purity of 99.6% was obtained from Janssen Research Foundation (Beerse, Belgium) which enabled recovery and plasma protein binding studies to be undertaken.

For the determination of recovery of fentanyl, plasma (2 mL) was spiked with both fentanyl (2.5 ng/mL) and tritiated fentanyl (approximately 10,000 dpm; 120 pg in 50 μL ethanol). A 0.1 mL aliquot was withdrawn and assayed for radioactivity by liquid scintillation spectrometry (LKB Wallac 1215 Rackbeta 11, Finland) after the addition of 5 mL of liquid scintillation fluid (Insta-Gel®, Packard Instrument Company Inc., Illinois, USA). A further 2 mL of the spiked plasma was then subjected to the extraction procedure for fentanyl as outlined in section 6.3.1. In the final step rather than evaporating the hexane (0.6 mL) under nitrogen, it was placed in a glass liquid scintillation (LSC) vial, 5 mL of Insta-Gel® was added and the radioactivity counted. Recovery was then determined by calculating the amount of radioactivity which would have been in 2 mL of plasma (i,e,. standard x 20) and dividing the actual count from the plasma extraction by this number.

Fentanyl binding to plasma proteins was measured by ultrafiltration using the Amicon MPS-1 micropartition system and YMT membranes (Amicon Division, W.R. Grace & Co.; Danvers, Ma, USA). An aliquot of each patient plasma sample (approximately 1.0 mL) was spiked with tritiated fentanyl (120 pg; approximately 10,000 dpm) and pipetted into the upper chamber of the unit. A 0.1 mL plasma sample was taken for counting (standard) after the addition of 5 mL of liquid scintillation fluid. The ultrafiltration unit was placed in a fixed angle rotor centrifuge (Jouan CT 1000) prewarmed to 37°C. Centrifugation was performed at 3,000 rpm for 10 min to produce approximately 0.2 mL ultrafiltrate, of which 0.1 mL was taken for counting.

The unbound fraction was then calculated:

counts per minute (ultrafiltrate)/counts per minute (standard) x 100%

The unbound fentanyl concentration was calculated as the product of the total fentanyl concentration and the unbound fraction. Counts per minute were used for calculations rather than absolute activity as preliminary tests confirmed that the counting efficiency was essentially constant.

Additional preliminary experiments in which fentanyl (2.5 ng/mL) in plasma was ultrafiltered showed that only minimal adsorption (3.2 ± 2.8%, n = 5) to the membrane or to the ultrafiltration device occurred. Spiked plasma samples (n = 5) were counted for radioactivity (0.1 mL), before 1 mL was pipetted into the ultrafiltration unit and centrifuged as above. Samples were taken from both the supernatant and the ultrafiltrate as well as measuring the volume in both compartments. This allowed the calculation of total radioactivity in the unit which was compared to the total expected radioactivity (calculated from the standard before ultrafiltration) and the percentage fentanyl adsorbed was calculated.

Also, experiments were performed in order to determine whether freezing and subsequent thawing of plasma samples affected the extent of protein binding of fentanyl. Human blood was taken by venous puncture with a hypodermic syringe from six healthy volunteers. Plasma was obtained by centrifugation, one half of which was frozen. The remainder was spiked with 2.5 ng/mL of fentanyl and tritiated fentanyl to measure unbound fraction. After two weeks the samples were thawed in a water bath at 37°C and the above steps repeated. Before freezing, fentanyl was 30.0 ± 3.4% free, whereas after freezing it was 29.7 ± 3.1% free. Paired t-tests suggested the change in fentanyl binding before and after freezing was not considered significant ($t = 0.4524$, $p = 0.67$).

6.3.4 Loss of Fentanyl and the CPB Apparatus

A one litre solution of 10 ng/mL fentanyl spiked with tritiated fentanyl (0.01 ng/mL; approximately 10^6 dpm) in lactated Ringer's solution was flushed through a circuit consisting of only silicone tubing (9.5 mm and 3 mm ID; Imamura Co Ltd, Tokyo, Japan). The solution was pumped (Manostat Varistaltic Pump, NY, USA) through at 200 mL/min for 120 min at 25 to 26°C (representing body temperature during bypass). Samples (500 μL) were drawn from the reservoir (1.5 L conical flask) at 0, 1, 2, 5, 10, 20, 30, 60, 90 and 120 min. The samples were assayed for radioactivity by liquid scintillation spectrometry after the addition of 5 mL of liquid scintillation fluid (see section 6.3.3). The fentanyl concentration remained unchanged over 120 min indicating that no fentanyl was lost to the silicone tubing (Figure 6.1). There was no loss in volume from the system due to evaporation.

The silicone tubing was flushed with distilled water to remove any traces of fentanyl before connection to the CPB apparatus which consisted of silicone tubing (9.5 mm and 3 mm ID) and either a CMS 30™ membrane oxygenator (Cobe Cardiovascular, Inc., Arvada, USA), or an Optima™-HVRF membrane oxygenator with open filtered reservoir (Cobe Cardiovascular, Inc., Arvarda, USA). The oxygenators used can be seen in Figure 6.2. The pump (Manostat Varistaltic Pump, NY, USA) circulated the solution of 10 ng/mL fentanyl (and tritiated fentanyl) in lactated Ringer's solution through the CPB apparatus at a rate of 200 mL/min at 25 to 26°C. Samples were drawn and analysed as above.

In a preliminary stability study, one litre of lactated Ringer's solution containing 10 ng/mL fentanyl was left in a 1.5 L conical flask for the same length of time at room temperature and analysed in a similar manner. The concentration remained unchanged over 120 min.

Figure 6.1: The concentration of fentanyl during a 120-min circulation in silicone tubing

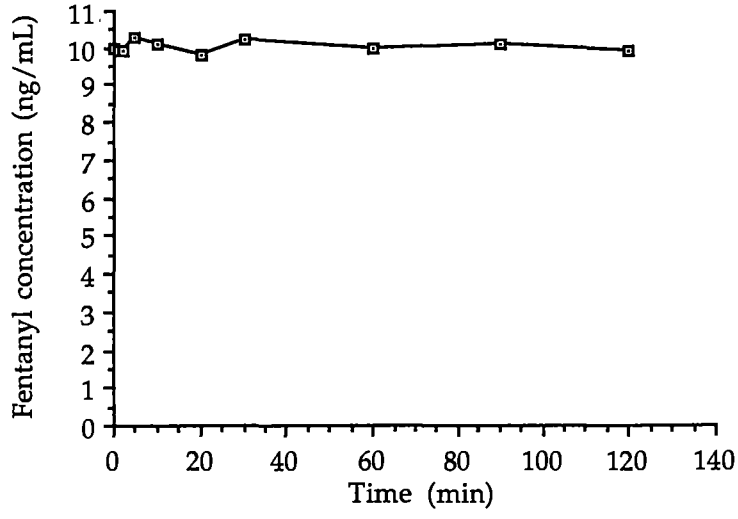


Figure 6.1a: The concentration of alcuronium during a 120-min circulation in silicone tubing

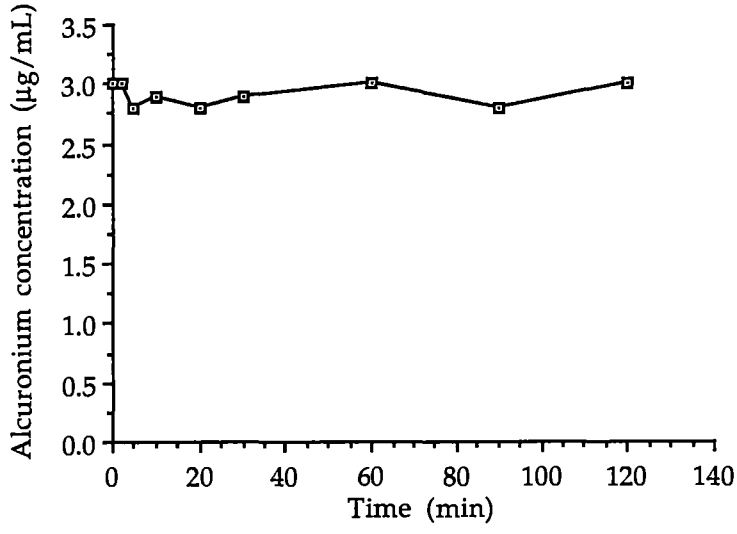
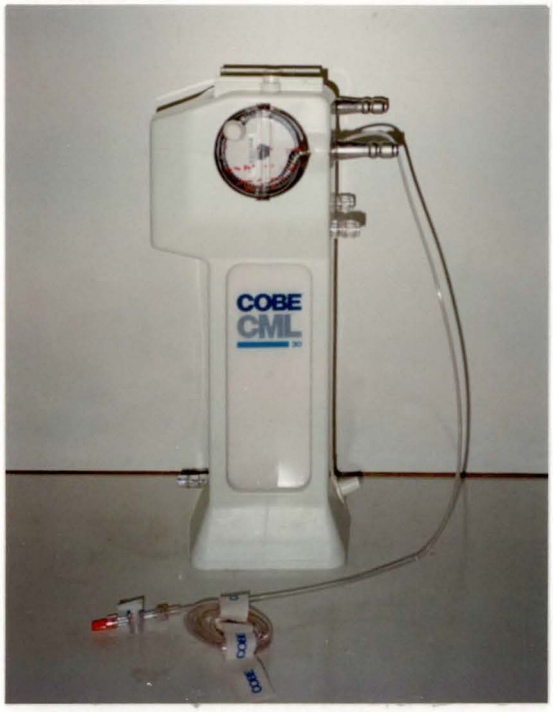


Figure 6.2: Cobe CMS 30^{TM} membrane oxygenator



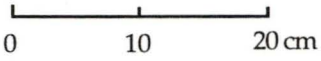
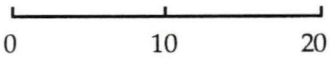


Figure 6.2a: Cobe Optima^{TM} - HVRF membrane oxygenator



6.4 Development of the Assay for Alcuronium in Plasma

6.4.1 Previous Methods

Quaternary amine neuromuscular blocking agents such as alcuronium are often considered difficult to chromatograph because of their large organic structures which contain one or two positively charged groups.

Walker *et al* (1983) used a spectrofluorimetric technique to measure alcuronium in plasma with a detection limit of 0.05 μg/mL. Recently HPLC methods with UV detection have been more frequently used, the differences being mainly in the preparation of samples. deBros *et al* (1990) used solid-phase extraction for preparing samples (Bond Elut™ columns) and achieved a sensitivity of 0.05 μg/mL. This method however was time-consuming and relatively expensive.

Bjorksten *et al* (1990) used isopropanol-dichloromethane for extraction from plasma and a silica column with a detection limit of 0.015 μg/mL. Although inexpensive, this method still had a number of extraction steps. Künzer *et al* (1994) developed an assay which used acetonitrile to precipitate proteins from the plasma sample and a Spherisorb 5-CN column for better separation yet reduced elution times. The sensitivity of the assay was reported as 0.025 μg/mL.

6.4.2 Assay Development

Because of its quick and simple pre-HPLC sample processing, the assay method of Künzer *et al* (1994) was chosen for plasma alcuronium determination in this study.

However, the assay could not be used directly as published due to several problems. Firstly, the internal standard used, laudanosine, did not chromatograph very well on our system so an alternative,

physostigmine, was used. Secondly, after injecting only a small number of plasma samples, the back pressure of the system increased to over 2,000 psi. This was eventually tracked down to a severely blocked guard column which had to be replaced. As it was most likely to have been caused by "dirty" samples, it was decided that they should be filtered in some way before injection into the system. Filtering the samples would remove any particles and insoluble chemical contaminants that were accumulating in the guard column and would also make the chromatography more reproducible.

A 0.45 μ cellulose acetate filter was tested initially but proved unsuitable as it was not acetonitrile-resistant. A material such as nylon is resistant to most solvents, so 0.45 μ, non-sterile, nylon membrane filters were used (Alltech Associates Pty Ltd; Baulkham Hills, Australia). After injecting over 250 samples, no increase in back pressure was noted indicating the value of pre-filtration in avoiding premature column replacement.

6.5 Analytical Methods-Alcuronium

6.5.1 Extraction from Plasma

When blood samples were received, the plasma and red blood cells were separated after centrifugation at 2,000 rpm for 15 min. The plasma (about 1 mL) was kept frozen in glass LSC vials at -18°C until analysis and was thawed by gently shaking in a water bath at 37°C. For preparing standard curves, outdated plasma from The Red Cross Society (Melville Street, Hobart) was used.

Plasma standards were spiked to give alcuronium concentrations of 0.1, 0.25, 0.5, 0.75, 1.0, and 1.5 μg/mL from an aqueous solution of 0.05 μg/μL. Aliquots (250 μL) of plasma (patient samples, drug-free plasma, and

plasma standards as above) were pipetted into cappable plastic vials (Eppendorf), and 400 µL of a solution containing 50 µg/mL physostigmine sulphate in acetonitrile was added to each vial. The addition of acetonitrile was to effect protein precipitation.

The vials were then vortex-mixed for 15 s, and centrifuged (Hettich Mikroliter; Tuttlingen, Germany) at 15,000 rpm for 10 min. From the supernatant liquid, 250 µL were filtered through 4 mm non-sterile disposable syringe filters with a 0.45 µ nylon membrane (Alltech Associates Pty Ltd; Baulkham Hills, Australia) and then centrifuged for 2 min at 15,000 rpm.

6.5.2 Quantification by High-Performance Liquid Chromatography (HPLC)

The materials and equipment were described in section 6.1.2 and the HPLC operating conditions were as follows.

The mobile phase consisted of 46% acetonitrile and 54% of an aqueous solution of 60 mM disodium sulphate and 5 mM sulphuric acid (Künzer *et al*, 1994). The system was operated at room temperature with a flow-rate of 1 mL/min resulting in a column pressure of 1300 psi. Aliquots (75 µL) of the supernatant liquid were injected into the HPLC and alcuronium was detected at 280 nm.

A standard curve was constructed using the peak area ratios of alcuronium/physostigmine. The recovery of the assay was examined by comparing the peak area for plasma extracted alcuronium and alcuronium dissolved in water (n = 5). The precision of the assay was assessed both within and between days. For the within-day testing, five 250 µL aliquots of a spiked plasma sample (1 µg/mL) were processed on the same day, while 250 µL aliquots of a single spiked plasma sample

(1 μg/mL) were processed on five consecutive days for the between-day assessment. The specificity of the assay was determined by testing plasma from six patient controls immediately prior to bypass surgery (before administration of alcuronium) to ensure that drugs typically taken by these patients did not interfere with the assay.

6.5.3 Loss of Alcuronium and the CPB Apparatus

A one litre solution of 3 μg/mL alcuronium in lactated Ringer's solution was flushed through a circuit consisting of only silicone tubing (9.5 mm and 3 mm ID; Imamura Co Ltd, Tokyo, Japan). The solution was pumped (Manostat Varistaltic Pump, NY, USA) through at 200 mL/min for 120 min at 25 to 26°C (representing body temperature during bypass). Samples (250 μL) were drawn from the reservoir (1.5 L glass conical flask) at 0, 1, 2, 5, 10, 20, 30, 60, 90 and 120 min. Internal standard (5 μg physostigmine) was added and an aliquot of about 30 μL was assayed for alcuronium concentration determination (see section 6.5.2). An additional standard curve was constructed for these higher concentrations in Ringer's solution. The alcuronium concentration remained unchanged over 120 min indicating that no alcuronium was lost to the silicone tubing (Figure 6.1a). There was no loss in volume from the system due to evaporation.

The silicone tubing was flushed with distilled water to remove any traces of alcuronium before connection to the CPB apparatus which consisted of silicone tubing (9.5 mm and 3 mm ID) and either a CMS 30™ membrane oxygenator (Cobe Cardiovascular, Inc., Arvada, USA), or an Optima™-HVRF membrane oxygenator with open filtered reservoir (Cobe Cardiovascular, Inc., Arvarda, USA). The pump (Manostat Varistaltic Pump, NY, USA) circulated the solution of 3 μg/mL alcuronium in lactated Ringer's solution through the CPB apparatus at a

rate of 200 mL/min at 25 to 26°C. Samples were drawn and analysed as above.

In a preliminary stability study, one litre of lactated Ringer's solution containing 3 μg/mL alcuronium was left in a 1.5 L conical flask for the same length of time at room temperature and analysed in a similar manner. The concentration remained unchanged over 120 min.

6.6 Human Procedures

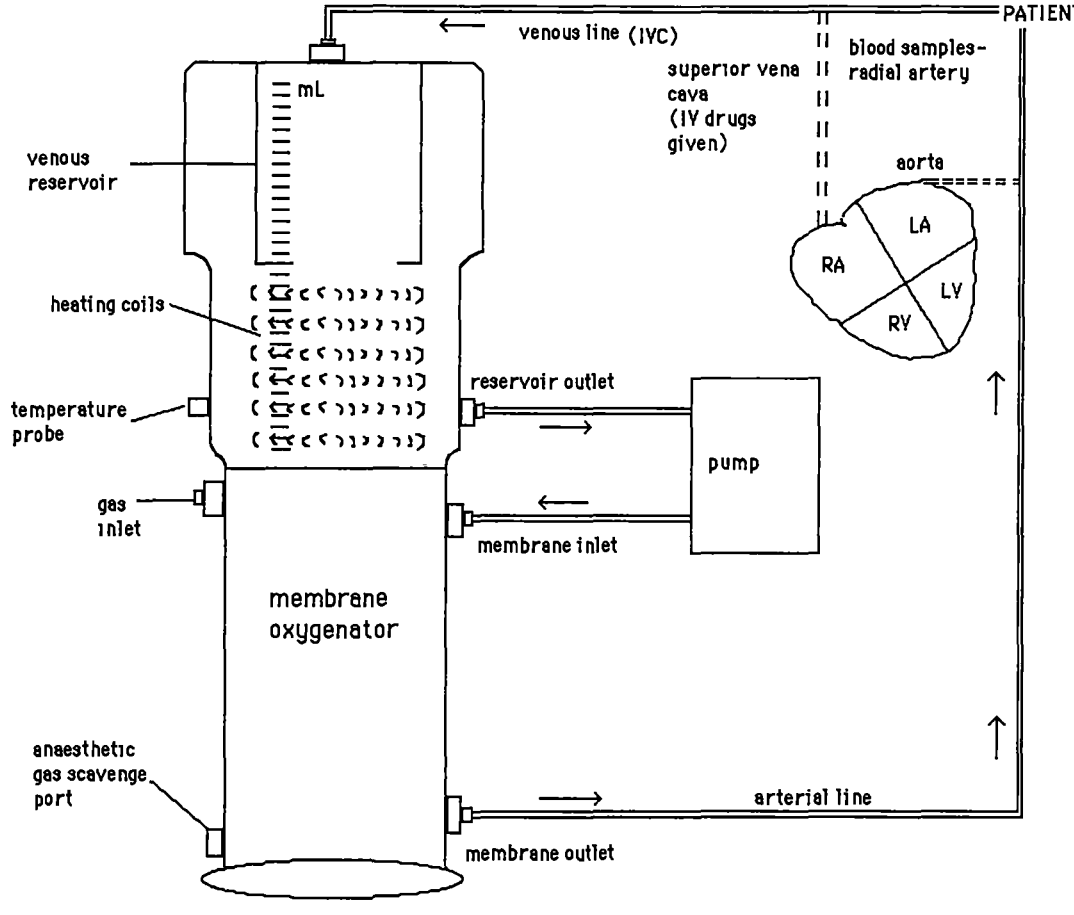
The study protocol was approved by the Research and Ethics Committees of the Royal Hobart Hospital and was carried out in collaboration with the Cardiac Surgery Unit at the hospital.

Subjects (n = 16) were chosen from a consecutive series of patients who were undergoing uncomplicated coronary artery surgery in which a cardiopulmonary bypass apparatus (COBE Membrane Lung with Integral Filter; COBE Cardiovascular, Inc., USA) containing 2.5 L of crystalloid priming solution temporarily assumed cardiac and pulmonary function (Figure 6.3). Relevant patient data were extracted from medical records, and included age, weight, height, drug therapy and serum creatinine concentrations (before surgery) and blood haemoglobin levels (before and during surgery). Estimated creatinine clearance was calculated using the equation (Cockroft & Gault, 1976):

$$\text{estimated creatinine clearance (mL/sec)} = \frac{(140 - \text{age}) \times \text{body weight(kg)}}{48{,}869 \times \text{serum creatinine (mmol/L)}}$$

Plasma was also collected from six preliminary patients (not included in results) in order to develop the blood sampling regimen. Each patient gave written, informed consent before entering the study and received a Patient Information Sheet (Appendices 6 and 7).

Figure 6.3: Cardiopulmonary bypass apparatus



Premedication typically consisted of 10 to 15 mg of diazepam and 10 mg of droperidol given orally approximately 90 min before the induction of anaesthesia. Anaesthesia was induced with an intravenous dose of 120 to 150 mg of thiopentone, 10 mg droperidol and 500 μg fentanyl and maintained with a total of a further 1500 to 2500 μg of fentanyl in up to five divided bolus doses and ventilation with 50% nitrous oxide. Corrected for weight, the total fentanyl dose ranged from 27.1 to 39.7 μg/kg (mean ± SD: 33.5 ± 3.5 μg/kg). Alcuronium was also given at the time of induction at an intravenous dosage of either 20 or 30 mg. A prophylactic antibiotic, 1 g of either cephalothin or cephamandole, was administered intravenously. Before the start of bypass 350 to 450 units/kg of heparin was given intravenously and each patient received 20 mg hydralazine. Ten patients who required extra neuromuscular blockade received 10 to 20 mg of tubocurarine. All patients were cooled to 25 to 26°C and gradually rewarmed towards the end of the procedure. After termination of CPB, by which time the patient was back to 37°C, the effect of heparin was reversed by the administration of 300 to 500 mg of protamine. An additional bolus fentanyl dose was given at this time in fifteen of the patients to ensure adequate anaesthesia until the end of surgery. Neuromuscular blockade was not reversed and the lungs were ventilated for at least six hours postoperatively. The time scale of drugs received and intraoperative events for a typical patient are shown in Table 6.2.

Blood samples (7 mL) were drawn from the radial artery at various intervals throughout surgery (1 min, 5 min and 10 min after the last fentanyl IV dose prior to the start of bypass; 5 min, 30 min and 60 min after the start of bypass; just before rewarming; and 1 min before, 1 hour, 2 hours and 3 hours after the end of bypass; Appendix 8) and placed into tubes containing lithium heparin as an anticoagulant. Plasma was

Table 6.2: An example of the drugs received and the time course of the operation (Patient AD)

Time	Event	Body temperature
1130	15 mg diazepam	
	10 mg droperidol	
1210	10 mg droperidol	
	500 μg fentanyl	
	125 mg sodium thiopentone	
	20 mg alcuronium	
1220	500 μg fentanyl	
1230	30 mM $MgSO_4$	
	20 mM KCl	
	1 g cephamandole	
1236	**surgery commenced**	36°C
1245	500 μg fentanyl	
1305	250 μg fentanyl	
1310	250 μg fentanyl	
1320	35,000 U heparin	
1325	500 μg fentanyl	
	20 mg hydralazine	
1337	**start of bypass**	32°C
1350	maximum hypothermia	26°C
1425	**rewarming commencement**	26°C
1445	10 mM $MgSO_4$	34°C
	20 mM KCl	
1522	**end of bypass**	38°C
	400 mg protamine	
1540	500 μg fentanyl	

separated by centrifugation and frozen at -18°C until determination of the total fentanyl, unbound fentanyl and total alcuronium concentrations.

6.7 Pharmacokinetic Analysis

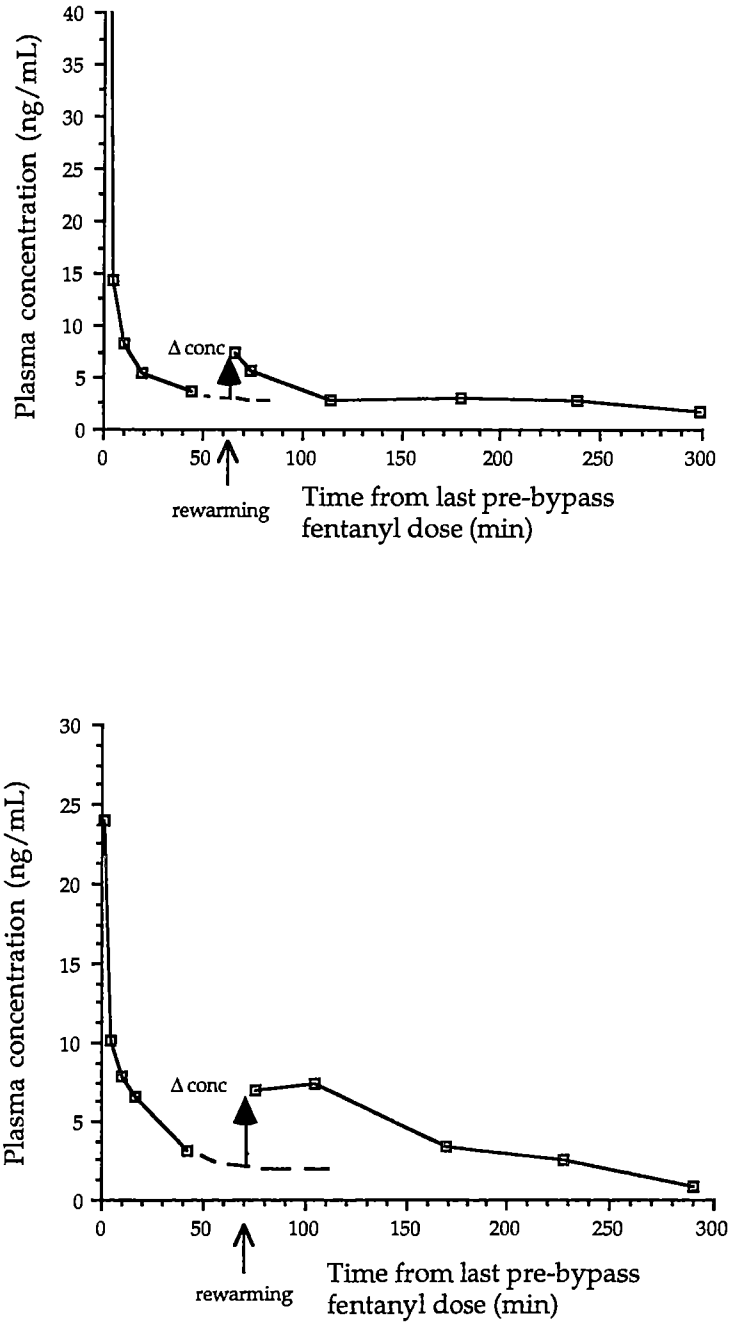
Blood sampling was timed from the end of the last pre-bypass fentanyl bolus injection. Biexponential equations were fitted to the fentanyl plasma versus time data (first five or six points) using the software package Minim 2.0.2® (RD Purves, Pharmacology Department, University of Otago, Dunedin, NZ) on a Macintosh® computer. The expected fentanyl concentration at a later time (t) was then estimated from the equation. This concentration was compared to the actual concentration found on rewarming to determine the size of the change in total fentanyl concentration on rewarming (Figure 6.4).

The elimination half-life of fentanyl was estimated from the semilogarithmic concentration-time plot of the last four (post-bypass) points in Figure 7.9, using the mean values from all sixteen patients. Only post-bypass points were used because of the disruptions to the plasma concentrations during CPB and the bolus of fentanyl administered after the end of CPB. It was not possible to estimate half-lives in individuals because of the occurrence of plasma level fluctuations about two hours after the end of bypass in some patients.

The elimination half-life of alcuronium was estimated individually from semilogarithmic plots of the plasma alcuronium concentration-time curve using the last four samples for each patient.

All data were stored and statistically analysed (Statview SE+Graphics®, Abacus Concepts; Palo Alto, Ca, USA) on a Macintosh® computer. Relationships were investigated using appropriate non-parametric

Figure 6.4. Calculation of the size of the increase in fentanyl plasma concentration on rewarming in two patients



statistical procedures (Spearman rank correlations and Mann-Whitney U-tests), with a p value below 0.05 considered statistically significant. Results are expressed as means ± SD, unless otherwise stated. The patient data file can be seen in Appendix 9.

CHAPTER 7: RESULTS

7.1 Analytical Variables-Fentanyl

7.1.1 Retention Times of Relevant Peaks

The approximate retention times for imipramine and fentanyl under the described chromatographic conditions were 5.4 and 6.9 min respectively. Blank plasma extractions demonstrated that using GC, there were no interfering peaks at these retention times. An example of a patient plasma sample is shown in Figure 7.1 indicating fentanyl and the internal standard, imipramine and a blank plasma trace is shown in Figure 7.2.

7.1.2 Standard Curve

The relationship between the plasma concentration of fentanyl and the peak area ratio (fentanyl/imipramine) was essentially linear ($r^2 = 0.993$) over the concentration range 0.25 to 15 ng/mL (Figure 7.3). A full standard curve was run each time samples were analysed.

7.1.3 Recovery and Reproducibility

The analytical recovery of the assay was examined using tritiated fentanyl. The mean overall recovery of the assay for five plasma samples (2.5 ng/mL) was 81.5 ± 3.7%. The intra- and inter-day coefficients of variation (CV) for the determination of fentanyl at 2.5 ng/mL were 5.7% (n = 5) and 4.9% (n = 5), respectively.

A lack of interfering peaks in any of the cardiac or palliative care controls was evidence for the specificity of the method. At a fentanyl concentration of 2.0 ng/mL, no degradation was observed for plasma samples stored at -18°C over a six month period compared with freshly spiked plasma samples.

Figure 7.1: GC trace of CPB patient plasma sample (containing fentanyl 13.7 ng/mL)

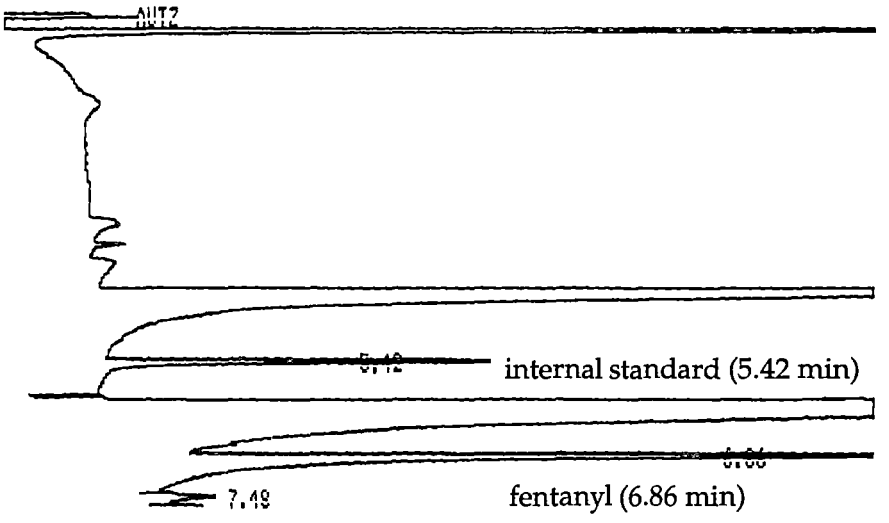


Figure 7.2: GC trace of plasma blank

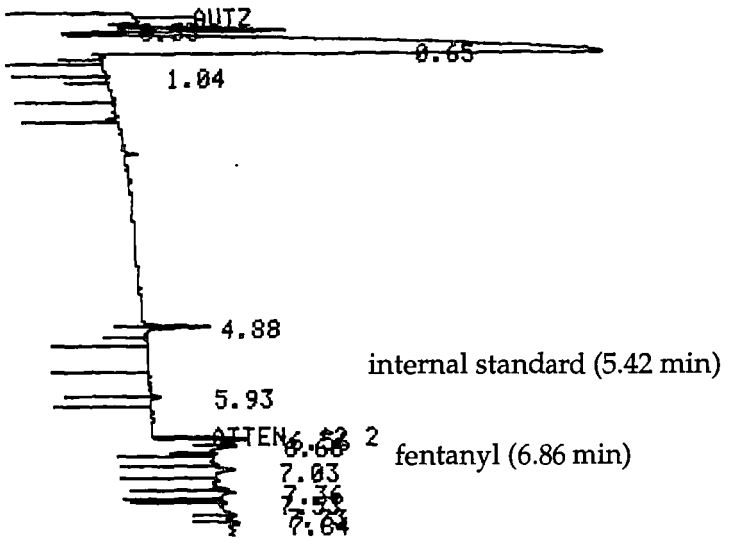
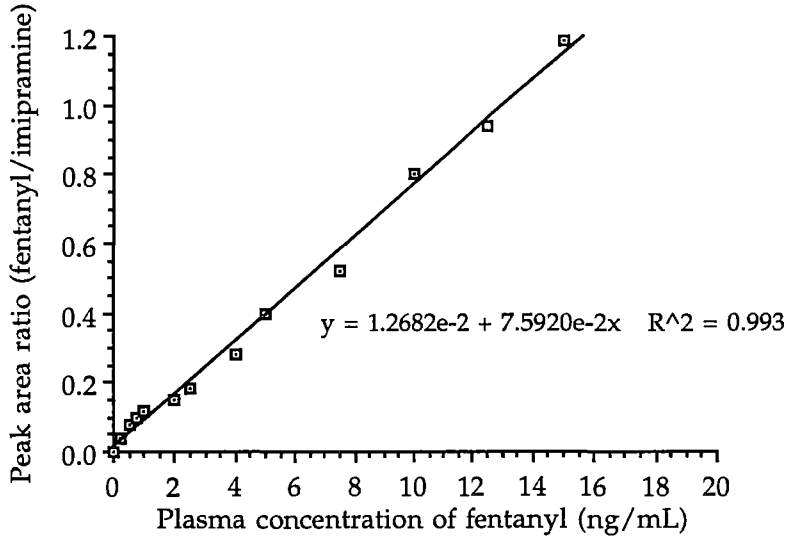


Figure 7.3: Fentanyl standard curve



7.1.4 Sensitivity

The sensitivity limit of the described procedure for measuring the fentanyl concentration in plasma (based on a signal to noise ratio greater than 2) was 0.25 ng/mL when 2 mL of plasma was used.

7.2 Analytical Variables-Alcuronium

7.2.1 Retention Times of Relevant Peaks

The approximate retention times for physostigmine and alcuronium under the described chromatographic conditions were 3.6 and 8.9 min respectively. Blank plasma extractions demonstrated that, using HPLC, there were no interfering peaks eluting at these retention times. An example of a patient plasma sample is shown in Figure 7.4 indicating alcuronium and the internal standard, physostigmine and a blank plasma trace is shown in Figure 7.5.

7.2.2 Standard Curve

The relationship between the plasma concentration of alcuronium and the peak area ratio (alcuronium/physostigmine) was essentially linear (r^2 = 0.993) over the concentration range 0.1 to 1.5 μg/mL (Figure 7.6).

7.2.3 Recovery and Reproducibility

The mean overall analytical recovery of the assay for five plasma samples (250 μL) was 68.9 ± 3.1%. The intra- and inter-day coefficients of variation for the determination of alcuronium at 1.0 μg/mL were 4.6% (n = 5) and 5.1% (n = 5), respectively. A lack of interfering peaks in any of the controls was evidence for the specificity of this method.

7.2.4 Sensitivity

The sensitivity of the described procedure for measuring the alcuronium concentration in plasma (based on a signal to noise ratio greater than 2) was 0.1 μg/mL when 250 μL of plasma was used.

Figure 7.4: HPLC trace of CPB patient plasma sample (containing alcuronium 0.6 μg/mL)

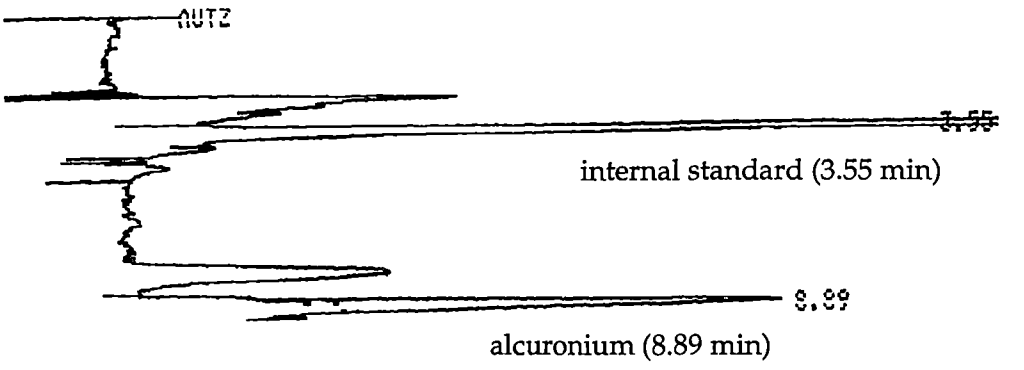


Figure 7.5 HPLC trace of plasma blank

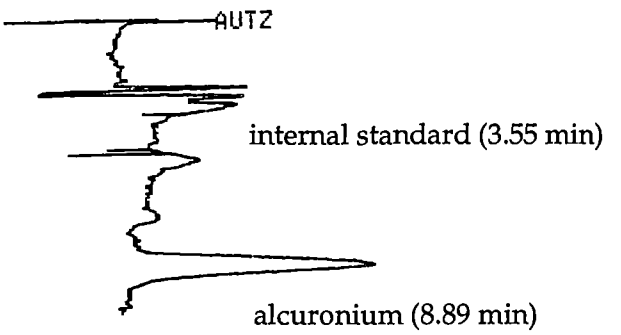
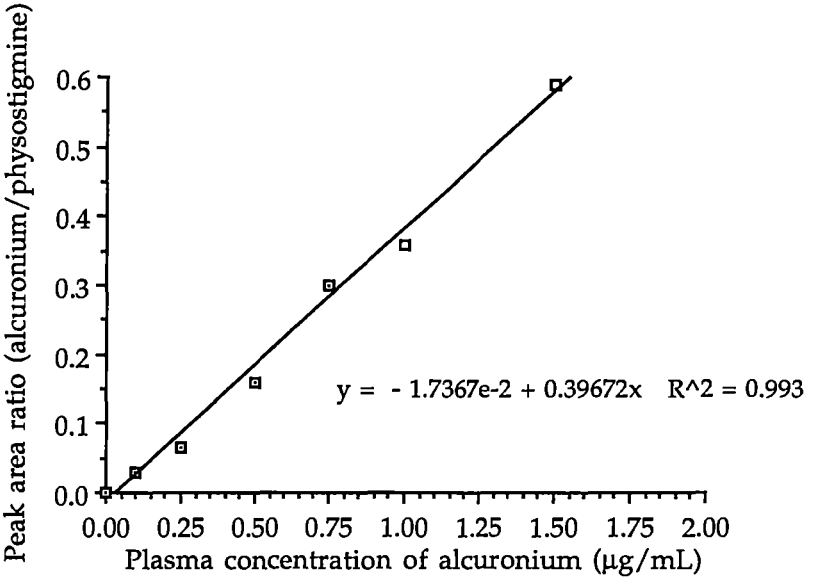


Figure 7.6: Alcuronium standard curve



7.3 Study Results

7.3.1 Patient Characteristics

The sample of 16 patients consisted of 13 males and 3 females, ranging in age from 47 to 83 years, with a median age of 65 years. The patients all had ischaemic heart disease and between one and four coronary vessel grafts (CVG) were performed in addition to a left internal mammary artery graft (LIMAG) in each case.

Serum concentration of creatinine prior to CPB ranged from 62 to 139 μmol/L (mean 94 μmol/L) and estimated creatinine clearance ranged from 44.5 to 116.7 mL/min (mean 75.2 mL/min).

Significant correlations did not exist between sex and either the serum creatinine or the estimated creatinine clearance (Mann-Whitney $U = 9$, $z = -1.4$, $p > 0.10$ and Mann-Whitney $U = 13$, $z = -0.9$, $p > 0.30$, respectively).

There were no significant associations between age and the serum creatinine or the estimated creatinine clearance (Spearman $\rho = 0.2$, $p > 0.30$ and Spearman $\rho = -0.50$, $p > 0.05$, respectively).

The mean elapsed time between induction of anaesthesia and commencement of extracorporeal circulation was 87 min (range 72 to 106 min). The lowest temperature during surgery was 25°C and the duration of bypass ranged from 57 to 124 min (mean 92 min) and was significantly related to the number of grafts being performed (Spearman $\rho = 0.50$, $p < 0.05$).

7.3.2 Fentanyl Concentrations in Plasma

Plasma concentration-time curves of six initial patients led to the development of the blood sampling regimen, in addition to a significant alteration in the fentanyl dosing regimen which was used throughout

the remainder of the study (Figure 7.7). Rather than the former practice of giving multiple fentanyl dosages during the whole procedure, it was decided to give all the fentanyl prior to the commencement of bypass to enable the effect of CPB to be ascertained more easily. In this preliminary study, plasma was collected sequentially from the venous then the arterial side of the pump just after connection to determine the degree of adsorption of fentanyl to the bypass apparatus. A mean change in fentanyl concentration of only 0.2 ± 0.3 ng/mL (n = 6) was seen which was not significant, although the instantaneous loss proved quite difficult to measure. The collection of these plasma samples was subsequently discontinued for the main study group of patients.

The onset and duration of CPB varied between patients and the timing of the blood samples during the surgery was different so it was not possible to show mean plasma concentration profiles based on actual times; instead intraoperative events were used as points of reference. Mean times were calculated with standard error bars for each event.

The peak total fentanyl level measured 1 min after the last dose showed great variation between patients and ranged from 9.2 to 106 ng/mL (mean 30.6 ± 26.1 ng/mL). This fell quickly to 10.7 ± 3.2 ng/mL after ten min. After initiation of CPB, several minutes later, there was a mean drop in the total fentanyl concentration of 58.8 ± 14.1% to 4.8 ± 1.9 ng/mL within five min of the start of extracorporeal circulation. The haemoglobin level dropped on average 47.3 ± 6.3% on initiation of CPB from 14.2 ± 1.2 to 7.5 ± 1.2 g/100 mL and this was used as an indicator of the degree of haemodilution. The percentage fall in plasma concentration of fentanyl at the start of CPB was related to the magnitude of the decline in haemoglobin level (Figure 7.8, Spearman $\rho = 0.65$, $p < 0.01$).

Figure 7.7: Preliminary patients' fentanyl plasma concentration-time curves

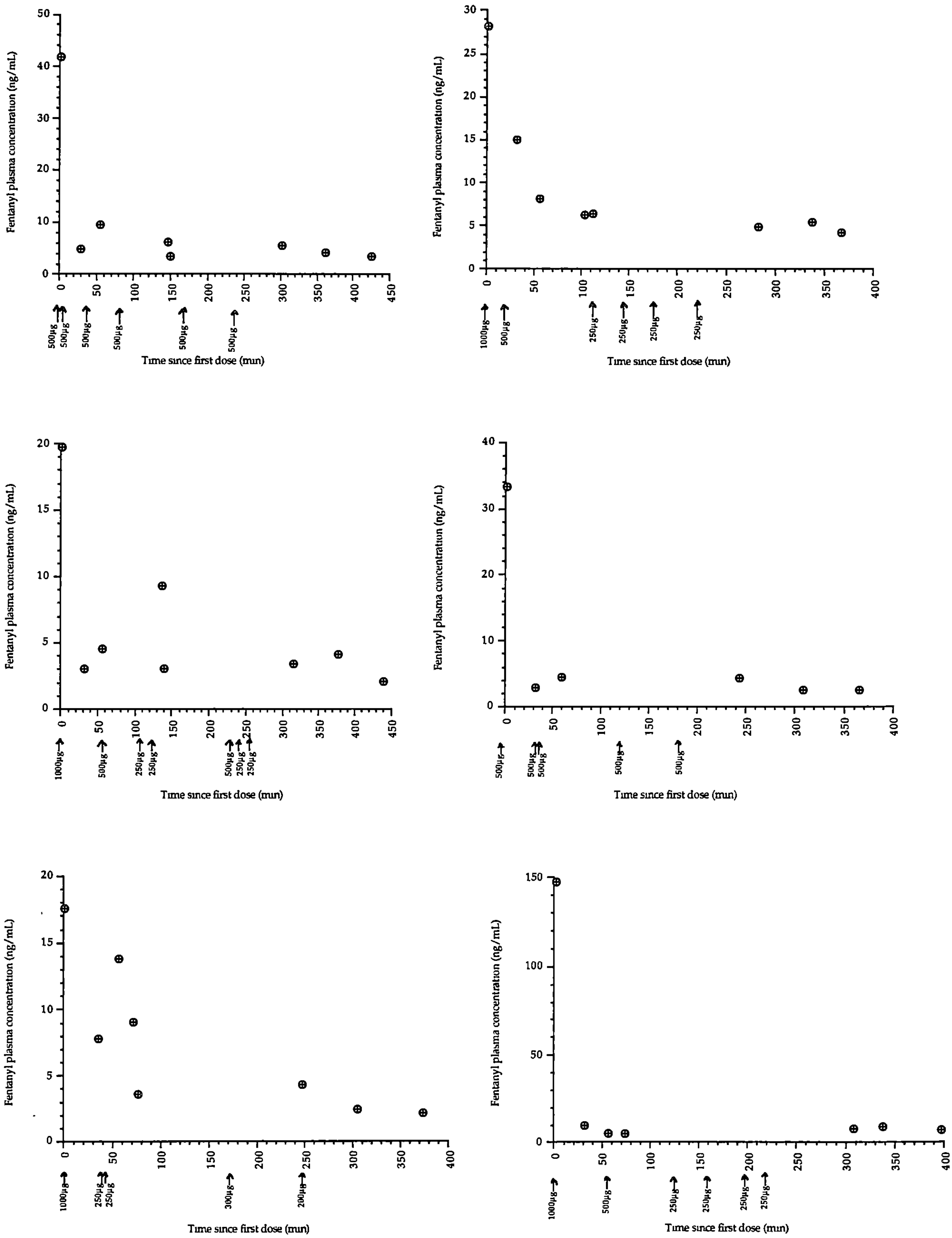
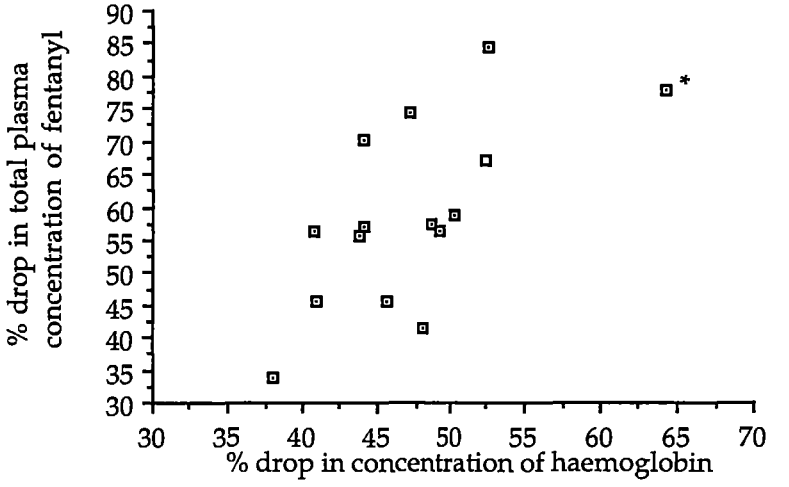


Figure 7.8: Percent drop in plasma concentration of haemoglobin versus % drop in plasma concentration of fentanyl at the start of CPB



* - patient had to be given blood transfusion because haemoglobin dropped to 4 g/L

The percentage dilutional effect produced by the start of CPB was also estimated by adding the pump volume (2.5 L) to an assumed initial blood volume of 80 mL/kg of body weight (Koska *et al*, 1984a). The measured percentage decrease in the plasma concentration of fentanyl on initiation of CPB was also related to this percentage dilution of blood volume which averaged 40.6%. (Spearman $\rho = 0.55$, $p < 0.05$). The drop in haemoglobin level was related to this estimated dilution at the start of CPB (Spearman $\rho = 0.43$, $p < 0.10$).

The fentanyl concentration remained relatively stable during bypass until near the end of CPB when the mean total concentration increased, coinciding with rewarming (Figure 7.9). The size of the increase was calculated and ranged from -0.4 to 5.4 ng/mL and was related to the body mass index (BMI = weight in kilograms/(height in metres)^2) of the patient (Figure 7.10; Spearman $\rho = 0.85$, $p < 0.001$). BMI was used in preference to body mass because it gave a better indication of body fat.

The percentage fall in plasma concentration of fentanyl at the start of CPB was also inversely related to the weight of the individual (Spearman $\rho = -0.53$, $p < 0.05$) and the size of the increase in fentanyl concentration on rewarming (Spearman $\rho = -0.67$, $p < 0.05$).

7.3.3 Protein Binding

The unbound fraction (f_u) of fentanyl rose 1.5-fold from a mean of 23.5 ± 5.5% (n = 13) pre-bypass to a maximum of 34.0 ± 7.7% (n = 13) after the onset of CPB (Figure 7.11). The unbound fraction was not measured in all patients before bypass because of an insufficient volume of plasma for analysis. The unbound fraction remained relatively high throughout surgery before falling to close to 27.7 ± 4.1% which is close to its pre-bypass value.

Figure 7.9: Plasma fentanyl concentrations versus time in a group of patients having coronary artery bypass grafting (n = 15)

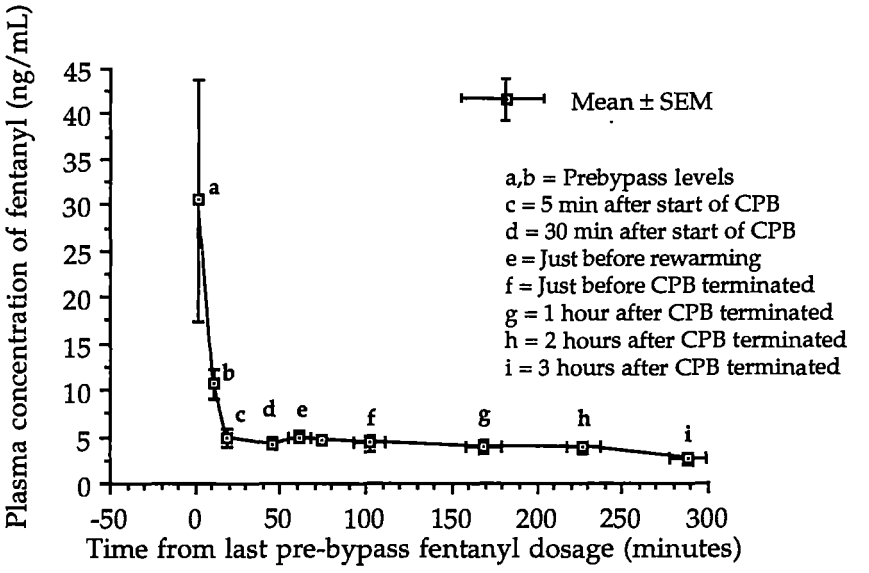


Figure 7.10: Change in total fentanyl concentration on rewarming vs BMI

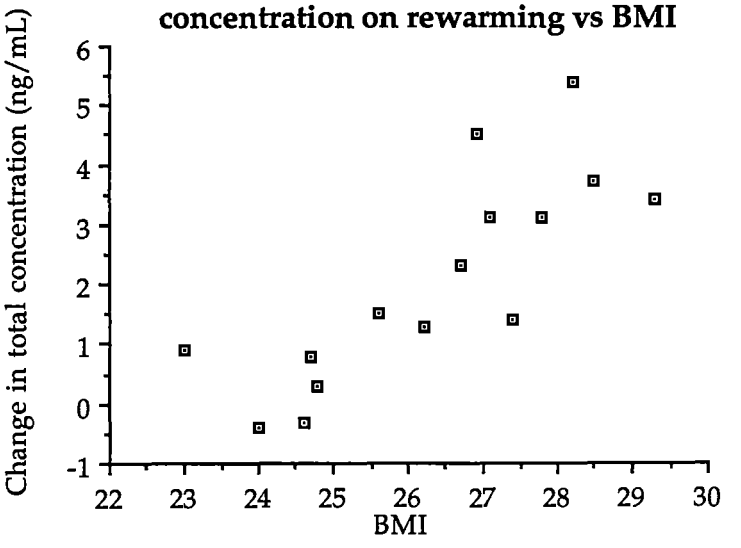
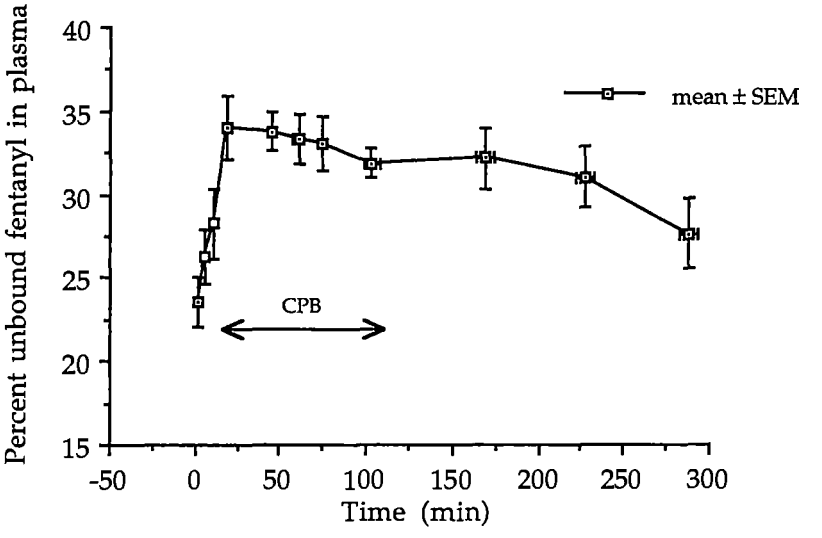


Figure 7.11: Percent unbound fentanyl versus time in a group of patients having coronary artery bypass grafting



The unbound concentration of fentanyl fell by a mean of 43% from its original value on initiation of bypass (3.0 ± 1.0 ng/mL to 1.7 ± 0.8 ng/mL within 5 min of CPB) and then stayed relatively constant during surgery before decreasing slightly after the end of the procedure (Figure 7.12).

7.3.4 Pharmacokinetics - fentanyl

From a semilogarithmic concentration-time plot using the grouped data (Figure 7.9), an elimination half-life of 4.7 hours was estimated.

7.3.5 Loss of Fentanyl and the CPB Apparatus

Following the priming of the pump with 10 ng/mL of fentanyl, the concentration fell to 8.8 ng/mL within one min and then remained relatively stable over the following 120 min during circulation through the CML30™ membrane oxygenator (Figure 7.13).

In the Optima™ membrane oxygenator, the initial fall was from 10.0 to 9.2 ng/mL within one min before falling further and stabilising at a level of 8.5 ng/mL by 120 min (Figure 7.14).

These decreases in fentanyl concentration represent total losses of 1.2 μg and 1.5 μg of fentanyl, respectively from each system. Translating this loss in vivo, it is less than 1% of the total fentanyl dose given.

7.3.6 Alcuronium Concentrations in Plasma

The alcuronium dosage was either 20 mg (n = 14) or 30 mg (n = 2) which translated to a range of 0.22 to 0.37 mg/kg. The resulting plasma concentrations decreased gradually pre-bypass before a more marked decline 5 min after connection of the CPB apparatus. The plasma concentrations of alcuronium were plotted using the last pre-bypass fentanyl dose as time zero; this was usually about one hour after the alcuronium dose was given. The mean decline in alcuronium

Figure 7.12: Total and unbound plasma fentanyl concentrations in a group of patients having coronary artery bypass grafting (n = 15) Mean and SEM are shown

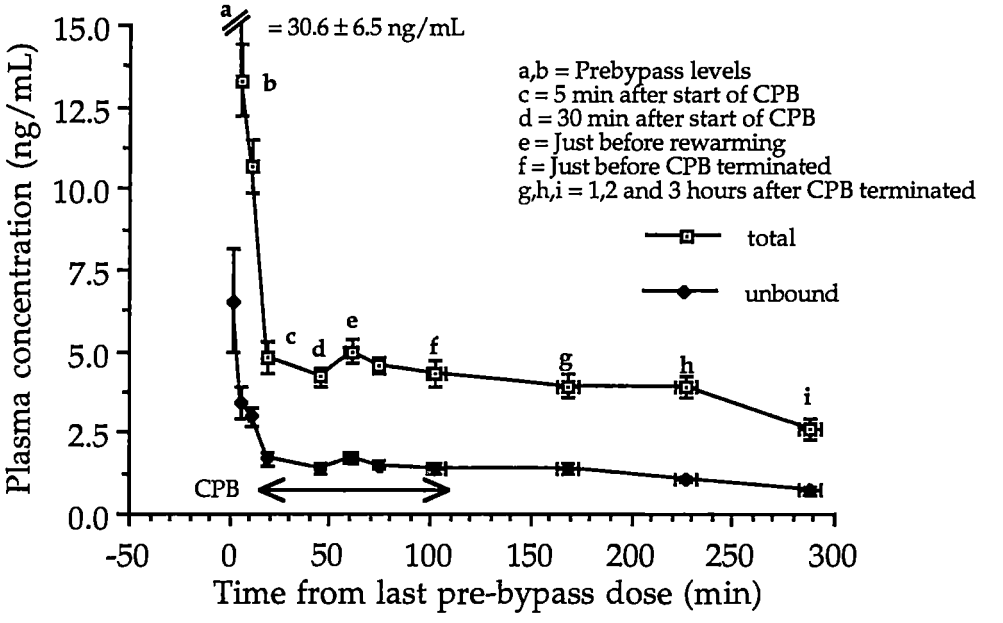


Figure 7.13: The concentration of fentanyl during a 120-min circulation through a membrane oxygenator (CML30™)

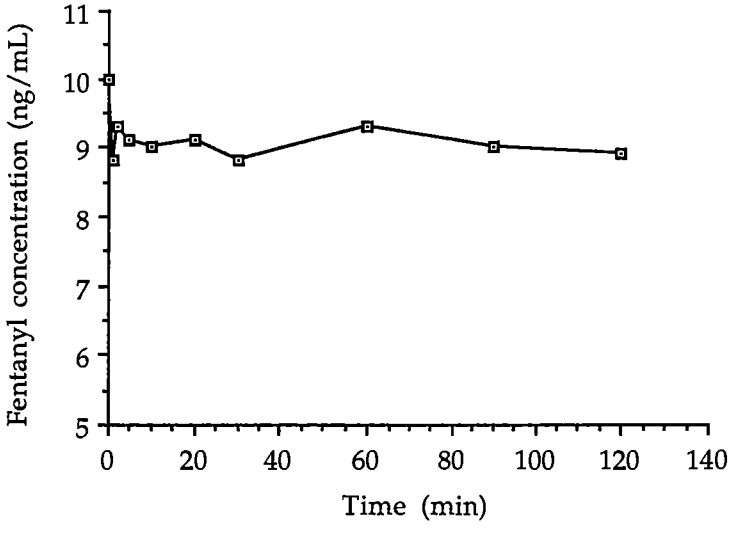
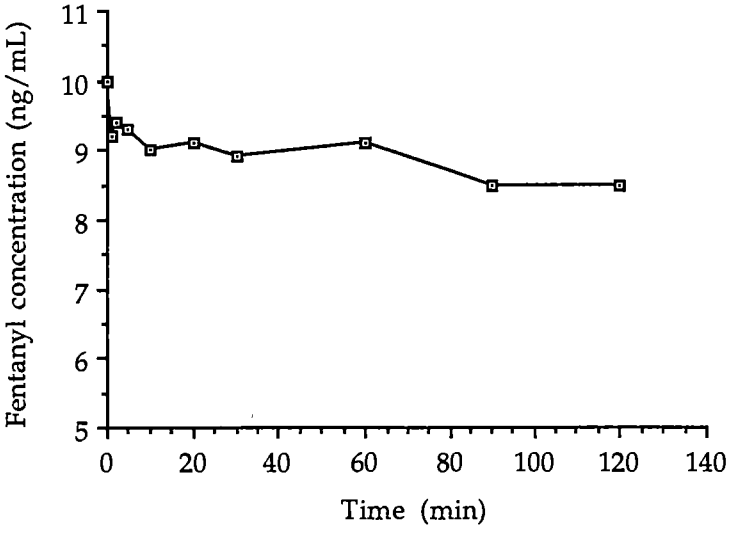


Figure 7.14: The concentration of fentanyl during a 120-min circulation through a membrane oxygenator (Optima™)



concentration on connection to CPB was 29.0 ± 10.9% (n = 16). The alcuronium concentrations remained relatively constant during surgery until falling due to elimination (Figure 7.15). There was no increase in the plasma concentration coinciding with rewarming.

7.3.7 Pharmacokinetics - alcuronium

The estimated average elimination half-life of alcuronium for the sixteen patients was 194 ± 44 min. Half-life calculated individually for each patient was significantly inversely related to estimated creatinine clearance (Spearman $\rho = -0.55$, $p < 0.05$). Significant correlations did not exist between the half-life and either age or sex of the patient (Spearman $\rho = 0.36$, $p > 0.10$ and Mann-Whitney $U = 11.0$, $z = -1.1$, $p > 0.25$, respectively).

7.3.8 Loss of Alcuronium and the CPB Apparatus

Following the priming of the pump with 3 μg/mL of alcuronium, virtually unchanged concentrations of the drug were measured at all times for both the CML30™ and the Optima™ (Figures 7.16 & 7.17). A drop from 3 μg/mL to 2.8 μg/mL in the one litre solution of Ringer's lactate represents a loss of only 0.2 mg of alcuronium from the system. When translated in vivo, this is 1% of the 20 mg intravenous dose. Using a published V_d of 329 mL/kg in bypass patients (Walker *et al*, 1983) the apparent loss of alcuronium on connection to CPB can be estimated. The average fall in plasma concentrations of alcuronium in the study patients is from 0.8 to 0.6 μg/mL or :

from

0.8 μg/mL x 329 mL/kg x 70 kg = 18424 μg or 18.4 mg

to

0.6 μg/mL x 329 mL/kg x 70 kg = 13818 μg or 13.8 mg

This represents an apparent loss of alcuronium of 4.6 mg with only 0.2 mg of this amount being attributed to adsorption to the membrane

Figure 7.15: Plasma alcuronium concentrations versus time in a group of patients having coronary artery bypass grafting (n = 16)

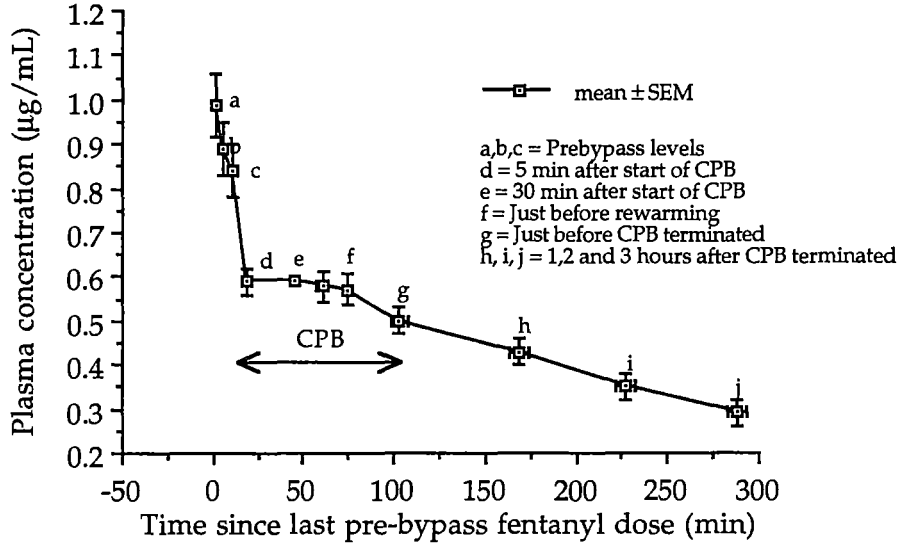


Figure 7.16: The concentration of alcuronium during a 120-min circulation through a membrane oxygenator (CML30™)

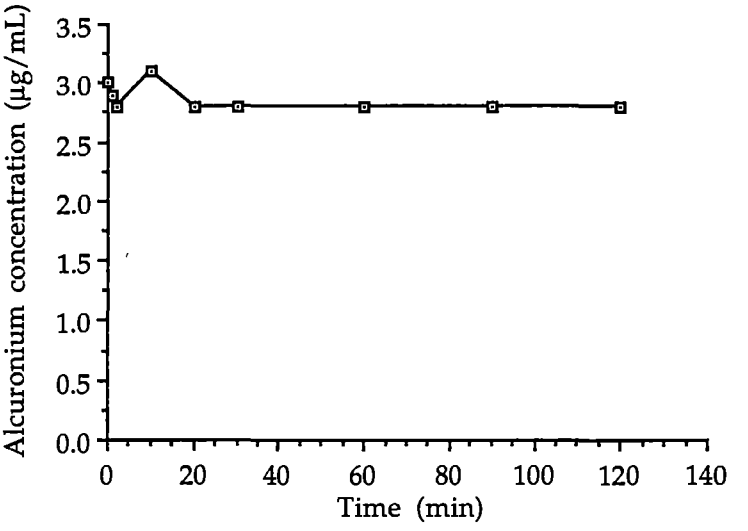
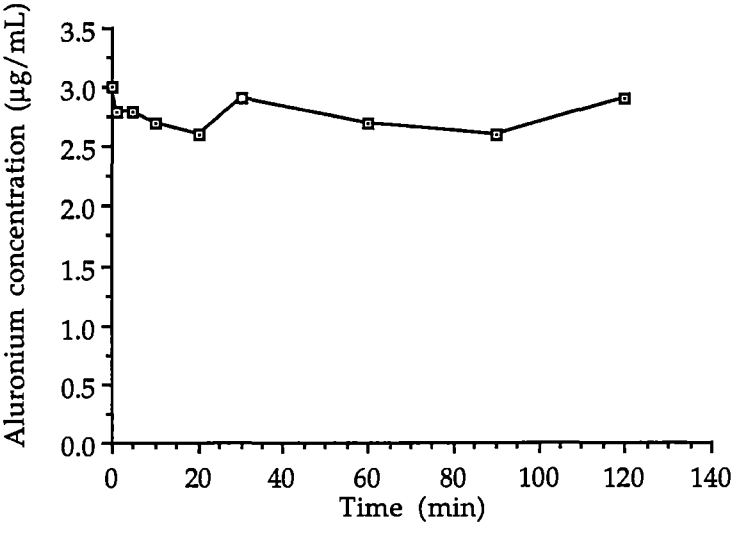


Figure 7.17: The concentration of alcuronium during a 120-min circulation through a membrane oxygenator (Optima™)



oxygenator in the in vitro study (4.3%). The decline in plasma concentration must therefore be due primarily to sequestration by the lungs and of course haemodilution.

CHAPTER 8 : DISCUSSION

This study presents a profile of the fate of intravenous fentanyl and alcuronium in patients undergoing cardiopulmonary bypass surgery. All major pharmacokinetic processes could be affected by CPB; however, any attempt at formal pharmacokinetic modelling assumes that the physiological status of the patient remains relatively constant over the given period. In this study, the number of factors which may affect pharmacokinetics such as other drug therapy, dosage regimen, haemodilution, hypothermia, lung isolation, adsorption of drug and protein to the CPB apparatus and hormonal and catecholamine release made the results difficult to deal with mathematically. For these reasons the study became largely an observational one.

Fentanyl

Some of the previously reported fentanyl assay methods proved unsuitable for plasma level monitoring in this study due to both the excessive costs of RIA and the unavailability of the internal standards used. The GC procedure described here is specific for the measurement of fentanyl and sensitive enough to measure the low levels after administration of fentanyl citrate for anaesthesia. The extraction is close to that of Kowalski *et al* (1987) but uses a different solvent and internal standard and extracts from plasma rather than blood. The limit of detection was found to be about 0.25 ng/mL when 2 mL of plasma was extracted for fentanyl determination. This is similar to the sensitivity reported in other studies (Laganière *et al*, 1993: 0.25 ng/mL; Kowalski *et al*, 1987: 0.10 ng/mL; Phipps *et al*, 1983: 20 pg/mL, Kumar & Morgan, 1987: 1.0 ng/mL). The recovery of the described method was 82%. This compares favourably with van Rooy *et al* (1981) and Kumar & Morgan

(1987) who claimed their extraction methods gave fentanyl recoveries of 76% and 89% respectively.

The total fentanyl dosage for each patient over the whole period ranged from 27.1 to 39.7 μg/kg with a mean dosage of 33.5 μg/kg, and was given at varied and unscheduled times. This is significantly lower than the dosages of fentanyl used in most of the other studies (Table 8.1) and differs also in that each study in Table 8.1 involved the administration of only a single bolus dose of fentanyl rather than up to six separate injections. Other studies have also looked at the pharmacokinetics of fentanyl following bolus and infusion (Hall *et al*, 1993) which would allow the establishment of a stable fentanyl concentration prior to CPB enabling any resultant effects on plasma concentration and binding to be determined more precisely.

Table 8.1: A summary of fentanyl doses used in cardiopulmonary bypass studies

Study	Total fentanyl dose given	Sole anaesthetic agent
Hug & Moldenhauer, 1982	75 μg/kg	yes
Bentley *et al*, 1983	100 μg/kg	yes
Koska *et al*, 1981	500 μg/70kg	no
Bovil & Sebel, 1980	60 μg/kg	yes
Hall *et al*, 1993	75 μg/kg	yes

It is important to study these lower dosages because the pharmacokinetics may differ to some degree. The lower dosage used in this study can be explained by the fact that fentanyl was not given as the sole anaesthetic agent unlike other studies, but was supplemented with sodium thiopentone, droperidol and nitrous oxide. Even though the latter is a short acting drug, it provides supplementation for induction of anaesthesia and may decrease the dose of opioid required to block the

haemodynamic responses to surgical stimuli before bypass. During and after CPB, smaller plasma concentrations of fentanyl might be sufficient especially considering that hypothermia itself depresses cerebral metabolic activity and promotes anaesthesia (Koren *et al*, 1984).

The larger dosages used in previous studies resulted in higher peak plasma concentrations of fentanyl than found in this study of 30.6 ± 26.1 ng/mL (range = 9.2 to 106 ng/mL) even though this will be critically dependent on timing of blood sampling. Hall *et al* (1993) reported a peak of 85 ± 11 ng/mL and Bovill and Sebel (1980) a concentration 1 minute after injection of 102.4 ± 36.5 ng/mL, with a range of 31.2 to 200 ng/mL.

The total plasma concentration of fentanyl decreased rapidly in the pre-bypass period mainly due to distribution (Cartwright *et al*, 1980) before a sudden decline of almost 60% in the concentration of total fentanyl in plasma on initiation of extracorporeal circulation. Other studies found a similar decline in total fentanyl concentration on CPB (Table 8.2).

Table 8.2: A summary of the % drop in fentanyl concentration on initiation of CPB found in other studies

Study	% drop in fentanyl concentration on CPB
Hug & Moldenhauer, 1982	42%
Howie *et al*, 1981	59%
Bovill & Sebel, 1980	53%
Koren *et al*, 1984a	75%
Lunn *et al*, 1979	37%
Koren *et al*, 1984b	71%
This study	59%

The magnitude of the decline was inversely related to the body weight of the individual suggesting that dilution has more effect in patients who

weigh less due to a smaller extracellular fluid volume for the 2.5 L of Ringer's solution to distribute within. It should also be noted that CPB initiation occurred on average only 13 minutes after the last injection of fentanyl and this may have made it difficult to separate the effects of redistribution and haemodilution.

On connection to the CPB apparatus, there is an extension of the initial volume of distribution (central compartment), however the 60% drop in concentration of fentanyl exceeded the expected effect of haemodilution (47% measured by Hb concentration decline or 41% estimated blood volume increase). This phenomenon may be explained by lung or pump sequestration. Bovill & Sebel (1980) reported that 24% of a fentanyl dose can be taken up by the lungs in 30 s and Taegar *et al* (1988) found that 43% to 87% of a dose can be sequestered by the lungs on the first passage. This drug is usually released gradually back into the bloodstream over a period of time so when the lungs are cut off from the general circulation on initiation of CPB, this loss could be quite significant to the resulting plasma concentration. Using the data of Hynynen (1987), the amount of fentanyl which is generally adsorbed to the CPB device represents only 1 to 8% of the total fentanyl dose given in this study. Our data from the in vitro study also suggests the amount adsorbed is less than 1% of the total fentanyl dose. Therefore this occurrence is probably not as important as the pulmonary isolation when attempting to interpret the sudden drop in concentration which is not due to haemodilution.

The mean drop in haemoglobin was almost 50%. Similarly, Bovill & Sebel (1980) reported an average drop in haematocrit of 41 % and Koren *et al* (1984a) found haemodilution to be 51 ± 12%. The effect of haemodilution is increased by fasting before the operation and moderate under-hydration in the pre-bypass phase of surgery (Bovill & Sebel, 1980).

Although physiological monitoring took place throughout the procedure (Appendix 10), it was not possible to relate fentanyl concentration at any stage to pharmacodynamic response variables because during bypass, both cardiac output and blood pressure were essentially determined by the pump conditions. Electroencephalographic (EEG) quantitation of narcotic effect may have been useful to determine any evidence of arousal or other loss of narcosis. There were no reports of awareness from any of the patients in this study.

The mean unbound fraction of fentanyl before CPB was 23.5% which compares to values of 19% and 21% found by McClain & Hug (1980) and Bower & Hull (1982), respectively, in healthy volunteers. The mean unbound fraction of fentanyl increased by a factor of 1.5 (from 23.5% to 34.0%) at the start of CPB which would allow more drug to diffuse across capillary membranes and into tissues. It has been suggested that heparin activates lipoprotein lipase increasing the concentration of free fatty acids, which may displace the drug from its binding site (Finegan *et al*, 1992). However, the administration of heparin has been found not to alter either the concentration of proteins or their binding capacity to alfentanil (Hug *et al*, 1994). The most likely explanations for this increase in unbound fraction are therefore the dilution of binding protein concentrations (particularly α_1–acid glycoprotein; Mather, 1983) in plasma by the protein-free priming solution of the CPB apparatus and/or adsorption of proteins onto the CPB equipment (Finegan *et al*, 1992). Various studies have documented a significant drop in plasma protein levels immediately after CPB connection (Table 8.3). By the end of the blood collection period, the unbound fraction of fentanyl had returned to close to its pre-bypass value even though the binding protein concentration may still be reduced (Kumar *et al*, 1988). Unbound fraction

of fentanyl could not be related to either plasma albumin or α_1–acid glycoprotein levels because they were not available in these patients.

Table 8.3: A summary of the % drop in protein concentration on initiation of CPB found in other studies

Study	% drop in protein concentration on CPB
Kumar *et al*, 1988	50 % drop in AAG & albumin
Hynynen *et al*, 1994	50 % drop in total protein & albumin
Hug *et al*, 1994	40 % drop in AAG

The fentanyl concentrations in plasma would be expected to drop at the start of CPB due to haemodilution, but the simultaneous dilution of plasma proteins and subsequent decrease in plasma protein binding of fentanyl would potentially result in an increase in the unbound concentration. The extent to which each of these occurs will determine whether the unbound concentration will rise or fall. In addition, hypothermia, non-pulsatile flow and hormonal changes can also affect the unbound concentration (Holley *et al*, 1982). In this study, the unbound fentanyl concentration dropped by 43% at the start of CPB. This is not as great as the decline in the total concentration (59%), attributable perhaps to the decreased binding fraction as mentioned above.

The relatively stable plasma concentrations of fentanyl during bypass indicate that there is a decreased clearance compared to the post-bypass period, which is most likely due to a combination of decreased liver blood flow (Koska *et al*, 1981) and a reduction in hepatic enzyme activity as a result of hypothermia (Bentley *et al*, 1983). As the patient is rewarmed (before the end of CPB) and the tissues (ie muscle and fat) are reperfused there is a washout of sequestered drug from the tissues which results in a transient rise in the fentanyl concentration. The significant relationship between the magnitude of the rise and BMI may indicate

that those with a higher BMI have a greater proportion of body fat leading to more storage of fentanyl which is subsequently released on rewarming. The actual amount of fentanyl being released was intended to be estimated using a published value of volume of distribution (V_d) and the measured change in plasma concentration, however it was not valid to assign a specific value of V_d because of constantly varying conditions.

The washout of fentanyl from the lungs has been documented by Koska *et al* (1981) who found a rapid 30% rise in the concentration of fentanyl with the resumption of pulmonary blood flow. After restoration of ventilation and perfusion to the lungs following disconnection from the cardiopulmonary bypass apparatus, we would expect a rise in the plasma concentration of fentanyl due to drug washout from the lungs, however it could not be measured in this study because of an additional fentanyl dose given at the same time as CPB termination to ensure adequate anaesthesia after rewarming is complete but before the end of surgery. For this reason, it would not have been known to what extent any rise in fentanyl concentration was due to lung washout alone.

The gross changes in physiological conditions over the bypass period precluded any reliable estimation of clearance or volume of distribution and did not allow the individual determination of half-life during the procedure in these patients. Also, peaks occurring within 2 hours of the end of surgery, probably due to increasing muscle tone and voluntary movement causing additional mobilisation of fentanyl from tissue depots, made the task even more uncertain. The calculation of apparent terminal half-life during the recovery period using the combined patient data gave a mean value of 4.7 hours. This is longer than the half-lives of 3.7 and 3.3 hours for healthy volunteers and non-CPB surgical patients, respectively reported by Hug and Moldenhauer (1982) but shorter than

values of 7.3 ± 1.4 hours and 5.2 ± 2.7 hours in CPB patients reported by Duthie *et al* (1986) and Koska *et al* (1981), respectively (Table 8.4). This method of calculating elimination half-life requires that samples are taken for a period at least equal to three times the half-life. The three hour sampling time in this study was less than the half-life, but concentrations would have been too small to measure 15 hours after the end of bypass especially given the small total fentanyl dosage used, and in addition ethical approval only allowed a maximum volume of 55 mL plasma to be sampled for each patient.

Table 8.4: A summary of fentanyl elimination half-life values found in other studies

Study	Patients	Half-life (hours)
Duthie *et al* (1986)	CPB	7.3 ± 1.4
Hug & Moldenhauer (1982)	CPB	11 ± 2
	surgical	3.3
	volunteers	3.7
Mather (1983)	surgical	2.5 - 7
	volunteers	2 - 4
Koska *et al* (1981)	CPB	5.2 ± 2.7
Bovill & Sebel (1980)	CPB	7.0 ± 0.6

The prolonged half-life in CPB patients is probably due to a combination of an increased volume of distribution and a decreased clearance with the rate-limiting step being the slow redistribution of fentanyl from the peripheral compartment. The main adverse effect of this slow elimination is possible persistance of fentanyl and ventilatory depression requiring assisted ventilation. McClain & Hug (1980) reported that respiratory effects become insignificant below 0.7 ng/mL and patients can be extubated at levels below 2.9 ± 0.1 ng/mL (Moldenhauer & Hug, 1982). At three hours after the end of bypass, none of the patients in the present

study had levels below 0.7 ng/mL but only three were above 2.9 ng/mL so it seems that fentanyl in this study sample will have generally provided postoperative analgesia without excessive respiratory depression. All patients in this study received respiratory support up to six hours postoperatively.

Alcuronium

The HPLC procedure described in this study was specific for the measurement of alcuronium and sensitive enough to measure the low levels in plasma after a single injection of alcuronium chloride during CPB. The limit of detection was found to be 0.1 μg/mL when 250 μL of plasma was extracted for alcuronium determination. This is similar to the sensitivity reported in other studies (Walker *et al,* 1983: 0.05 μg/mL; deBros *et al,* 1990: 0.05 μg/mL and Künzer *et al,* 1994: 0.025 μg/mL). The recovery of alcuronium in the described method was 69 ± 3% which seems acceptable; the recovery achieved by the extraction method of Künzer *et al,* 1994 was not documented.

The alcuronium dosage ranged from 0.22 to 0.37 mg/kg with a mean dosage of 0.27 mg/kg. This is similar to dosages used in other studies (Table 8.5).

Table 8.5: A summary of alcuronium doses used in previous studies

Study	Alcuronium dose given
Diefenbach *et al,* 1995	0.25 mg/kg
Walker *et al,* 1980	0.25 mg/kg (n = 11), 0.375 mg/kg (n = 8)
Walker *et al,* 1983	0.25 mg/kg + infusion = 0.48 mg/kg total

The average decline in plasma alcuronium concentration on connection to the CPB apparatus was 29 ± 6.6% which was about one-half the drop in

total fentanyl concentration (59%). This can probably be explained by the fact that alcuronium is hydrophilic and there is less tissue uptake initially and it has been shown that it is not expected to be significantly bound by the bypass pump in vivo, and so the drop in concentration is mainly due to haemodilution and some sequestration by the lungs. Also the distribution phase would be complete by this time ($t_{1/2\alpha}$ = 13.8 min; Walker *et al*, 1980) as the start of blood sample collection was about one hour after the administration of the alcuronium dose in all cases, so there would be no decrease in alcuronium concentration due to distribution.

It has been reported that the minimum plasma level required for significant neuromuscular blockade is 0.3 μg/mL (deBros *et al*, 1990). This level was exceeded in all patients during the procedure indicating expected satisfactory depression of twitch response.

The elimination half-life for alcuronium was estimated for all patients and was found to be 194 ± 44 min which is not significantly different to that found in normal surgery. In surgical patients, Walker *et al* (1980) reported a value of 198 minutes and deBros *et al* (1990) a value of approximately 200 minutes, however the elimination half-life was found to be prolonged to 532 minutes in CPB patients receiving a combined bolus and infusion dosage of alcuronium (Walker *et al*, 1983; Buylaert *et al*, 1989).

The half-life of alcuronium when estimated individually was significantly related to estimated creatinine clearance which would be expected as alcuronium is 85% excreted unchanged by the kidneys so renal function is a good indicator of drug clearance in this case.
The main explanation for the possibility of an increased elimination half-life of alcuronium following CPB is the reduction in glomerular

filtration rate (and therefore clearance) due to hypotension, hypothermia and other factors related to both CPB and surgery itself. The influence of hypothermia on the sensitivity of the patient to the effects of neuromuscular blockers may make it difficult to link any of the changes in pharmacokinetic parameters found during CPB to the actual pharmacodynamic effects of the drug in the same period.

It has previously been reported that hypothermia may decrease the renal elimination of the neuromuscular blockers pancuronium, *d*-tubocurarine and alcuronium (Wierda *et al*, 1990), and Holley *et al* (1982) claimed that non-pulsatile flow during cardiopulmonary bypass may temporarily impair renal function. The relatively stable plasma levels of alcuronium found in this study during the actual period of hypothermia and CPB may be indicative of this reduction.

However, Wierda *et al* (1990) reported that the overall effect of hypothermia and bypass did not significantly influence the terminal half-life of pipercuronium when given as a single bolus dose, as alcuronium was in this study. Also Avram *et al* (1987) found a fall in metocurine concentration after initiation of CPB due to haemodilution followed by no important changes in terminal drug clearance. In a previous report pertaining to alcuronium kinetics and CPB, Walker *et al*, (1983) used a combined bolus and infusion dosage regimen and noted an increase in the plasma concentration upon institution of CPB and subsequently a prolonged elimination half-life. The increase in plasma concentration can be explained by a sudden decrease in the volume of distribution with the lungs being cut off while there is a continuing input of drug into the body.

This study showed that although the clearance of alcuronium during CPB was reduced, once extracorporeal circulation was terminated and

rewarming had taken place, the terminal half-life of alcuronium was virtually unaffected when compared to that found after normal surgery.

The in vitro experiment with alcuronium examined the possibility that a similar adsorption mechanism to that of fentanyl may be responsible for the decline in plasma concentrations of alcuronium at the onset of CPB. The results showed that alcuronium does not appear to be bound by the components of the extracorporeal circuit to any significant extent.

Conclusions

This study has shown that there is a marked drop in both total and unbound fentanyl concentrations and total alcuronium concentrations on initiation of bypass. However, suitable plasma concentrations of both drugs were maintained even given the extreme physiological changes occurring over the bypass period. The findings are consistent with haemodilution, alterations in plasma binding and reduced hepatic and renal perfusion during and after CPB.

It also showed that adsorption of drugs to the extracorporeal circuit in vitro does not necessarily translate to a significant effect in vivo due to the large drug reservoir that exists.

PART III

PLASMA CONCENTRATIONS OF FENTANYL WITH SUBCUTANEOUS INFUSION IN PALLIATIVE CARE PATIENTS

CHAPTER 9 : INTRODUCTION

9.1 Use of Fentanyl in Palliative Care

Long-term opioid administration is widespread in the treatment of cancer pain, with 60 to 90% of patients with advanced disease requiring an opioid analgesic to control their pain (Moulin *et al*, 1992; Schug *et al*, 1992; Knowles, 1993). Best pain relief is achieved by regular oral opioid administration (Walsh and West, 1988) and this route is preferred for convenience and cost-effectiveness (Schug *et al*, 1992; Agency for Health Care Policy and Research, 1994). Oral morphine can control the pain sufficiently in most patients (Storey *et al*, 1990), and is the drug of choice because of its wide availability, efficacy and flexibility in dosing (Walsh, 1994).

It has been reported that 70% of patients can take oral drugs to within 72 hours of death (Walsh and West, 1988), but because of intractable vomiting, nausea, dysphagia, inadequate absorption and other GI symptoms, a substantial proportion of patients require an alternative (non-oral) route (Storey *et al*, 1990; Dover, 1987; O' Neill, 1994; Zech *et al*, 1994). These may include continuous subcutaneous infusion, IV infusion and rectal administration. It has been documented that one-half of dying patients will require parenterally administered analgesics during the last days and hours of life (Zech *et al*, 1994).
The rectal route is the traditional alternative and is safe and inexpensive, but suppositories are not very useful for long-term opioid

administration, especially where surgical resection has occurred or rectal discharge and incontinence are present (Maddocks, 1992).

Intravenous lines are difficult to maintain and are not very suitable for patients wishing to be treated at home, whereas bolus IV doses can result in pain and distress due to multiple injections (Storey *et al*, 1990) and should not be used for routine analgesia because of poor control and a relatively high risk of adverse effects (Walsh and West, 1988).

Continuous subcutaneous infusions using syringe drivers are a safe, simple and effective alternative, and greatly benefit patients unable to take oral medication and their carers. The portable, low volume pumps are easy to manage, particularly when the patient is at home and they avoid the need for four hourly injections (Reid, 1989). They also allow flexibility of dosing and the simultaneous administration of opioids with anti-emetics, neuroleptics, sedatives and anti-spasmodics (O'Neill, 1994; Maddocks, 1992).

Other advantages of subcutaneous infusions include the production of stable blood concentrations which can be easily titrated for each individual and that the peak-concentration sedation and trough-concentration breakthrough pain associated with intermittent dosage regimens can be avoided. Continuous subcutaneous therapy has also been associated with a lower incidence of nausea, sedation and constipation (Moulin *et al*, 1992).

Some disadvantages of continuous subcutaneous therapy include the possibility of local irritation, discomfort or infection at the indwelling needle site and the fact that the portable pumps are relatively expensive and often require skilled attention (Westerling *et al*, 1994).

Morphine is the preferred opioid for continuous subcutaneous infusion in Australia with the daily requirement by this route being only about one-third the total daily oral dosage due to the subcutaneous bioavailability approaching 100% (Maddocks, 1992; Dover, 1987). The therapeutic dosage range is enormous with a reported range of 40 - 4,024 mg morphine per day (Storey *et al*, 1990). In the UK, diamorphine (heroin) is available and is considered the narcotic of choice because of its superior water solubility (Storey *et al*, 1990; Beswick, 1987) which is important when bearing in mind that 67% of advanced cancer patients are anorexic and have reduced muscle mass and subcutaneous tissue for the volume to be injected into (Regnard & Tempest, 1992). Heroin is not available for medical use in Australia.

For patients with inadequate pain control or dose-limiting adverse effects from one opioid, other opioids, such as fentanyl, should be tried (Agency for Health Care Policy and Research, 1994).

Fentanyl is a potent opiate analgesic which, because of its relatively short duration of action, is commonly used intravenously as an anaesthetic agent for major and minor surgery (see section 5.2.1). Although more expensive than morphine, the use of fentanyl has also now extended to palliative care units, to provide analgesia if morphine causes persistent distressing side effects such as hallucinations, nightmares, nausea and sedation (Maddocks, 1992; Agency for Health Care Policy and Research, 1994). It has been reported that subcutaneous fentanyl is being used commonly or occasionally by 12% of respondents in a survey of ninety-six teaching hospitals and palliative care services throughout Australia (Drummond *et al*, 1995). There is also speculation that fentanyl might cause less constipation than other opioids but this is yet to be confirmed (Zech *et al*, 1994). Because of significant first-pass metabolism in the liver after gastrointestinal tract absorption, fentanyl is ineffective when given

orally (Mather & Gourlay, 1991). Apart from the subcutaneous route, the recent development of a transdermal therapeutic system for fentanyl has also allowed it to be delivered continuously through the skin for up to 72 hours (Portenoy *et al*, 1993). This analgesic option is not suitable for rapid dose titration and is best for patients with stable pain and only low to medium opioid requirements. Thus, although it represents a more invasive route of administration than transdermal delivery, subcutaneous administration of fentanyl is probably a safe, practical and very effective treament for both moderate and severe cancer pain in a number of palliative care patients.

Minimum effective analgesic plasma concentrations of fentanyl in opioid-naive patients have reportedly ranged from 0.2 to 2 ng/mL (Duragesic® product information). Lehmann *et al* (1988) found a mean minimum effective plasma concentration of 1.2 ng/mL (range 0.2 to 8.0 ng/mL) when fentanyl was used for postoperative analgesia. It has been documented that the risk of adverse effects including hypoventilation increases with plasma concentrations greater than 2 ng/mL in non-opioid tolerant patients, especially those with a concurrent underlying pulmonary condition (van Lersberghe *et al*, 1994), and CNS effects have been reported to increase at serum concentrations greater than 3 ng/mL (Duthie *et al*, 1988). Plasma concentrations, however, do not always reflect patient sensitivity to fentanyl and so should probably not be used as the only indicator of efficacy or toxicity. In addition, pain can act as a physiologic antagonist to the central depressant effects and so when fentanyl is used for the relief of cancer pain, the documented respiratory depression is not always a problem. Opioid tolerance occurs in many patients to a variable extent and both the minimum effective concentration and the concentration at which toxicity occurs will rise with this increasing tolerance.

In a study by Portenoy *et al* (1993) of the pharmacokinetics of fentanyl following transdermal administration for cancer pain, the steady-state plasma fentanyl concentrations were characterised by a large interindividual variability (range 0.6-3.1 ng/mL). Similarly, Varvel *et al* (1989) found an average plasma fentanyl concentration of 1.8 ng/mL with a range of 0.5 to 3.1 ng/mL after transdermal administration.

Since fentanyl is known to undergo extensive hepatic metabolism, a decrease in intrinsic clearance due to underlying disease or an alteration in liver function may explain some of the variation in analgesic dosage required.

Renal disease may also affect (increase) the plasma fentanyl concentration due to an altered volume of distribution (Data on file, Janssen Pharmaceutica).

9.2 Objectives of this Study

While the pharmacokinetics of fentanyl following intravenous administration have been well characterised (Bower, 1982), there are no published data on plasma concentrations of fentanyl with continuous subcutaneous therapy.

The objectives of this study were to gather data on steady-state total and unbound plasma concentrations of fentanyl in patients receiving chronic subcutaneous therapy and to examine the inter-patient variability in these concentrations. Another aim was to compare these plasma concentrations with those reported in the literature following transdermal administration of fentanyl. In addition, relationships between plasma concentrations and dosage, and the age, sex, liver function and pain control of each patient were assessed.

CHAPTER 10 : MATERIALS AND METHODS

10.1 Materials

As described in **Chapter 6.1.**

10.2 Analytical Methods

As described in **Chapter 6.3.**

10.3 Human Procedures

The study protocol was approved by the Research and Ethics Committee at Repatriation General Hospital, Daw Park, Adelaide. A consecutive sample of in-patients within the Palliative Care Unit at the hospital receiving continuous treatment with fentanyl administered as a subcutaneous infusion, generally through a needle inserted into the chest wall (via a Graseby® portable syringe pump) were studied. Proprietary ampoules (David Bull, Mulgrave, Australia) of fentanyl 50 μg/mL in Water for Injection were used and patients in the unit were routinely assessed for pain at least four times daily using visual analogue scales, and changes to the infusion rate and/or the administration of bolus dosages occurred, if necessary. All patients gave informed consent and received a patient information sheet (Appendices 11 & 12).

In order to achieve steady-state plasma concentrations of fentanyl, a venous blood sample (5 to 10 mL) was drawn after at least 24 hours of therapy at a constant rate of infusion with no bolus doses. Plasma was separated by centrifugation and frozen at -18°C, and freighted in batch to the University of Tasmania where total plasma concentrations of fentanyl were determined using the gas chromatographic assay described in section 6.3.2. Unbound fractions of fentanyl in plasma were measured by ultrafiltration (See section 6.3.3).

Clinical and demographic variables were extracted from the medical record of each patient. Biochemical tests of liver and renal function were performed by the Clinical Chemistry Department of the Repatriation General Hospital, Daw Park, Adelaide, using standard methods on automatic analysers. Hepatic impairment was defined as the presence of hypoalbuminaemia (serum albumin below 35 g/L) with abnormal serum concentrations of at least two of bilirubin, alanine aminotransferase, alkaline phosphatase, or gamma glutamyl transpeptidase. Abnormal renal function was defined as a serum creatinine above 120 μmol/L. Estimated creatinine clearance was calculated using the equation (Cockroft & Gault, 1976):

$$\text{estimated creatinine clearance (mL/sec)} = \frac{(140 - \text{age}) \times \text{body weight(kg)}}{48{,}869 \times \text{serum creatinine (mmol/L)}}$$

Pain control at the time of blood sampling was assessed using a visual analogue scale (a 10 cm line with extremes marked 'no pain' and 'worst possible pain'). A copy of the data sheet is attached (Appendix 13).

Since more than half of the sample of patients were pain free, the total sample of patients was also divided into those with any pain and those who were free of pain.

10.4 Statistical Analysis

Plasma concentrations of fentanyl were compared to literature values reported with intravenous and transdermal administration. Relationships between the plasma concentrations of fentanyl and subcutaneous dosage, and factors such as age, sex, the presence of hepatic dysfunction and pain control were investigated using appropriate non-parametric statistical procedures including the Spearman rank correlation and Mann-Whitney U-tests, using Statview® SE + Graphics

(Abacus Concepts, Palo Alto, California, USA) on a Macintosh® computer. A p-value below 0.05 was considered statistically significant. The patient data file can be seen in Appendix 14.

CHAPTER 11 : RESULTS

11.1 Analytical variables

11.1.1 Retention Times of Relevant Peaks

An example of a patient plasma sample is shown in Figure 11.1. A blank plasma trace is shown in Figure 7.3.

11.1.2 Standard Curve

The calibration curve showed linearity ($r^2 = 0.993$) over the range 0.1 to 15 ng/mL fentanyl added to blank plasma (Figure 7.1).

11.1.3 Recovery, Reproducibility and Sensitivity

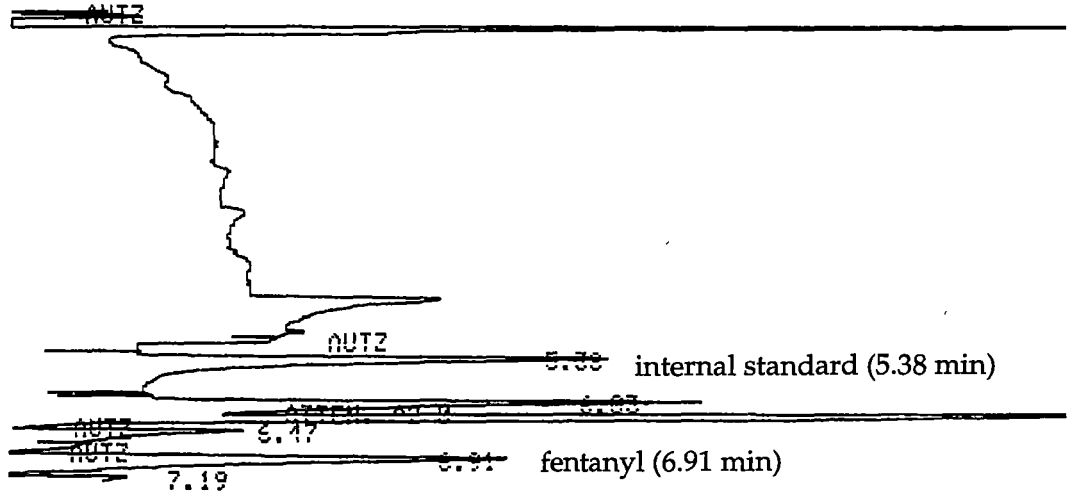
All as described in **Chapter 7.1**.

11.2 Study results

11.2.1 Patient Characteristics

The sample of 20 patients consisted of 12 males and 8 females, ranging in age from 54 to 86 years, with a median age of 75 years. The patients had various forms of cancer: genitourinary (7 patients), lung (6), gastrointestinal (4), breast (2) and skin (1). The patients were receiving other drugs in addition to fentanyl (median 8 drugs; range 3 to 15), including antiemetics (18 patients), laxatives (18), corticosteroids (13), benzodiazepines (14), antifungals (6), tricyclic antidepressants (5) and nonsteroidal anti-inflammatory agents (5). Nine patients had biochemical evidence of hepatic disease while three patients had abnormal renal function. Serum concentration of creatinine ranged

Figure 11.1: GC trace of palliative care patient plasma sample (containing fentanyl 0.5 ng/mL)



from 46 to 179 μmol/L (mean 91.8 μmol/L) and estimated creatinine clearance ranged from 19.2 to 83.3 mL/min (mean 50.8 mL/min).

The total duration of subcutaneous fentanyl therapy at the time of blood sampling ranged from 1 to 157 days with a median value of 7 days (n = 19). The median dosage of fentanyl by continuous subcutaneous infusion was 1200 μg/day, with a range of 100 to 5000 μg/day. There were no significant associations between either the sex or age of the patient and the fentanyl dosage (Mann-Whitney U = 41.5, z = -0.50, $p > 0.20$ and Spearman $\rho = 0.22$, $p > 0.20$, respectively). The dosage of fentanyl was significantly related to the duration of subcutaneous fentanyl therapy (Spearman $\rho = 0.56$, $p < 0.05$).

The patients with biochemical evidence of liver disease (n = 9) tended to be receiving lower dosages of fentanyl than the other (n = 11) patients (respective medians 800 and 1600 μg/day; Mann-Whitney U = 24.5, z = -1.67, $p < 0.10$).

11.2.2 Fentanyl Concentrations in Plasma

The steady-state plasma concentrations of fentanyl displayed a marked inter-patient variability. The median total concentration was 1.0 ng/mL, with a range of 0.1 to 9.0 ng/mL (Figure 11.2).

The unbound fraction of fentanyl in the plasma ranged from 17.8% to 44.4%, with a median value of 33.6% (n = 14). The unbound fraction was not measured in all patients because some plasma volumes were insufficient. The unbound fraction and the plasma albumin concentration were moderately inversely related (Spearman $\rho = -0.5$, $p = 0.07$: Figure 11.3). The unbound fentanyl concentration ranged from 0.1 ng/mL to 1.9 ng/mL, with a median value of 0.35 ng/mL (n = 14). The

Figure 11.2: Frequency distribution of plasma concentrations of fentanyl

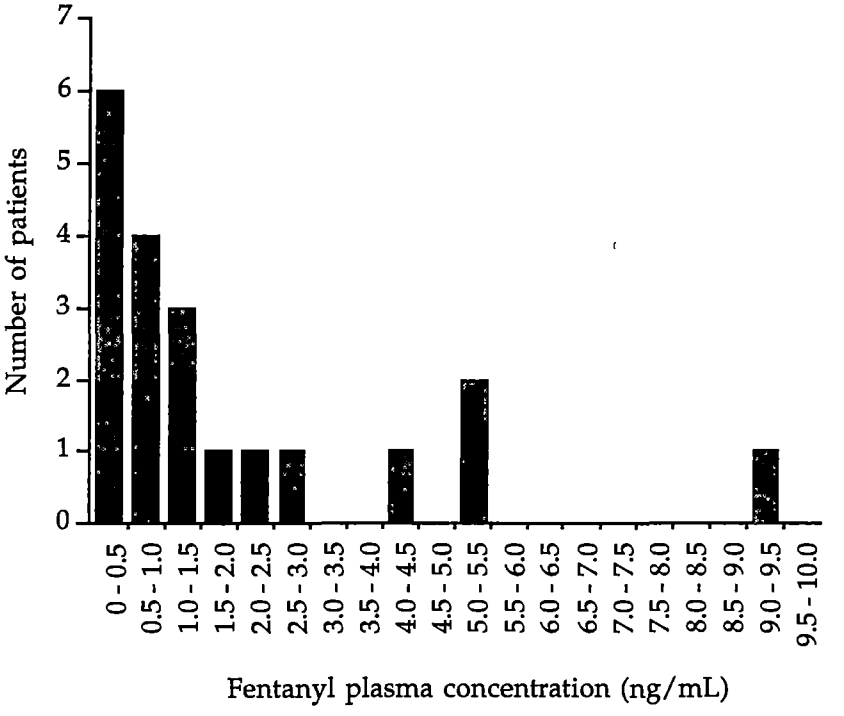


Figure 11.3: The relationship between the unbound percentage of fentanyl and the plasma albumin

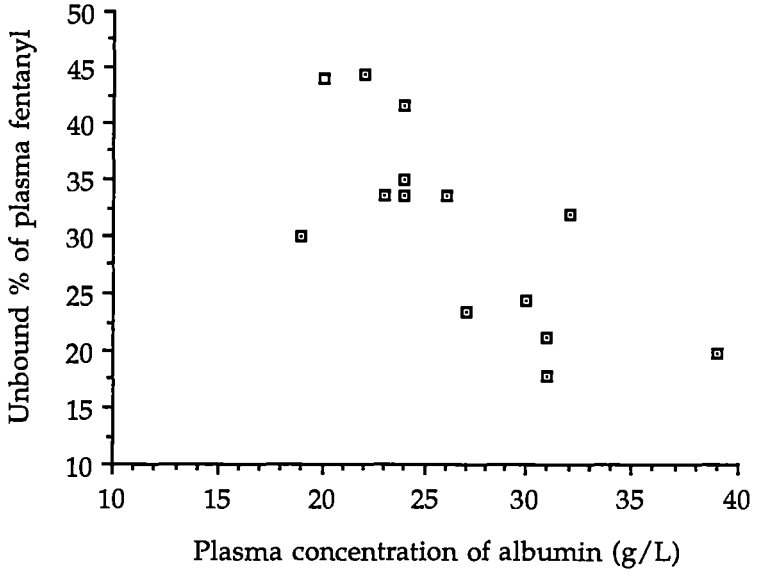
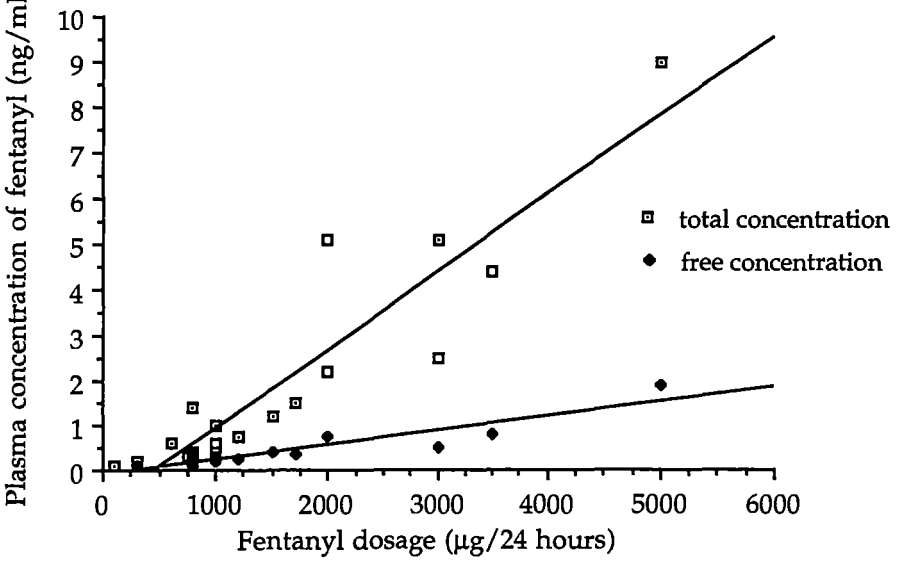


Figure 11.4: Fentanyl dosage vs plasma concentrations



total and unbound plasma concentrations of fentanyl were strongly correlated (Spearman $\rho = 0.98$, $p < 0.001$).

There was also considerable variation in the ratio of total and unbound plasma concentrations of fentanyl divided by the daily dosage; the ratio varied 8-fold for the total plasma concentrations and 3.5-fold for the unbound plasma concentrations. A significant correlation existed between fentanyl dosage and both the steady-state total plasma concentration and unbound plasma concentration (Spearman $\rho = 0.92$, $p < 0.05$ in each case; Figure 11.4).

Significant correlations did not exist between age and either the total plasma concentration of fentanyl, the unbound plasma concentration, the unbound fraction, the total plasma concentration to dosage ratio or the unbound plasma concentration to dosage ratio (Spearman $\rho = 0.18$, $p > 0.20$; Spearman $\rho = 0.43$, $p > 0.10$; Spearman $\rho = -0.19$, $p > 0.40$, Spearman $\rho = 0.04$, $p > 0.20$, Spearman $\rho = 0.11$, $p > 0.60$, respectively).

There were no significant associations between the presence of liver disease and either the total plasma concentration of fentanyl, the unbound plasma concentration, the unbound fraction, the total plasma concentration to dose ratio or the unbound plasma concentration to dosage ratio (Mann-Whitney $U = 24$, $z = -1.72$, $p = 0.09$; Mann-Whitney $U = 20.5$, $z = -0.45$, $p > 0.50$; Mann-Whitney $U = 14.5$, $z = -1.23$, $p > 0.20$, Mann-Whitney $U = 35.5$, $z = -0.78$, $p > 0.20$ and Mann-Whitney $U = 16.5$, $z = -0.97$, $p > 0.30$, respectively).

There was a significant inverse relationship between the fentanyl plasma concentration and estimated creatinine clearance (Spearman $\rho = -0.68$, $p < 0.01$).

There were no significant associations between the sex of the patient and the total plasma concentration of fentanyl, the unbound plasma concentration, the unbound fraction or the total plasma concentration to dose ratio (Mann-Whitney U = 35.5, z = -0.96, $p > 0.20$; Mann-Whitney U = 13, z = -1.27, $p > 0.20$; Mann-Whitney U = 20, z = -0.33, $p > 0.50$ and Mann-Whitney U = 35, z = -1.00, $p > 0.20$, respectively). The unbound plasma concentration to dose ratio, however, was significantly lower in the female patients (Mann-Whitney U = 6.0, z = -2.20, $p < 0.03$).

The duration of fentanyl therapy was significantly related to the total fentanyl plasma concentration and modest correlations existed between the duration of fentanyl therapy and the unbound fentanyl plasma concentration (Spearman $\rho = 0.67$, $p < 0.01$, $n = 19$ and Spearman $\rho = 0.55$, $p = 0.06$, $n = 13$, respectively).

Assuming a systemic bioavailability of 100% for fentanyl from continuous subcutaneous infusion (fentanyl losses in portable pumps and patient-controlled delivery systems have been found to be insignificant; Kowalski & Gourlay, 1990; Tu *et al*, 1990), values of estimated fentanyl clearances were calculated using the equation:

$$C_{SS} = F \times D/Cl \times \tau$$

where C_{SS} is steady state plasma fentanyl concentration, F is availability of the drug (assumed to be 1), D is dosage of fentanyl, Cl is estimated fentanyl clearance and τ is dosing interval (1 day)

The values ranged from 273.2 to 2,222.2 mL/min with a mean value of 915.3 mL/min. This is similar to clearance values reported in other studies (Table 11.1).

Table 11.1 Summary of other studies examining fentanyl clearance

Study	Patient type	Clearance
Mather, 1983	surgical	400 - > 1500 mL/min
Koska *et al*, 1981	surgical	11.2 mL/min/kg
Varvel *et al*, 1989	surgical	770 mL/min
Bower & Hull, 1982	healthy subjects	1530 (1470 - 2022) mL/min*
McClain & Hug, 1980	healthy subjects	956 (575 - 1179) mL/min*
Janssen Pharmaceutica, 1993	surgical hepatically impaired renally impaired	450 - 1250 mL/min 50 - 1333 mL/min** 500 - 1300 mL/min**

* Results expressed as mean (range) ** Estimated

11.2.3 Plasma Fentanyl Concentrations in Relation to Pain Control

Visual analogue pain scores ranged from zero to 5.8, with a median score of zero indicating good pain control in the study patients. Significant correlations did not exist between pain control and either the fentanyl dosage, the total plasma concentration or the unbound plasma concentration of fentanyl (Spearman's = 0.08, $p > 0.50$; Spearman $\rho = 0.02$, $p > 0.50$ and Spearman $\rho = -0.24$, $p > 0.30$, respectively).

Total and unbound steady-state plasma concentrations of fentanyl in patients experiencing some degree of pain ($n = 9$) were not significantly different from those in patients ($n = 11$) free from pain (Mann-Whitney $U = 47$, $z = -0.19$, $p > 0.80$ and Mann-Whitney $U = 18.5$, $z = -0.71$, $p > 0.40$, respectively).

CHAPTER 12: DISCUSSION

There was considerable interpatient variability in subcutaneous dosage requirements and resulting steady-state plasma concentrations of fentanyl in this sample of patients. The subcutaneous dosages of fentanyl varied 50-fold between 100 to 5000 μg/day, with a median of 1200 μg/day. The dosages are similar to those studied elsewhere for transdermal administration (see Table 12.1). It has been reported that 92% of the transdermal dosage is delivered to the systemic circulation (Varvel *et al*, 1989), implying that fentanyl is not susceptible to any significant cutaneous metabolism and so comparisons with subcutaneous dosages are valid.

Table 12.1: Summary of studies examining steady-state fentanyl concentrations in plasma following transdermal administration

Study	No. Patients	Dosage (μg/day)	Concentrations (ng/mL)
Varvel *et al*, 1989	8 (surgical)	2400	1.8 ± 0.8
Portenoy *et al*, 1993	10 (palliative care)o	2400	1.6 ± 0.8
Miser *et al*, 1989	5 (palliative care)	1800-8400	2.5 - 3.5 for 3000 μg/day
Zech *et al*, 1994	*	600	0.3 - 0.6
		1200	0.5 - 2.0
		1800	0.8 - 3.0
		2400	1.0 - 4.0
Data on file, Janssen Pharmaceutica, 1993	*	600	0.3 - 1.2
		1200	0.6 - 1.8
		1800	1.1 - 2.6
		2400	1.9 - 3.8

* Information not provided

o - receiving other opioids

The great variation in dosage of fentanyl required to control pain may be partly explained by the interpatient variability in elimination half-life and clearance. Miser *et al* (1989) noted that the clearance of fentanyl in cancer patients appears to be significantly lower than in normal volunteers which may be as a result of decreased hepatic microsomal enzyme activity. Also of importance in explaining the dosage variability are the differing degrees of severity of the pain and the tolerance to the narcotic effect (pharmacodynamic sensitivity to fentanyl).

The fact that the duration of subcutaneous fentanyl therapy in this study was significantly related to the current fentanyl dosage suggests that tolerance to its narcotic effect may be occurring or, perhaps more likely, that the need for these increased dosages may be reflecting worsening pain with the progress of the disease.

The steady-state total fentanyl plasma concentrations in this study also varied greatly (90-fold) ranging from 0.1 to 9.0 ng/mL with a median concentration of 1.0 ng/mL. This is similar to concentrations reported in other studies (Table 12.1). There was a significant correlation between the subcutaneous fentanyl dosage and the resulting plasma concentrations. Miser *et al* (1989) also found an excellent correlation (r^2 = 0.8) between fentanyl steady-state plasma concentrations and the transdermal delivery rate.

This study found no significant associations between the sex or age of the patient and either the fentanyl dosage or steady-state plasma concentration. The unbound plasma concentration to dose ratio was significantly lower in the female patients, suggesting that the clearance of unbound fentanyl may have been higher in these patients. Holdsworth *et al* (1994) reported that previous pharmacokinetic studies following both intravenous and transdermal administration of fentanyl have not

demonstrated any important gender differences. Also, it has been noted that there is no correlation between fentanyl clearance and weight or age, following both intravenous and transdermal delivery (Holley and Van Steennis, 1988).

Values for unbound fractions of fentanyl in plasma in control patients have been reported as 13 to 21% (Mather, 1983). The unbound fraction of fentanyl in the plasma in this study was higher, ranging from 18 to 44%. This difference may be explained by the high incidence of hypoalbuminaemia among these palliative care patients (18 of the 20 patients). Fentanyl also binds to glycoproteins to a high extent in addition to albumin in the plasma; in a 4.0% albumin solution only 46% of fentanyl was bound compared with 79 - 87% in plasma (Meuldermans *et al*,1982). This probably explains the relatively poor relationship between the unbound fraction and the plasma albumin concentration.

There were no significant correlations between the steady-state plasma concentrations or dosage of fentanyl and the analgesic effect. Examination of possible relationships was limited by the finding that pain control was generally excellent, with more than half the patients being pain free and the highest visual analogue pain score recorded being only 5.8/10. By waiting for at least 24 hours of therapy at a constant infusion rate with no bolus doses in order to achieve a steady-state, it is not surprising that good pain relief had been attained. Patients still in pain would most likely be having infusion rate changes and/or bolus doses thus excluding them from the study. A larger sample size of patients with varying degrees of pain control would be required to perform meaningful statistical analyses.

Conclusion

This study has demonstrated the large interpatient differences in both the dosage of subcutaneous fentanyl (50-fold) and the resulting steady-state total (90-fold) and unbound (19-fold) plasma concentrations of fentanyl required to produce pain control in the palliative care setting. Even with standardisation for dosage, there was still an eight-fold variation in total plasma concentrations and 3.5-fold variation in unbound plasma concentrations. This may contribute to the variability in therapeutic response to subcutaneous fentanyl between patients and highlights the need for careful dosage individualisation and titration based on clinical response.

PART IV

CONTROLLED STUDY OF NEBULISED MORPHINE FOR TERMINAL DYSPNOEA IN PALLIATIVE CARE PATIENTS

CHAPTER 13 : INTRODUCTION

13.1 Terminal Dyspnoea

13.1.1 Aetiology and Clinical Features

Dyspnoea, or "uncomfortable awareness of breathing" (Bruera *et al*, 1993a), occurs in up to 70% of patients with terminal cancer at some point during the course of their illness and is a very difficult symptom to manage (Reuben and Mor, 1986; Willcock *et al*, 1994). It can range in severity from simple shortness of breath to a feeling of imminent death and suffocation. The incidence of dyspnoea increases as death approaches and is usually associated with the additional symptoms of tachypnoea and anxiety. Lung, breast, and to a lesser extent, colorectal cancers are the most common tumours associated with dyspnoea (Reuben & Mor, 1986), which may be caused by the tumour itself (e.g., compression of the airways, pleural effusion), medical complications (e.g., respiratory infection), treatment of the tumour (e.g., radiation therapy induced fibrosis), or underlying chronic obstructive lung disease (Figure 13.1).

13.1.2 Treatment

Initially, the treatment should be aimed at the cause of the dyspnoea if possible such as treating of infections and draining of fluid. The main aim of further treatment is to relieve the perception of breathlessness and suffocation but it is rarely possible to control completely. deConno *et al* (1991) reported a previous finding that as few as 18% of sufferers are successfully controlled. A cool draft of air on the face is often effective

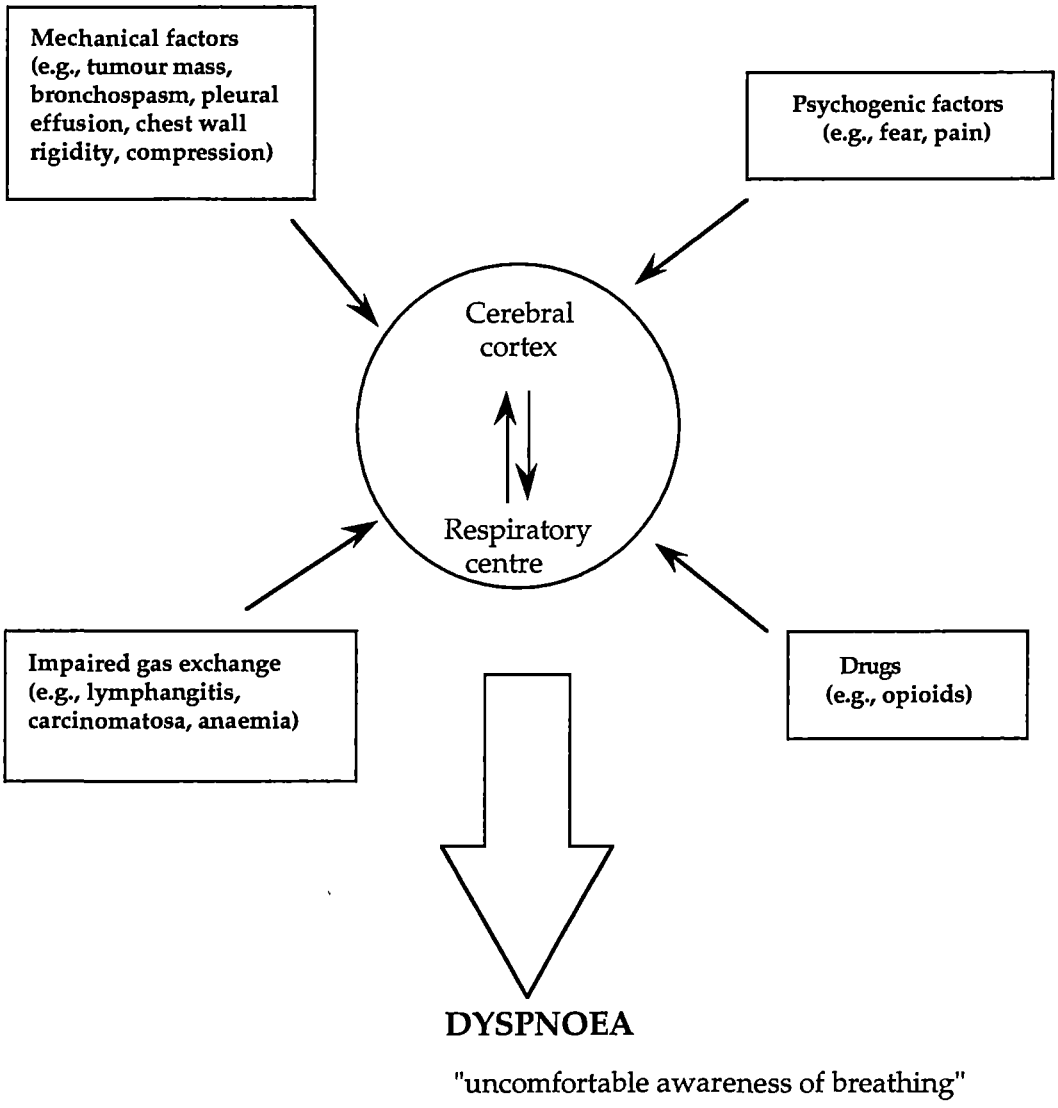


Figure 13.1: Mechanisms of Dyspnoea (from Sodha & Frampton, 1995)

and can be achieved by an open window or a fan. Oxygen is often used in the treatment of dyspnoea, although its use is not always indicated as few patients with advanced cancer suffer dyspnoea due to hypoxia (deConno *et al*, 1991; Bruera *et al*, 1993b). If oxygen is used, it should be humidified because a dry mouth is also a common symptom in advanced cancer. Nebulised saline by itself will moisten the airways and assist with the expectoration of thick secretions (Sodha & Frampton, 1995). An anxiolytic such as diazepam can be helpful in treating shallow breathing especially if it is associated with anxiety. Chlorpromazine is also used in intractable cases and can aid in drying bronchial secretions (Sodha & Frampton, 1995).

Oral morphine (5 - 10 mg every four hours; Twycross, 1993) is effective in reducing the rate of breathing to a comfortable level (e.g., 15 - 20 inspirations/min at rest), but patients are often already taking some oral morphine for control of pain so side effects such as nausea, sedation, and constipation may be poorly tolerated during repeat administration.

Previous studies have shown that morphine administered subcutaneously (30 - 40 mg) can be of assistance in treating dyspnoea (Bruera *et al*, 1993a; Bruera *et al*, 1993b). Additionally, there is evidence that low doses of nebulised morphine (5 mg in 5 mL saline) can lead to improvement in the exercise capacity of patients with chronic lung disease (Young *et al*, 1989), and there are case reports of the successful use of nebulised morphine (5 mg) in dyspnoea in patients with end-stage chronic lung and cardiac disease (Farncombe and Chater, 1993) and terminal cancer (Tooms *et al*, 1993). The relief of dyspnoea occurred within 15 minutes and lasted over four hours in more than 50% of patients (Farncombe *et al*, 1994).

The mode of action of nebulised morphine in dyspnoea is not yet fully understood, but it may be through a direct effect on lung afferent nerves or by acting centrally on opioid receptors and relieving dyspnoea by altering the central perception of breathlessness, pain and anxiety. It has also been shown to diminish ventilatory responses to hypoxia and hypercapnia at chemoreceptor levels (deConno *et al*, 1991). The central action is presumably due to small amounts of drug being absorbed from the buccal and airway mucosa during the nebulisation process and subsequently bypassing liver metabolism (Young *et al*, 1989). This may suggest that lower doses are required in nebulisation to yield the same benefits thus avoiding some of the central side effects. Relative to an IV dose, the bioavailability of a 10mg dose is less than 5% (Davis & Hardy, 1994).

Although its benefit has not clearly been proven, or indeed studied in any clinical trials, nebulised morphine is now commonly used in palliative care units to manage dypsnoea (Regnard & Tempest, 1992; Davis & Hardy, 1994; Tooms *et al*, 1993) as it often appears to be rapidly effective and involves a non-invasive route of administration. One theoretical risk of nebulised morphine worth considering is bronchospasm induced by histamine whose release may be triggered either by morphine itself or its preservative.

11.2 Objectives of this Study

The present controlled trial was designed to determine the effect of low dose nebulised morphine on the intensity of dyspnoea and respiratory function in terminally ill patients.

CHAPTER 14 : METHODS

14.1 Human Procedures

The study protocol was approved by the Research and Ethics Committees of the Royal Hobart Hospital.

Between March 1994 and November 1995, all inpatients at the Palliative Care Unit (Repatriation General Hospital) with dyspnoea due to terminal illnesses were asked to participate in the study. All patients (or their relatives) who agreed to participate were required to fill out a consent form (Appendix 15).

A baseline assessment of the intensity of dyspnoea was made using a visual analogue scoring system (a 10cm line with extremes marked 'no shortness of breath' and 'worst possible shortness of breath') (Bruera *et al*, 1993b). The patient was instructed to mark the line at any point they wished to rate the severity of dyspnoea. A baseline measurement of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) was taken using a bedside spirometer (Vitalograph® Compact Spirometer, England). Daily calibration of the spirometer was performed using a 9 L syringe. Initially measurements of respiratory function were taken on three consecutive days in a healthy subject to determine the between-day variability of the spirometer (FEV_1-3.0%; FVC-1.5%). In addition, each time respiratory function was measured, at least three tests were performed until the CV between readings was less than 5% (as calculated instantaneously by the spirometer) and the highest obtained values of FEV_1 and FVC were recorded.

After daily baseline assessment, patients received 3 mL of isotonic (0.9%) saline, morphine 2.5 mg in 3 mL saline and morphine 5 mg in 3 mL

saline on three consecutive days delivered by a nebuliser 4 times a day over 15 minutes. Dyspnoea was again assessed at 1 hour after each dose. Also at 1 hour after the second dose, another reading of respiratory function was taken. A nurses information sheet and timing schedule can be found in Appendix 16.

It should be noted that, initially the study was designed and approved as a randomised double-blind crossover trial. Unfortunately, this element of deception with placebo usage discouraged some patients from consenting to participate and the order of administration of the three test treatments had to be made consistent as outlined above.

14.2 Statistical Analysis

All data was stored and statistically analysed (Statview IV®) on a Macintosh® computer. Changes in intensity of breathlessness and respiratory function after morphine or saline nebulisation from control values on the same day were compared using the Analysis of Variance statistical test.

CHAPTER 15 : RESULTS

15.1 Patient characteristics

The sample of eleven patients consisted of 5 males and 6 females, ranging in age from 49 to 79 years, with a median age of 69 years. The patients had various forms of terminal illness: lung cancer (5 patients), breast cancer (1), colon cancer (1), cancer of the pharynx (1), thymoma (1), motor neurone disease (1), and congestive cardiac failure (1). The patients were regularly receiving other drugs in addition to nebulised morphine (median 9 drugs; range 3 to 12), including oral or subcutaneous morphine (10 patients), benzodiazepines (9), laxatives (7),

antiemetics (6), corticosteroids (6), tricyclic antidepressants (4), nonsteroidal anti-inflammatory agents (4), and antifungals (3). At least four other patients were forced to withdraw from the study (in addition to those listed below) due to worsening condition, increasing drowsiness and inability to perform respiratory function tests.

Individual case studies are outlined below.

Case 1

A 53 year old man with a 14 month history of motor neurone disease was admitted with episodes of acute shortness of breath, tiredness and a lack of sleep. He agreed to take part in the morphine trial and after the second nebulised morphine dose (2.5 mg) he reported some improvement. Some dizziness (attributed to waxy build up in his ears) precluded measurement of respiratory function on Day 2, but he slept well and seemed to gain relief from the morphine. On Day 3, a noticeable improvement in breathing made him decide to continue with the nebulised morphine (5mg in 3mL of normal saline) four times a day after the end of the trial. Measured respiratory function and subjective assessment of dyspnoea improved over the three day trial. He was discharged on nebulised morphine and continued this therapy at a nursing home until his death 2 months later.

Case 2

A 69 year old nonsmoking woman with no previous illnesses until four weeks previously when she presented with increasing shortness of breath on exertion, cough, tiredness, malaise, anorexia, night sweats, and yellow/green sputum. She was then diagnosed with metastatic adenocarcinoma of the lung with persistent pleural effusion and lymphangitis in the lungs. Chemotherapy or radiotherapy had little to offer due to the widespread disease and her frail mental and physical

state. Breathlessness on minimal exertion progressively became dyspnoea at rest by 3 weeks after admission with an increasing respiratory rate evident. The nebuliser study was commenced and by Day 2 she was subjectively feeling better and sleeping better. On Day 3 she was more settled and relaxed and found the morphine nebules had helped quite a lot and was happy to continue them regularly four times a day. She was now experiencing nil shortness of breath at rest which was indicated by a decrease in her subjective dyspnoea score. There was no significant improvement in her measured respiratory function over the study period. Nebulised morphine (5 mg in 3 mL) continued for two weeks until her condition deteriorated, her chest began to rattle, she refused the nebuliser as it overly distressed her and she died the next morning.

Case 3

A 72 year old man who was a chronic smoker with bronchitis and emphysema. He was diagnosed with squamous cell carcinoma of the left lung in 1991 and a carcinoma of the rectum in 1991 which had recently recurred. He had received both chemotherapy and radiotherapy with multiple hospital admissions over the past three years. He was admitted in November 1994 with increasing shortness of breath and lower back pain and commenced the study two days later. By Day 2 he was experiencing only shortness of breath on exertion rather than at rest and by Day 3 he showed marked improvement and decided to continue the nebulised morphine (5 mg in 3 mL) four times a day. Despite this subjective feeling of improvement, there was no significant changes in respiratory function or dyspnoea scores. One week later he thought that four times daily was too often (in addition to nebulised salbutamol) so he asked to be cut back to three times a day and when required. A further two weeks later he became sick of receiving morphine nebules after

claiming they took too long to give and were of no benefit to him any more. He was discharged soon after.

In May 1995 he was readmitted because of a large bowel obstruction and had an operation for the formation of a colostomy. After the operation, he became very anxious and died one week later.

Case 4

A 49 year old man with a history of chronic alcohol abuse and alcohol related seizures had been diagnosed 10 months previously with a squamous cell carcinoma in the left pharyngeal wall. He developed metastases to the cervical lymph node and experienced pain in his neck and jaw, controlled by morphine in a syringe driver. Other symptoms on admission included left sided weakness, dysphagia and a choking sensation in the throat. He agreed to participate but due to worsening cyanosis and shallow breathing, the use of the nebuliser was inappropriate, he was unable to even commence the study became semiconscious later that same day and died early the next morning.

Case 5

A 72 year old man with an inoperable squamous cell carcinoma of the right lung diagnosed twelve months ago. He had received no radiotherapy or chemotherapy. He was admitted with a one week history of lethargy, shortness of breath, constipation, decreased appetite and malignant hypercalcaemia. Three weeks after admission he began the trial, but after the first two nebulised doses (saline only), the patient felt too drowsy to continue, the study was stopped and he died two days later.

Case 6

A 74 year old woman with a history of chronic obstructive pulmonary disease, smoking, ischaemic heart disease and hypothyroidism presented

with increasing dyspnoea over the past six to nine months, weight loss and recent pneumonia. About ten days ago a large malignant mass was found in her left lung and her peak flows were very poor. She was experiencing severe shortness of breath on exertion and atrovent nebules were given with good effect. Within one week her shortness of breath was worsening at rest and on transfer to the Whittle Ward was commenced on the nebulised morphine trial. There was no significant improvement in either respiratory function or subjective assessment of dyspnoea over the three day trial. However, she claimed the morphine nebules were effective and she continued to receive them (morphine 5 mg) regularly four times a day after the trial for the next week until she died. Two days before her death she had an extreme episode of shortness of breath which was not well controlled with nebulised morphine.

Case 7

A 59 year old woman with a two year history of metastatic breast cancer, with multiple bone and liver involvement. She had a recent episode of pneumonia and a three day history of nausea, vomiting and abdominal pain on admission. Over the next month, her dyspnoea increased and so the amount of morphine in her driver was increased and saline nebules were given with some effect. The morphine trial was commenced and despite documented relief from acute episodes of dyspnoea, there was no significant improvement in respiratory function or assessment of dyspnoea. After the trial she continued to receive morphine nebules when required for dyspnoea.

Case 8

A 58 year old woman with congestive cardiac failure and chronic obstructive airways disease was admitted due to increasing dyspnoea, pain and tightness in the legs, epistaxis, malaena, ascites, and oxygen dependence. Two weeks after admission she began receiving nebulised

morphine. Her respiratory function improved and her assessment of dyspnoea was reduced significantly after the first day of nebulised morphine. Because of weekend leave, the third day of the trial was not fully completed although she continued the nebules at home and on return to the ward. Two days before her death she ceased both morphine and oxygen therapy as they were no longer able to be tolerated.

Case 9

A 79 year old woman with an eighteen month history of colon cancer (colostomy) with metastases to the liver, lungs and kidneys was admitted with symptoms of moist cough, incontinence, anorexia, nausea, mild constipation and dull but not unbearable pain. She complained of episodic shortness of breath at rest and whilst washing herself but said it was relieved by taking a deep breath. It was thought that the nebulised morphine trial would be beneficial to her dyspnoea but after the first two doses she withdrew because of intolerance to the nebulisation process. She died one week later.

Case 10

A 63 year old man who was diagnosed four months ago with a squamous cell carcinoma of the lung with widespread bony metastases after a three month history of backache, cough, 8-10 kg weight loss, hoarse voice and increased sputum. He had been a heavy smoker for many years and was admitted due to increasing weakness and debility and hip pain which was relieved by subcutaneous ketorolac. Increasing shortness of breath and difficulties in getting around led to the morphine trial being commenced. Initially, he was not keen to receive the nebules but after the second morphine dose he said they were helping his breathing and he continued to receive regular morphine nebules for another five days until he died.

Case 11

A 72 year old lady with a history of unstable angina and myocardial infarctions who had open heart surgery six months ago. During the lead up to surgery, a thymoma with widespread mediastinal invovement was found. She was admitted two days ago with sudden shortness of breath, a choking sensation, nausea, dry mouth, palpitations and pain in the chest and back. The morphine nebule trial was commenced. She gained some relief from the nebulised morphine and continued receiving the nebules (morphine 5 mg) for two weeks after the end of the trial until she became semi-conscious and her deteriorating condition made the use of the nebuliser inappropriate.

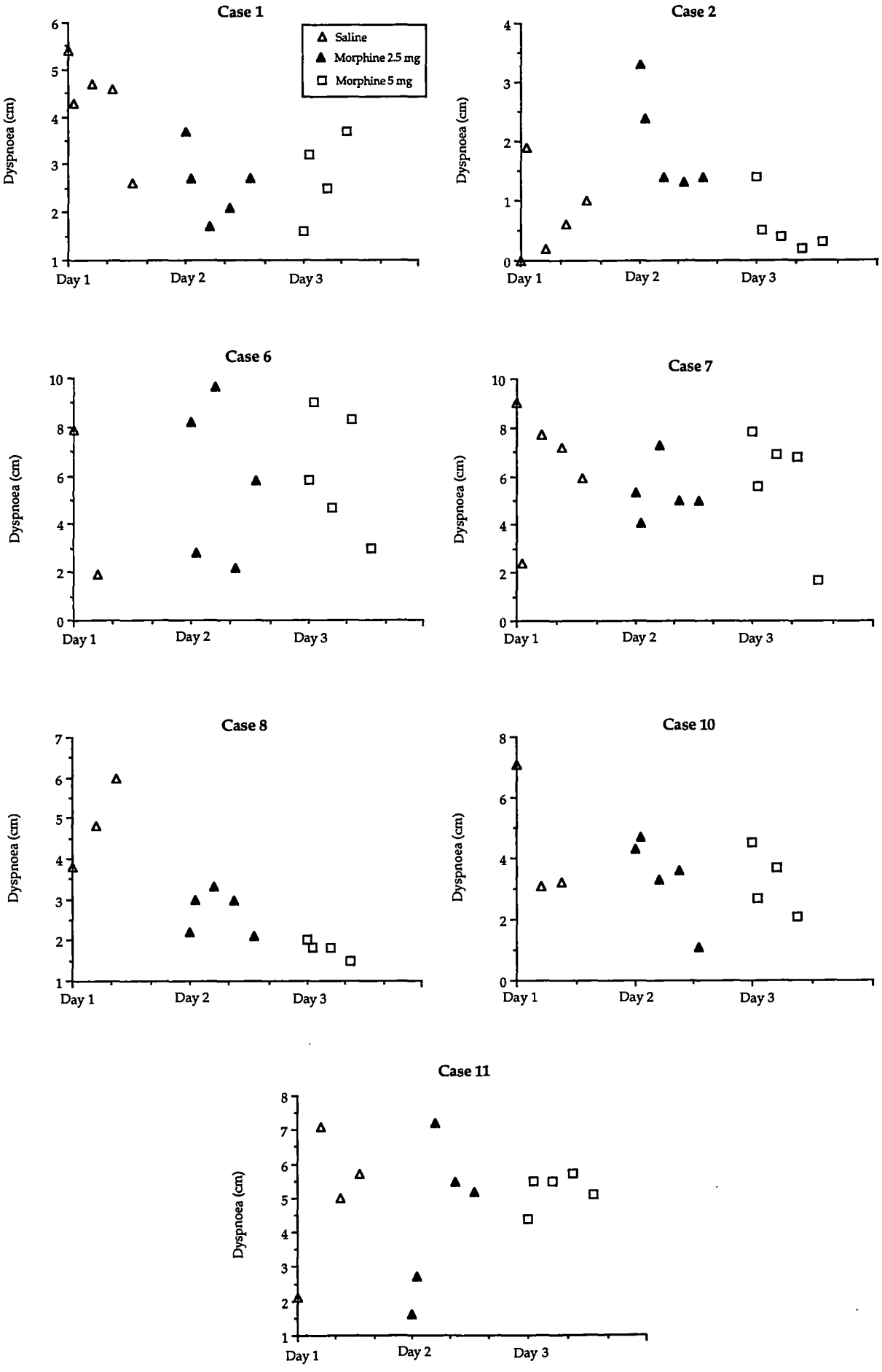
15.2 Statistical Analysis

The small sample size and the intersubject variability did not facilitate an extensive statistical analysis. Figure 15.1 clearly shows that there is some benefit of nebulised morphine over saline for particular patients (for example, case 8) without the need for a statistical test and the individual case studies reflect this also. Table 15.1 gives the mean values of dyspnoea and respiratory function over the course of the study for the eight patients who completed the trial.

Table 15.1: Values of dyspnoea and respiratory function obtained over three days (n = 8)

	mean ± SD	minimum	maximum
Dyspnoea (cm)	3.34 ± 2.60	0	9.7
FVC (L)	1.24 ± 0.34	0.73	2.12
FEV_1 (L)	0.66 ± 0.21	0.37	0.91

Figure 15.1: Visual analogue scores for dyspnoea (patients who completed trial)



15.2.1 Effect of Morphine on Subjective Symptoms of Dyspnoea

Not surprisingly, analysis of variance tests indicated that there was a statistically significant difference in subjective symptoms of dyspnoea between individuals ($F = 22.4$, $p < 0.001$; Table 15.2). For analysing the value of a treatment (whether it be morphine or saline), scores of dyspnoea were allocated into one of two groups - either a baseline measurement (one per day) or a measurement one hour after receiving a nebule (four per day). Analysis of variance tests suggested that treatment (over the three days) resulted in significantly lower scores of dyspnoea compared with baseline values measured on each of the three days ($F = 8.0$, $p < 0.01$). However, saline treatment could not be differentiated from either morphine 2.5 mg or morphine 5 mg in its efficacy. That is, there was no difference in symptom scores between days ($F = 1.7$, $p > 0.2$). Table 15.2 shows the results of the statistical analysis.

Table 15.2: Analysis of variance - nebulised morphine trial dyspnoea symptom scores

Source of variation	degrees of freedom	sum of squares	mean square	F-value	P-value
between individuals	7	297.3	49.5	22.4	<0.001
between treatments	2	7.4	3.7	1.7	0.20
between times (ie, either baseline or after treatment)	1	17.6	17.6	8.0	<0.01

15.2.2 Effect of Morphine on Respiratory Function

Again, there was significant variation in measured respiratory function between individuals ($F = 6.3$, $p < 0.01$; Table 15.3).

Table 15.3: Analysis of variance - nebulised morphine trial respiratory function (FVC)

Source of variation	degrees of freedom	sum of squares	mean square	F-value	P-value
between individuals	7	1.387	0.28	6.3	0.001
between treatments	2	2.5E-3	1.2E-3	0.02	0.90
between times (ie, either baseline or after treatment)	1	0.25	0.25	5.8	0.02

FVC was found to be significantly better during treatment than at baseline over the three day study period ($F = 5.8$, $p < 0.05$) but there was no difference in values of FEV_1. The effect of nebulised morphine (2.5 mg and 5 mg) was found to be no better than that of nebulised saline for improving respiratory function ($F = 0.02$, $p > 0.8$).

CHAPTER 16: DISCUSSION

There are many difficulties involved in performing blinded and randomised trials of drugs or drug therapies in palliative care patients, and so relatively few treatment strategies have been subjected to controlled clinical trials. N-of-1 trials have been used successfully to evaluate the efficacy of various treatments in individual patients in settings other than palliative care (Guyatt *et al*, 1994). However, randomisation of treatments within the patient is important for the success of such trials and both a stable medical condition and a previously well investigated treatment are other prerequisites, making the current study unsuitable for this method of approach.

This study highlighted some of the problems with clinical trials in palliative care. Problems were encountered with both patient recruitment and attrition, and the initial randomised double-blind crossover design of the study had to be altered in the hope of increasing the patient numbers by presenting a study where patients were in no doubt about receiving therapy. It would clearly be easier to obtain recruits by presenting a study with no uncertainties about whether a patient is receiving the best available or new treatment, than making it randomised or double-blind. Thus, the ultimate design used here did not control for variation in the natural history of the illness which is likely to have progressed from day 1 to day 3 in many cases.

There are only small numbers of patients in the Whittle Ward and few may suffer from dyspnoea. The 'breathless at rest' criteria for subject selection in this study further limited the number of available patients since these patients were often recruited in the final stages of their

disease and were thus too unwell or insufficiently stable to participate in the study either at all or for the total three days.

Often the question of unethical use of the placebo in clinical trials is raised. One problem is that even though in many cases witholding an acceptable treatment may not in fact lead to any serious harm, it is still unethical if patients do not receive the most effective known therapy to treat their condition (Rothman & Michels, 1994). Especially in palliative care patients, who are suffering in what is likely to be the last few days of their lives, there is really no justification in using a treatment which may not offer optimum relief from symptoms. In this study, the use of saline as a control should not be considered a placebo because nebulised saline has been used as an effective treatment for dyspnoea (Sodha & Frampton, 1995; Farncombe & Chater, 1994) (and it controls for the psychological effect of receiving some treatment) and so the test is not whether nebulised morphine is better than nothing but whether it is better than a potentially effective treatment.

This study found some evidence of the benefit of nebulised morphine for dyspnoea in palliative care as documented in individual cases but this was not supported by statistical tests. Seven out of the eight patients who completed the trial continued to receive regular nebulised morphine after the end of the study period claiming it was beneficial to their condition. This represents 87% of patients, which is similar to the 81% of patients treated with nebulised opioids who reported good results in a chart review of 42 patients at a palliative care facility by Farncombe *et al* (1994). Similarly, in a study by Young *et al* (1989), 82% (9 out of 11) of the patients with chronic lung disease receiving nebulised morphine showed an increase in exercise endurance time which was significantly greater than with nebulised saline ($p < 0.01$). Other previous studies describing the use of nebulised morphine in palliative care have

involved only individual cases or reports without statistical tests or controlled trials (Tooms *et al*, 1993; Farncombe & Chater, 1994). They found, however, that nebulised morphine did provide effective relief of dyspnoea and there was no evidence that it was unsafe. Other reported benefits in individual cases in these studies included an increased exercise tolerance, improved mood, better sleep quality and a more relaxed state.

However, some problems were also encountered in the current study. Dyspnoeic patients frequently found the use of the nebuliser claustrophobic, distressing and restrictive, and subsequently were unable to tolerate the regular administration of nebules. This effect was only seen in a small number of patients (10%) in the review by Farncombe *et al* (1994) and was even less prevalent in studies involving patients with chronic lung disease who are likely to be accustomed to receiving nebulised medications (Farncombe & Chater, 1993; Young *et al*, 1989). Also there may have been some tolerance to the effect of nebulised morphine illustrated by Case 3 who received it for three weeks and then claimed that the treatment was no longer of any benefit. Clearly, many palliative care patients would not be receiving nebulised morphine for any length of time, but the effect must be considered.

Conclusion

With such small numbers in this study, no definite conclusions can be made as to the benefit of nebulised morphine for dyspnoea despite anecdotal evidence in some individuals. There was a statistical indication that nebulisation of saline (with or without morphine) had favourable effects on the subjective symptoms of dyspnoea with no data to support any additional benefit of morphine. More subjects are needed to generate useful results, perhaps incorporating palliative care wards in other hospitals or patients in the community.

GENERAL CONCLUSION

The research presented here has confirmed that there are a number of clinical situations where there exists large inter-individual variations in drug plasma concentrations and clinical response creating a potential for difficulties in optimum management. In the following cases, the clinicians seemed to have overcome this by close clinical monitoring and subsequent adjustments where necessary.

Fluphenazine study

Inter-individual differences in the pharmacokinetics of antipsychotic drugs has led to great variability in the steady-state plasma levels of patients receiving the same dosage. Over the last ten years there has been an increased interest in research examining the relationships between the antipsychotic drug plasma level and both clinical efficacy and adverse effects. Being able to recognise patients who are seemingly therapy-resistant despite high or optimal plasma levels may help reduce the overall duration of exposure to antipsychotics (which has been associated with tardive dyskinesias) and reduce the incidence of adverse effects (given the possible association between extrapyramidal symptoms and plasma level).

This study investigated the steady-state plasma concentrations of fluphenazine in 24 subjects suffering from chronic schizophrenia. Considerable inter-patient variability was found with plasma concentrations ranging from less than 0.1 ng/mL to 27.9 ng/mL. We used the Andreasen Scale for positive and negative symptoms as a measure of clinical response which was found to be inversely related to both log transformed plasma fluphenazine concentrations and fluphenazine decanoate dosage. Another finding was that patients

receiving an anticholinergic agent (for the treatment of extrapyramidal symptoms) had significantly higher plasma concentrations of fluphenazine than those not receiving such drugs.

These results indicate that plasma level monitoring of antipsychotics may fulfil a role in improving the treatment outcome in some patients with chronic psychotic disorders but observing for clinical responses and adverse effects are also important.

Cardiopulmonary bypass study

With the number of operations involving cardiopulmonary bypass steadily increasing it is important to determine the effect that such a massive perturbation of normal body function has on the pharmacokinetics of the many drugs administered in the perioperative period.

The research presented in this study investigated two drugs commonly used as part of the anaesthetic regime in such operations - fentanyl and alcuronium. Plasma concentrations of both drugs were characterised by a marked decline on initiation of CPB, however, during CPB it was difficult to estimate pharmacokinetic parameters because of the gross changes in physiological conditions. In vitro studies also showed that the amount of drug generally adsorbed to the bypass apparatus was only a small proportion of the total dose and large in vivo drug reservoirs prevented this from being a significant occurrence.

The clinical implications of the present study are that even given the drug adsorption to the bypass apparatus and the extreme physiological changes occurring over the bypass period, suitable plasma concentrations of both drugs and adequate clinical responses were maintained.

Additional bolus dosages were administered as required based on intraoperative clinical monitoring such as evidence of arousal.

Subcutaneous fentanyl study

Given that responses to the opioid analgesic, fentanyl, are variable between individuals and within individuals over time, it is important to continually individualise and titrate dosage based on clinical response.

The study presented in this section of the thesis highlighted the variability in subcutaneous fentanyl dosage required for pain control and the resulting steady-state plasma concentrations of fentanyl in palliative care patients. It also demonstrated some degree of tolerance to the analgesic effect of fentanyl over time.

Such variability in the palliative care setting was explained by differences in the clearance of fentanyl (pharmacokinetic), severity of pain and pharmacodynamic sensitivity to fentanyl, all of which are likely to be changing constantly in these patients. The pain control in this setting was adequate indicating that despite the variability displayed, the clinicians were managing by carefully adjusting dosage.

Nebulised morphine study

Dyspnoea is a very common and distressing symptom in patients with advanced cancer and one which has proved difficult to manage successfully. Nebulised morphine use for dyspnoea in palliative care patients is a relatively recent development and the present study was designed to ascertain its benefits over and above nebulised saline.

Problems with a small and heterogenous sample precluded the ability to make reliable conclusions despite individual patients claiming a perceived subjective benefit. Further studies in a larger group of patients

are required to confirm the results obtained. The decision to continue treatment with nebulised morphine in any one individual should be based on initial symptom improvement and the patient's desire to receive the therapy.

Thus, even though large clinical trials can predict the outcome of drug treatments in populations and can propose suitable dosages, responses to drugs are never totally foreseeable or consistent. Any individual may behave differently to the population group as a result of variability in pharmacokinetics and pharmacodynamics. This emphasises the need for individualisation of therapy based either on plasma level monitoring or on clinical response depending on the drug regimen in question and these above-mentioned studies have indicated that in many clinical situations this is very achievable.

REFERENCES

Agency for Health Care Policy and Research (1994) Management of cancer pain: adults. *American Journal of Hospital Pharmacy*, **51**: 1643-1656.

Albertioni F, Herngren L, Juliusson G, Liliemark J (1994) Protein binding of 2-chloro 2'-deoxyadensine (cladribine) in healthy subjects and in patients with leukaemia. *European Journal of Clinical Pharmacology*, **46**: 563-564.

American Psychiatric Association (1987) *Diagnostic and statistical manual of mental disorders DSM-III-R*. 3rd edition-revised. Washington, DC: American Psychiatric Association.

Andreasen NC (1985) Positive vs. negative schizophrenia: a critical evaluation. *Schizophrenia Bulletin*, **11**: 380-389.

Auseums ME, Hug CC, Stanski DR, Burm AGL (1986) Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for general surgery. *Anesthesiology*, **65**: 362-373.

Avram MJ, Shanks CA, Henthorn TK, Ronai AK, Kinzer J, Wilkinson CJ (1987) Metocurine kinetics in patients undergoing operations requiring cardiopulmonary bypass. *Clinical Pharmacology and Therapeutics*, **42**: 576-581.

Axelsson R (1990) Plasma level monitoring of neuroleptic drugs - a way to improve the treatment of psychotic patients. In: Strandberg K, Beermann B, Lonnerholm G, eds. *Treatment with neuroleptics*. Uppsala, Sweden: National Board of Health and Welfare Drug Information Committee, 39-51.

Balant-Gorgia AE, Balant L (1987) Antipsychotic drugs: clinical pharmacokinetics of potential candidates for plasma concentration monitoring. *Clinical Pharmacokinetics*, **13**: 65-90.

Balant-Gorgia AE, Balant LP, Andreoli A (1993) Pharmacokinetic optimisation of the treatment of psychosis. *Clinical Pharmacokinetics*, **25**: 217-236.

Bentley JB, Conahan TJ, Cork RC (1983) Fentanyl sequestration in lungs during cardiopulmonary bypass. *Clinical Pharmacology and Therapeutics*, **34**: 703-706.

Beswick DT (1987) Use of syringe driver in terminal care. *The Pharmaceutical Journal*, November 28: 656-658.

Björkman S, Stanski DR (1988) Simultaneous determination of fentanyl and alfentanil in rat tissues by capillary column gas chromatography. *Journal of Chromatography, Biomedical Applications*, **433**: 95-104.

Björkman S, Stanski DR, Harashima H, Dowrie R, Harapat SR, Wada DR, Ebling WF (1993) Tissue distribution of fentanyl and alfentanil in the rat cannot be described by a blood flow limited model. *Journal of Pharmacokinetics and Biopharmaceutics*, **21**: 255-79.

Bjorksten AR, Beemer GH, Crankshaw DP (1990) Simple high-performance liquid chromatographic method for the analysis of the non-depolarizing neuromuscular blocking drugs in clinical anaesthesia. *Journal of Chromatography, Biomedical Applications*, **533**: 241-247.

Blanchard J, Harvey S (1990) Comparison of ultrafiltration devices for assessing theophylline protein binding. *Therapeutic Drug Monitoring*, **12**: 398-403.

Bleasel MD, Peterson GM, Dunne PF (1994) Plasma concentrations of midazolam during subcutaneous administration in palliative care. *Palliative Medicine*, **8**: 231-236.

Bollini P, Pampallona S, Orza MJ, Adams ME, Chalmers TC (1994) Antipsychotic drugs: is more worse? A meta-analysis of the published randomized control trials. *Psychological Medicine*, **24**: 307-316.

Boulieu R, Bonnefous JL, Lehot JJ, Durand PG, Chassignolle JF, Ferry S (1994) Effect of cardiopulmonary bypass on plasma concentrations of diltiazem and its two active metabolites. *Journal of Pharmacy and Pharmacology*, **46**: 310-312.

Bovill JG, Sebel PS (1980) Pharmacokinetics of high-dose fentanyl-A study in patients undergoing cardiac surgery. *British Journal of Anaesthesiology*, **52**: 795-801.

Bower S (1981) Plasma protein binding of fentanyl. *Journal of Pharmacy and Pharmacology*, **33**: 507-14.

Bower S, Hull CJ (1982) Comparative pharmacokinetics of fentanyl and alfentanil. *British Journal of Anaesthesia*, **54**: 871-877.

Brown GR, Miyata M, McCormack JP (1993) Drug concentration monitoring - an approach to rational use. *Clinical Pharmacokinetics*, **24**: 187-194.

Bruera E, Brenneis C, Michaud M, MacMillan K, Hanson J, MacDonald RN (1988a) Patient-controlled subcutaneous hydromorphone versus continuous subcutaneous infusion for the treatment of cancer pain. *Journal of the National Cancer Institute*, **80**: 1152-1154.

Bruera E, Brenneis C, Michaud M, Bacovsky R, Chadwick S, Emeno A, MacDonald N (1988b) Use of the subcutaneous route for the administration of narcotics in patients with cancer pain. *Cancer*, **62**: 407-411.

Bruera E, MacEachern T, Ripamonti C, Hanson J (1993a) Subcutaneous morphine for dyspnoea in cancer patients. *Annals of Internal Medicine*, **119**: 906-7.

Bruera E, deStoutz N, Velasco-Leiva A, Schoeller T, Hanson J (1993b) Effects of oxygen on dyspnoea in hypoxaemic terminal-cancer patients. *The Lancet*, **342**: 13-14.

Buylaert WA, Herregods LL, Mortier EP, Bogaert MG (1989) Cardiopulmonary bypass and the pharmacokinetics of drugs-an update. *Clinical Pharmacokinetics*, **17**: 10-26.

Cartwright DP, Chapman JC, Davies JR, Scoggins AM (1981) Pharmacokinetics of high-dose fentanyl. *British Journal of Anaesthesia*, **53**: 780.

Clotz MA, Nahata MC (1991) Clinical uses of fentanyl, sufentanil, and alfentanil. *Clinical Pharmacy*, **10**: 581-591.

Cockroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. *Nephron*, **16**: 31-41.

Dagan O, Klein J, Gruenwald C, Bohn D, Barker G, Koren G (1993) Preliminary studies of the effects of extracorporeal membrane oxygenator on the disposition of common pediatric drugs. *Therapeutic Drug Monitoring*, **15**: 263-66.

Dahl SG (1986) Plasma level monitoring of antipsychotic drugs: clinical utility. *Clinical Pharmacokinetics*, **11**: 36-61.

Davis CL, Lam W, Butcher M, Joel SP, Slevin ML (1992) Low systemic bioavailability of nebulised morphine: potential therapeutic role for the relief of dyspnoea. *British Journal of Cancer*, **65** (supplement 16): 12.

Davis CL (1994) The therapeutics of dyspnoea. *Cancer Surveys*, **21**: 85-98.

Davis CL, Hardy JR (1994) Palliative Care. *British Medical Journal*, **308**: 1359-1362.

Davis JM, Metalon L, Watanabe MD, Blake L (1994) Depot antipsychotic drugs. Place in therapy. *Drugs*, **47**: 741-773.

deBros F, Okutani R, Inada E, Lawrence K (1990) Determination of alcuronium in plasma and urine by high-performance liquid chromatography. *Journal of Chromatography, Biomedical Applications*, **529**: 449-454.

deConno F, Spoldi E, Caraceni A, Ventafridda V (1991) Does pharmacological treatment affect the sensation of breathlessness in terminal cancer patients. *Palliative Medicine*, **5**: 237-43.

Diefenbach C, Abel M, Buzello W (1992) Greater neuromuscular blocking potency of atracurium during hypothermic than during normothermic cardiopulmonary bypass. *Anesthesia and Analgesia*, **75**: 675-678.

Diefenbach C, Künzer T, Buzello CW, Theisohn M (1995) Alcuronium: a pharmacodynamic and pharmacokinetic update. *Anesthesia and Analgesia*, **80**: 373-377.

Dover SB (1987) Syringe driver in terminal care. *British Medical Journal*, **294**: 553-555.

Downing SW, Edmunds LH (1992) Release of vasoactive substances during cardiopulmonary bypass. *Annals of Thoracic Surgery*, **54**: 1236-1243.

Drummond SH, Peterson GM, Galloway JG, Keefe PA (1995) National survey of drug use in palliative care. *Palliative Medicine* (in press).

Duthie DJR, McLaren AD, Nimmo WS (1986) Pharmacokinetics of fentanyl during constant rate IV infusion for the relief of pain after surgery. *British Journal of Anaesthesia*, **58**: 950-956.

Duthie DJR, Rowbotham DJ, Wyld R, Henderson PD, Nimmo WS (1988) Plasma fentanyl concentrations during transdermal delivery of fentanyl to surgical patients. *British Journal of Anaethesia*, **60**: 614-618.

Dysken MW, Javaid JL, Chang SS (1981) Fluphenazine pharmacokinetics and therapeutic response. *Psychopharmacology*, **73**: 205-210.

Escobar JI, Barron A, Kiriakos R (1983) Serum levels of fluphenazine: effect of dosage and route of administration and relation to side effects and clinical response. *Psychopharmacology Bulletin*, **19**: 131-134.

Farmer AE, Blewett A (1993) Drug treatment of resistant schizophrenia. Limitations and recommendations. *Drugs*, **45**: 374-383.

Farncombe M, Chater S (1993) Case studies outlining use of nebulised morphine for patients with end-stage chronic lung and cardiac disease. *Journal of Pain and Symptom Management*, **8**: 221-5.

Farncombe M, Chater S (1994) Clinical application of nebulised opioids for treatment of dyspnoea in patients with malignant disease. *Supportive Care in Cancer*, **2**: 184-187.

Farncombe M, Chater S, Gillin A (1994) The use of nebulised opioids for breathlessness: a chart review. *Palliative Medicine*, **8**: 306-312.

Finegan BA, Hussain MD, Tam YK (1992) Pharmacokinetics of diltiazem in patients undergoing coronary artery bypass grafting. *Therapeutic Drug Monitoring*, **14**: 485-492.

Flacke JW, Bloor BC, Flacke WE (1987) Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing cardiopulmonary bypass. *Anesthesiology*, **67**: 11-19.

Franklin M, Wiles DH, Harvey DJ (1978) Sensitive gas-chromatographic determination of fluphenazine in human plasma. *Clinical Chemistry*, **24**: 41-44.

Furet Y, Breteau M, Etienne T (1991) Etude des taux résiduels de neuroleptiques à action prolongée. *Therapie*, **46**: 119-123.

Gourlay GK, Kowalski SR, Plummer JL, Cherry DA, Gaukroger P, Cousins MJ (1989) The transdermal administration of fentanyl in the treatment of postoperative pain: pharmacokinetics and pharmacodynamic effects. *Pain*, **37**: 193-202.

Grasela TH (1994) The role of therapeutic drug monitoring in pharmacoepidemiology. In: Brian L Strom (ed) *Pharmacoepidemiology* (2nd edition). John Wiley & Sons Ltd, Chichester, England: 413-430.

Gunne LM (1990) Neurological side effects during neuroleptic treatment. Considerations regarding prevention of tardive symptoms. In: Strandberg K, Beermann B, Lonnerholm G, eds. *Treatment with neuroleptics*. Uppsala, Sweden: National Board of Health and Welfare Drug Information Committee, 133-141.

Guyatt GH, Jaeschke R, Roberts R (1994) N-of-1 randomized clinical trials in pharmacoepidemiology. In: Brian L Strom (ed) *Pharmacoepidemiology* (2nd edition). John Wiley & Sons Ltd, Chichester, England: 507-524.

Hale T (1993) Will the new antipsychotics improve the treatment of schizophrenia? Depot preparations still hold the key to compliance [editorial]. *British Medical Journal*, **307**: 749-750.

Hall R (1991) The pharmacokinetic behaviour of opioids administered during cardiac surgery. *Canadian Journal of Anaesthesia*, **38**: 747-56.

Hall R (1993) Anaesthesia for coronary artery surgery - a plea for goal-directed approach. *Canadian Journal of Anaesthesia*, **40**: 1178-1194.

Hall RI, Molderhauer CC, Hug CC (1993) Fentanyl plasma concentrations maintained by a simple infusion scheme in patients undergoing cardiac surgery. *Anesthesia and Analgesia*, **76**: 957-963.

Hatzopoulos FK, Rodvold KA, Sullivan-Bolyai J, Levitsky S (1993) Pharmacokinetics of intravenous vancomycin in pediatric cardiopulmonary bypass surgery. *The Pediatric Infectious Disease Journal*, **12**: 300-304.

Henry DA, Smith AJ, Hennessy S (1994) Basic principles of clinical pharmacology relevant to pharmacoepidemiology studies. In: Brian L Strom (ed) *Pharmacoepidemiology* (2nd edition). John Wiley & Sons Ltd, Chichester, England: 39-56.

Heyse-Moore LH, Ross V, Mullee MA (1991) How much of a problem is dyspnoea in advanced cancer? *Palliative Medicine*, **5**: 20-6.

Holdsworth MT, Forman WB, Killilea TA, Nystrom KM, Paul R, Brand SC, Reynolds R (1994) Transdermal fentanyl disposition in elderly subjects. *Gerontology*, **40**: 32-37.

Holley FO, Ponganis KV, Stanski DR (1982) Effect of cardiopulmonary bypass on the pharmacokinetics of drugs. *Clinical Pharmacokinetics*, **7**: 234-251.

Holley FO, Van Steennis C (1988) Postoperative analgesia with fentanyl: pharmacokinetics and pharmacodynamics of constant-rate IV and transdermal delivery. *British Journal of Anaesthesia*, **60**: 608-613.

Howie MB, Varma A, Sparks J, Reilley T, Cook R (1981) The relationship of plasma fentanyl levels to the post-operative course of open heart surgery patients. *Anesthesiology*, **55**: A45.

Hug CC, Moldenhauer CC (1982) Pharmacokinetics and dynamics of fentanyl infusions in cardiac surgical patients. *Anesthesiology*, **57**: A45.

Hug CC, Burm AGL, de Lange S (1994) Alfentanil pharmacokinetics in cardiac surgical patients. *Anesthesia and Analgesia*, **78**: 231-239.

Hunter JM (1994) Muscle relaxants in renal disease. *Acta Anaesthesiologica Scandinavica*, **38** (supplement 102): 2-5.

Hynynen M, Olkkola KT, Näveri E, Palojoki R, Neuvonen PJ, Heinonen J (1989) Thiopentone pharmacokinetics during cardiopulmonary bypass with a nonpulsatile or pulsatile flow. *Acta Anaesthesiologica Scandinavica*, **33**: 554-560.

Hynynen M (1987) Binding of fentanyl and alfentanil to the extracorporeal circuit. *Acta Anaesthesiologica Scandinavica*, **31**: 706-710.

Hynynen M, Olkkola KT, Palojoki R, Tikkanen I, Fyhrquist F (1992) Pharmacokinetics and effects of atrial naturetic factor during hypothermic cardiopulmonary bypass. *European Journal of Clinical Pharmacology*, **43**: 647-50.

Hynynen M, Hynninen M, Soini H, Neuvonen PJ, Heinonen J (1994) Plasma concentration and protein binding of alfentanil during high-dose infusion for cardiac surgery. *British Journal of Anaesthesia*, **72**: 571-576.

Jann MW, Ereshefsky L, Saklad SR (1985) Clinical pharmacokinetics of the depot antipsychotics. *Clinical Pharmacokinetics*, **10**: 315-333.

Javaid JI, Dekirmenjian H, Liskevych U, Lin R-L, Davis JM (1981) Fluphenazine determination in human plasma by a sensitive gas chromatographic method using nitrogen detector. *Journal of Chromatographic Science*, **19**: 439-443.

Javaid JI, Janicak PG, Holland D (1991) Blood level monitoring of antipsychotics and antidepressants. *Psychiatric Medicine*, **9**: 163-187.

Kane JM, Rifkin A, Quitkin F, Nayak D, Ramos-Lorenzi J (1982) Fluphenazine vs placebo in patients with remitted, acute first-episode schizophrenia. *Archives of General Psychiatry*, **39**: 70-73.

Killian KJ (1988) Assessment of Dyspnoea. *European Respiratory Journal,* **1**: 195-197.

Kirkegaard-Nielsen H, Helbo-Hansen HS, Toft P, Severinsen IK (1994) Anthropometric variables as predictors for duration of action of vecuronium-induced neuromuscular block. *Anesthesia and Analgesia,* **79**: 1003-1006.

Knowles S (1993) Symptom management in palliative care. *On Continuing Practice,* **20**: 20-25.

Koreen AR, Lieberman J, Alvir J, Chakos M, Loebel A, Cooper T, Kane J (1994) Relation of plasma fluphenazine levels to treatment response and extrapyramidal side effects in first-episode schizophrenic patients. *American Journal of Psychiatry,* **151**: 35-39.

Koren G, Crean P, Klein J, Goresky G, Villamater J, MacLeod SM (1984a) Sequestration of fentanyl by the cardiopulmonary bypass (CPBP). *European Journal of Clinical Pharmacology,* **27**: 51-56.

Koren G, Goresky G, Crean P, Klein J, MacLeod SM (1984b) Pediatric fentanyl dosing based on pharmacokinetics during cardiac surgery. *Anesthesia and Analgesia,* **63**: 577-582.

Koska AJ, Romagnoli A, Kramer WG (1981) Effect of cardiopulmonary bypass on fentanyl distribution and elimination. *Clinical Pharmacology and Therapeutics,* **29**: 100-105.

Kowalski SR, Gourlay GK, Cherry DA, McLean CF (1987) Sensitive gas liquid chromatography method for the determination of fentanyl concentrations in blood. *Journal of Pharmacological Methods,* **18**: 347-355.

Kowalski SR, Gourlay GK (1990) Stability of fentanyl citrate in glass and plastic containers and in a patient-controlled delivery system. *American Journal of Hospital Pharmacy*, **47**: 1584-1587.

Krasnow SH, Cohen MH (1994) Morphine for dyspnoea in patients with cancer. *Annals of Internal Medicine*, **120**: 692-693.

Kumar K, Morgan DJ (1987) Determination of fentanyl and alfentanil in plasma by high performance liquid chromatography with ultraviolet detection. *Journal of Chromatography, Biomedical Applications*, **419**: 464-468.

Kumar K, Crankshaw DP, Morgan DJ, Beemer GH (1988) The effect of cardiopulmonary bypass on plasma protein binding of alfentanil. *European Journal of Clinical Pharmacology*, **35**: 47-52.

Künzer T, Buzello CW, Theisohn M, Diefenbach C (1994) Simple and rapid high - performance liquid chromatography method for the determination of alcuronium in human plasma and urine. *Journal of Chromatography, Biomedical Applications*, **653**: 63-68.

Laganière S, Goernert L, Gallicano K, Otson R (1993) Improved extraction, sensitivity, specificity, and stability for measuring fentanyl in plasma by gas chromatography with nitrogen detection. *Clinical Chemistry*, **39**: 2206-7.

Lehmann KA, Heinrich C, van Heiss R (1988) Balanced anesthesia and patient controlled postoperative analgesia with fentanyl: minimum effective concentrations, accumulation and acute tolerance. *Acta Anaesthesiologica Belgium*, **39**: 11-23.

Leow KP, Wright AWE, Cramond T, Smith MT (1993) Determination of the serum protein binding of oxycodone and morphine using ultrafiltration. *Therapeutic Drug Monitoring*, **15**: 440-447.

Lunn JK, Stanley TH, Eisele J, Webster L, Woodward A (1979) High dose fentanyl anesthesia for coronary artery surgery: plasma fentanyl concentrations and influence of nitrous oxide on cardiovascular response. *Anesthesia and Analgesia*, **58**: 390-395.

Mabe SR, Connelly JF (1995) Nebulised morphine for the relief of dyspnea. *American Journal of Health-System Pharmacy*, **52**: 146-148.

Maddocks I (1992) Subcutaneous administration of fluid and drugs in palliative care. *Australian Journal of Hospital Pharmacy*, **22**: 181-184.

Mahler DA, Wells CK (1988) Evaluation of clinical methods for rating dyspnoea. *Chest*, **93**: 580-584.

March C, Blanke RV (1985) Determination of free valproic acid concentrations using the Amicon Micropatition MPS-1 ultrafiltration system. *Therapeutic Drug Monitoring*, **7**: 115-120.

Marder SR, Midha KK, Van Putten T, Aravagiri M, Hawes EM, Hubbard JW, McKay G, Mintz J (1991) Plasma levels of fluphenazine in patients receiving fluphenazine decanoate. Relationship to clinical response. *British Journal of Psychiatry*, **158**: 658-665.

Marder SR (1994) The role of dosage and plasma levels in neuroleptic relapse prevention. *Acta Psychiatrica Scandinavica*, **89**: 25-27.

Martensson E (1990) Interindividual variation in the kinetics of neuroleptic drugs. In: Strandberg K, Beermann B, Lonnerholm, eds. *Treatment with neuroleptics*. Uppsala, Sweden: National Board of Health and Welfare Drug Information Committee, 9-17.

Masters NJ, Bennett MRD, Wedley JR (1985) Nebulised morphine: a new delivery method for pain relief. *The Practitioner*, **229**: 649-53.

Mather LE (1983) Clinical pharmacokinetics of fentanyl and its newer derivatives. *Clinical Pharmacokinetics*, **8**: 422-446.

Mather LE, Gourlay GK (1991) Pharmacokinetics of Fentanyl. In: Lehmann KA (ed) *Transdermal fentanyl - a new approach to prolonged pain control*. Springer Verlag, Berlin, 73-97.

Mavroidis ML, Kanter DR, Hirschowitz J, Garver DL (1984) Fluphenazine plasma levels and clinical response. *Journal of Clinical Psychiatry*, **45**: 370-373.

McClain DA, Hug CC (1980) Intravenous fentanyl kinetics. *Clinical Pharmacology and Therapeutics*, **28**: 106-114.

McCreadie RG, Robertson LJ, Wiles DH (1992) The Nithsdale schizophrenia surveys IX: akathisia, parkinsonism, tardive dyskinesia and plasma neuroleptic levels. *British Journal of Psychiatry*, **161**: 793-799.

Meuldermans WEG, Hurkmans RMA, Heykants JJP (1982) Plasma protein binding and distribution of fentanyl, sufentanil, alfentanil and lofentanil in blood. *Archives Internationales de Pharmacodynamie et de Therapie*, **257**: 4-19.

Midha KK, Marder SR, Jaworski TJ, McKay G, Hubbard JW, Hawes EM, Van Putten T, Wirshing WC, Aravagiri M (1993) Clinical perspectives of some neuroleptics through development and application of their assays. *Therapeutic Drug Monitoring*, **15**: 179-189.

Miser AW, Narang PK, Dothage JA, Young RC, Sindelar W, Miser JS (1989) Transdermal fentanyl for pain control in patients with cancer. *Pain*, **37**: 15-21.

Moulin DE, Johnson NG, Murray-Parsons N, Geoghegan MF, Goodwin VA, Chester MA (1992) Subcutaneous narcotic infusions for cancer pain: treatment outcome and guidelines for use. *Canadian Medical Association Journal*, **146**: 891-897.

Murkin JM, Farrar JK, Tweed A (1987) Cerebral autoregulation and flow/metabolism coupling during cardiopulmonary bypass: the influence of $PaCO_2$. *Anesthesia and Analgesia*, **66**: 825-832.

Noseda A, Carpiaux J, Schmerber J, Yernault J (1992) Dyspnoea assessed by visual analogue scale in patients with chronic obstructive lung disease during progressive and high intensity exercise. *Thorax*, **47**: 363-368.

Ohshima T, Johno I, Kitazawa S (1988) Comparative evaluation of microfiltration devices for determination of protein binding. *Therapeutic Drug Monitoring*, **10**: 310-315.

O'Neill WM (1994) Subcutaneous infusions - a medical last rite. *Palliative Medicine*, **8**: 91-93.

Phipps JA, Sabourin MA, Buckingham W, Strunin L (1983) Detection of picogram concentrations of fentanyl in plasma by gas-liquid chromatography. *Journal of Chromatography, Biomedical Applications,* **272**: 392-395.

Portenoy RK, Southam MA, Gupta SK, Lapin J, Laymen M, Inturrisi CE, Foley KM (1993) Transdermal fentanyl for cancer pain - repeated dose pharmacokinetics. *Anesthesiology,* **78**: 36-43.

Psychotropic Drug Guidelines Sub-Committee, Victorian Drug Usage Advisory Committee. (1993) Psychotropic drug guidelines. 2nd ed. Melbourne, Australia: Victorian Medical Postgraduate Foundation Inc.

Ramzan MI, Somogyi AA, Walker JS, Shanks CA, Triggs EJ (1981) Clinical pharmacokinetics of the non-depolarising muscle relaxants. *Clinical Pharmacokinetics,* **6**: 25-60.

Regnard CFB, Tempest S (1992) A guide to symptom relief in advanced cancer (3rd edition). Haigh & Hochland, Manchester, England.

Reid DB (1989) The syringe driver in hospice care - A useful tool. *Current Therapeutics,* **30**: 15-19.

Reuben DB, Mor V (1986) Dyspnoea in terminally ill cancer patients. *Chest,* **89**: 234-236.

Reves JG, Croughwell N, Jacobs JR, Greeley W (1989) Anesthesia during cardiopulmonary bypass: does it matter? In: John H. Tinker (ed) *Cardiopulmonary bypass: current concepts and conroversies.* WB Saunders Company, Philadelphia, USA, 69-97.

Rinck G, Kleijnen J, Van den Bos TG, de Haes HJ, Schade E, Veenhof CH (1994) Trials in palliative care. *British Medical Journal*, **310**: 598-599.

Rivera-CalimLim L, Siracusa A (1977) Plasma assay of fluphenazine. *Psychopharmacology Communications*, **1**: 233-242.

Rivera-CalimLim L, Hershey L (1984) Neuroleptic concentrations and clinical response. *Annual Review of Pharmacology and Toxicology*, **24**: 361-386.

Robbins GR, Wynands JE, Whalley DG, Donati F, Ramsay JG, Srikant CB, Patel YC (1990) Pharmacokinetics of alfentanil and clinical responses during cardiac surgery. *Canadian Journal of Anaesthesia*, **37**: 52-57.

Roos PJ, Glerum JH, Meilink JW (1992) Stability of sufentanil citrate in a portable pump reservoir, a glass container and a polyethylene container. *Pharmaceutisch Weekblad Scientific*, **14**: 196-200.

Rothman KJ, Michels KB (1994) The continuing unethical use of placebo controls. *The New England Journal of Medicine*, **331**: 394-398.

Rowland M, Tozer TN (1989) Variability in drug response. In: *Clinical Pharmacokinetics-concepts and applications*, Philadelphia; Lea & Febiger.

Russell GN, Wright EL, Fox MA, Douglas EJ, Cockshott ID (1989) Propofol-fentanyl anaesthesia for coronary artery surgery and cardiopulmonay bypass. *Anaesthesia*, **44**: 205-208.

Schug SA, Dunlop R, Zech D (1992) Pharmacological management of cancer pain. *Drugs*, **43**: 44-53.

Schwinn DA, Leone BJ, Spahn DR, Chesnut LC, Page SO, McRae RL, Liggett SB (1991) Desensitization of myocardial β-adrenergic receptors during cardiopulmonary bypass. *Circulation*, **84**: 2559-2567.

Shafer SL, Stanski DR (1992) Improving the clinical utility of anesthetic drug pharmacokinetics. *Anesthesiology*, **76**: 327-330.

Sharpe MD (1992) The use of muscle relaxants in the intensive care unit. *Canadian Journal of Anaesthesia*, **39**: 949-962.

Simpson GM, Kashinath Y (1985) Blood levels of neuroleptics: state of the art. *Journal of Clinical Psychiatry*, **46**: 22-28.

Skacel M, Knott C, Reynolds F, Aps C (1986) Extracorporeal circuit sequestration of fentanyl and alfentanil. *British Journal of Anaesthesia*, **58**: 947-949.

Smith RC, Crayton J, Dekirmenjian H, Klass D, Davis JM (1979) Blood levels of neuroleptic drugs in nonresponding chronic schizophrenic patients. *Archives of General Psychiatry*, **36**: 579-584.

Sramek JJ, Potkin SG, Hahn R (1988) Neuroleptic plasma concentrations and clinical response in search of a therapeutic window. *Drug Intelligence and Clinical Pharmacy*, **22**: 373-380.

Stark RD (1988) Dyspnoea: Assessment and pharmacological manipulation. *European Respiratory Journal*, **1**: 280-287.

Storey P, Hill HH, St Louis RH, Tarver EE (1990) Subcutaneous infusions for control of cancer symptoms. *Journal of Pain and Symptom Management*, **5**: 33-41.

Svensson CK, Woodruff MN, Baxter JG Lalka D (1986) Free drug concentration monitoring in clinical practice : Rationale and current status. *Clinical Pharmacokinetics*, **11**: 450-469.

Szenohradsky J, Fisher DM, Segredo V, Caldwell JE, Bragg P, Sharma ML, Gruenke LD, Miller RD (1992) Pharmacokinetics of rocuronium bromide (ORG 9426) in patients with normal renal function or patients undergoing cadaver renal transplantation. *Anesthesiology*, **77**: 899-904.

Taeger K, Weninger E, Schmelzer F, Adt M, Franke N, Peter K (1988) Pulmonary kinetics of fentanyl and alfentanil in surgical patients. *British Journal of Anaesthesia*, **61**: 425-434.

Tan ST, Boniface PJ (1990) High-performance liquid chromatography of droperidol in whole blood. *Journal of Chromatography, Biomedical Applications*, **532**: 181-186.

Thomson IR, MacAdams CL, Hudson RJ, Rosenbloom M (1992) Drug interactions with sufentanil - haemodynamic effects of premedication and muscle relaxants. *Anesthesiology*, **76**: 922-929.

Tooms A, McKenzie A, Grey H (1993) Nebulised morphine. *The Lancet*, **342**: 1123-4.

Tu YH, Stiles ML, Allen LV (1990) Stability of fentanyl citrate and bupivacaine hydrochloride in portable pump reservoirs. *American Journal of Hospital Pharmacy*, **47**: 2037-40.

Tulla H, Takala J, Alhava E, Huttunen H, Kari A (1991) Hypermetabolism after coronary artery bypass. *Journal of Thoracic and Cardiovascular Surgery*, **101**: 598-600.

Twycross RG (1993) Symptom control: the problem areas. *Palliative Medicine*, **7** (supplement 1): 1-8.

Twycross RG, Bergl S, John S, Lewis K (1994) Monitoring drug use in palliative care. *Palliative Medicine*, **8**: 137-143.

van Lersberghe C, Camu F, de Keersmaecker E, Sacré S (1994) Continuous administration of fentanyl for postoperative pain: a comparison of the epidural, intravenous, and transdermal routes. *Journal of Clinical Anesthesia*, **6**: 308-314.

Van Putten T, Aravagiri M, Marder SR, Wirshing WC, Mintz J, Chabert N (1991) Plasma fluphenazine levels and clinical response in newly admitted schizophrenic patients. *Psychopharmacology Bulletin*, **27**: 91-96.

Van Putten T, Marder SR, Wirshing WC, Aravagiri M, Chabert N (1991) Neuroleptic plasma levels. *Schizophrenia Bulletin*, **17**: 197-216.

Van Rooy HH, Vermeulen NPE, Bovill JG (1981) The assay of fentanyl and its metabolites in plasma of patients using gas chromatography with alkali flame ionisation detection and gas chromatography-mass spectrometry. *Journal of Chromatography, Biomedical Applications*, **223**: 85-93.

Varvel JR, Shafer SL, Hwang SS, Coen PA, Stanski DR (1989) Absorption characteristics of transdermally administered fentanyl. *Anesthesiology*, **70**: 928-934.

Ventafridda V, Spoldi E, deConno F (1990) Control of dyspnoea in advanced cancer patients. *Chest*, **98**: 1544-5.

Verghese C, Kessel JB, Simpson GM (1991) Pharmacokinetics of neuroleptics. *Psychopharmacology Bulletin*, **27**: 551-563.

Vorum H, Jørgensen HRI, Broderson R (1993) Variation in the binding affinity of warfarin and phenprocoumon to human serum albumin in relation to surgery. *European Journal of Clinical Pharmacology*, **44**: 157-162.

Walker J, Shanks CA, Triggs EJ (1980) Clinical pharmacokinetics of alcuronium chloride in man. *European Journal of Clinical Pharmacology*, **17**: 449-457.

Walker JS, Brown KF, Shanks CA (1983) Alcuronium kinetics in patients undergoing cardiopulmonary bypass surgery. *British Journal of Clinical Pharmacology*, **15**: 237-244.

Walker JS, Shanks CA, Brown KF (1984) Altered d-tubocurarine disposition during cardiopulmonary bypass surgery. *Clinical Pharmacology and Therapeutics*, **35**: 686-694.

Walsh D (1993) Dyspnoea in advanced cancer. *The Lancet*, **342**: 450-1.

Walsh D (1994) Palliative care: management of the patient with advanced cancer. *Seminars in Oncology*, **21**: 100-16.

Walsh TD, West TS (1988) Controlling symptoms in advanced cancer. *British Medical Journal*, **296**: 477-481.

Westerling D, Höglund P, Lundin S, Svedman P (1994) Transdermal administration of morphine to healthy subjects. *British Journal of Clinical Pharmacology*, **37**: 571-576.

Whiteford HA, Peabody CA, Warner MD, Berger PA, Csernansky JG (1987) Maintenance therapies in schizophrenia. *The Medical Journal of Australia*, **147**: 240-242.

Whitlam JB, Brown KF (1981) Ultrafiltration in serum protein binding determinations. *Journal of Pharmaceutical Sciences*, **70**: 146-150.

Wierda JM, Karliczek GF, Vandenbrom RHG, Pinto I, Kersten-Kleef UW, Meijer DKF, Agoston S (1990) Pharmacokinetics and cardiovascular dynamics of pipercuronium bromide during coronary artery surgery. *Canadian Journal of Anaesthesia*, **37**: 183-191.

Wilcock A, Corcoran R, Tattersfield AE (1994) Safety and efficacy of nebulised lignocaine in patients with cancer and breathlessness. *Palliative Medicine*, **8**: 35-38.

Wilhelm D, Kemper A (1990) High-performance liquid chromatographic procedure for the determination of clozapine, haloperidol, droperidol and several benzodiazepines in plasma. *Journal of Chromatography, Biomedical Applications*, **525**: 218-224.

Wistedt B, Jørgensen A, Wiles D (1982) A depot neuroleptic withdrawal study. Plasma concentration of fluphenazine and flupenthixol and relapse frequency. *Psychopharmacology*, **78**: 301-304.

Yesavage JA, Tanke ED, Sheikh JI (1987) Tardive dyskinesia and steady-state serum levels of thiothixene. *Archives of General Psychiatry*, **44**: 913-915.

Young IH, Daviskas E, Keena VA (1989) Effect of low dose nebulised morphine on exercise endurance in patients with chronic lung disease. *Thorax*, **44**: 387-90.

Youngs EJ, Shafer SL (1994) Pharmacokinetic parameters relevant to recovery from opioids. *Anesthesiology*, **81**: 833-842.

Zech DFJ, Grond SUA, Lynch J, Dauer HG, Stollenwerk B, Lehmann KA (1992) Transdermal fentanyl and initial dose-finding with patient-controlled analgesia in cancer pain. a pilot study with 20 terminally ill cancer patients. *Pain*, **50**: 293-301.

Zech DFJ, Lehmann KA, Grond S (1994) A new treatment option for chronic cancer pain. *European Journal of Palliative Care*, **1**: 26-30.

APPENDICES 1 - 4

PART I - FLUPHENAZINE STUDY

Appendix 1: Fluphenazine study consent form

Appendix 2: Fluphenazine study data collection form

Appendix 3: SAPS & SANS questionnaires

Appendix 4: Fluphenazine patient data file

CONSENT FORM
FLUPHENAZINE STUDY

Fluphenazine (Modecate) is a drug often used alone or with other drugs to treat emotional disturbances. This joint study between the Rehabilitation and Long Term Support Service and the School of Pharmacy at the University of Tasmania is involved with measuring the levels of fluphenazine in the bloodstream of patients who have been on this drug for at least several months. Hopefully, from this study information will be gathered which can improve the use of this drug and reduce the possibility of side effects.

As a patient receiving fluphenazine you are being asked to take part in this study. This would involve having one blood sample taken (five to ten mL) to measure the level of fluphenazine. If the dosage of your medication is changed, it may be appropriate to take another blood sample for comparison. Also, we will record some data (age, sex, weight, and possibly biochemical test results) from your medical record. This information will be kept completely confidential. Your personal identification will be known only to those staff from the Rehabilitation and Long Term Support Service (Elizabeth House / Club 422) who are directly involved in the study. Staff from the School of Pharmacy will know you only by a given reference number.

Prior to participating in this research, we have to ask if you would please sign this form indicating your consent, on the understanding that:-

1. The research study will be carried out in a manner conforming with the principles set out by the National Health and Medical Research Council.

2. I comprehend the general purposes, methods, demands and possible risks, inconvenience or discomforts of the study which have been explained to me.

3. In giving my consent I acknowledge that my participation in this study is voluntary and that I may withdraw at any time.

Your continued attendance at Elizabeth House and / or Club 422 and any ongoing support given by the staff of the Rehabilitation and Long Term Support Service will in no way be affected by your participation or non-participation in the study.

Thank you.

Signature: Date:

Witnessed by: Date:

FLUPHENAZINE STUDY

CRN: Study number:

Age: Sex : Date:

Weight (kg):

Diagnosis: Approximate duration of condition (year of diagnosis)

Relevant medical history:

Current drug therapy (drugs and dosages):

Approximate duration of fluphenazine therapy:

Last fluphenazine dose (date):

Total amount of fluphenazine received over past 12 months (if determinable):

CLINICAL ASSESSMENT

Andreasen scale

Positive symptoms: *Negative symptoms:*

Biddisch Behavioural Assessment Scale (and date of assessment):

Case manager:

Extrapyramidal movement disorders:

Present mild
moderate
severe

Parkinsonism Y/N

Tardive dyskinesia Y/N

Absent

CLINICAL CHEMISTRY DATA

Serum creatinine:

Liver function:

Bilirubin:

ALT:

GGT:

AP:

Albumin:

Evidence of liver disease **Y/N**

Fluphenazine plasma level:

Other comments:

SCALE FOR ASSESSMENT OF POSITIVE SYMPTOMS (SAPS)

NAME:_____ CARD NO: __ __ (1) ID NO: __ __ __ __ __ __ __ __ __ __ (1 2 3 4 5 6 7 8 9 10)

DATE: __ __ __ __ __ __ (11 12 13 14 15 16) AGE: __ __ (17 18) SEX: __ (19) DIAGNOSIS: __ (20) MEDICATION: __ (21)

0-None 1-Questionable 2-Mild 3-Moderate 4-Marked 5-Severe

HALLUCINATIONS

1	Auditory Hallucinations The patient reports voices, noises, or other sounds that no one else hears	0 1 2 3 4 5	(27)
2	Voices Commenting The patient reports a voice which makes a running commentary on his behaviour or thoughts	0 1 2 3 4 5	(28)
3	Voices Conversing The patient reports hearing two or more voices conversing	0 1 2 3 4 5	(29)
4	Somatic or Tactile Hallucinations The patient reports experiencing peculiar physical sensations in the body	0 1 2 3 4 5	(30)
5	Olfactory Hallucinations The patient reports experiencing unusual smells which no one else notices	0 1 2 3 4 5	(31)
6	Visual Hallucinations The patient sees shapes or people that are not actually present	0 1 2 3 4 5	(32)
7	Global Rating of Hallucinations This rating should be based on the duration and severity of the hallucinations and their effects on the patient's life	0 1 2 3 4 5	(33)

DELUSIONS

8	Persecutory Delusions The patient believes he is being conspired against or persecuted	0 1 2 3 4 5	(34)
9	Delusions of Jealousy The patient believes his spouse is having an affair with someone	0 1 2 3 4 5	(35)
10	Delusions of Guilt or Sin The patient believes that he has committed some terrible sin or done something unforgiveable	0 1 2 3 4 5	(36)
11	Grandiose Delusions The patient believes he has special powers or abilities	0 1 2 3 4 5	(37)
12	Religious Delusions The patient is preoccupied with false beliefs of a religious nature	0 1 2 3 4 5	(38)
13	Somatic Delusions The patient believes that somehow his body is diseased, abnormal, or changed	0 1 2 3 4 5	(39)

14 Delusions of Reference — 0 1 2 3 4 5 (40)
The patient believes that insignificant remarks or events refer to him or have special meaning

15 Delusions of Being Controlled — 0 1 2 3 4 5 (41)
The patient feels that his feelings or actions are controlled by some outside force

16 Delusions of Mind Reading — 0 1 2 3 4 5 (42)
The patient feels that people can read his mind or know his thoughts

17 Thought Broadcasting — 0 1 2 3 4 5 (43)
The patient believes that his thoughts are broadcast so that he himself or others can hear them

18 Thought Insertion — 0 1 2 3 4 5 (44)
The patient believes that thoughts that are not his own have been inserted into his mind

19 Thought — 0 1 2 3 4 5 (45)
The patient believes that thoughts have been taken away from his mind

20 Global Rating of Delusions — 0 1 2 3 4 5 (46)
This rating should be based on the duration and persistence of the delusions and their effect on the patient's life

BIZARRE BEHAVIOUR

21 Clothing and Appearance — 0 1 2 3 4 5 (47)
The patient dresses in an unusual manner or does other strange things to alter his appearance

22 Social and Sexual Behaviour — 0 1 2 3 4 5 (48)
The patient may do things considered inappropriate, according to usual social norms, (eg. masturbating in public)

23 Aggressive and Agitated Behaviour — 0 1 2 3 4 5 (49)
The patient may behave in an aggressive, agitated manner, often unpredictably

24 Repetitive or Stereotyped Behaviour — 0 1 2 3 4 5 (50)
The patient delvelops a set of repetitive actions or rituals that he must perform over and over

25 Global Rating of Bizarre Behaviour — 0 1 2 3 4 5 (51)
This rating should reflect the type of behaviour and the extent to which it deviates from social norms

POSITIVE FORMAL THOUGHT DISORDER

26 Derailment — 0 1 2 3 4 5 (52)
A pattern of speech in which ideas slip off track onto ideas obliquely related or unrelated

27 Tangentiality — 0 1 2 3 4 5 (53)
Replying to a question in an oblique or irrelevant manner

28 Incoherence
A pattern of speech which is essentially incomprehensible at times
0 1 2 3 4 5 __ (54)

29 Illogicality
A pattern of speech in which conclusions are reached which do not follow logically
0 1 2 3 4 5 __ (55)

30 Circumstantiality
A pattern of speech which is very indirect and delayed in reaching its goal idea
0 1 2 3 4 5 __ (56)

31 Pressure of Speech
The patient's speech is rapid and difficult to interrupt: the amount of speech produced is greater than that considered normal
0 1 2 3 4 5 __ (57)

32 Distractible Speech
The patient is distracted by nearby stimuli which interrupt his flow of speech
0 1 2 3 4 5 __ (58)

33 Clanging
A pattern of speech in which sounds rather than meaningful relationships govern word choice
0 1 2 3 4 5 __ (59)

34 Global Rating of Positive Formal Thought Disorder
This rating should reflect the frequency of abnormality and degree to which it affects the patient's ability to communicate
0 1 2 3 4 5 __ (60)

SOURCES: Interview __ (73) Staff __ (74) Family __ (75) Friends __ (76) Other __ (77)

RELIABILITY: 1 2 3 4 5 __ (78) FORM NO: __ (79) __ (80)

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SCALE FOR ASSESSMENT OF NEGATIVE SYMPTOMS (SANS)

Name: _____ Card No: __ __ (1 2) ID No: __ __ __ __ __ __ __ __ (3 4 5 6 7 8 9 10)

Date: __ __ __ __ __ __ (11 12 13 14 15 16) Age: __ __ (17 18) Sex: __ __ (19 20) Diagnosis __ (21) Medication

0 = None; 2 = Questionable; 2 = Mild; 3 = Moderate; 4 = Marked; 5 = Severe

AFFECTIVE FLATTENING OR BLUNTING

1 Unchanging Facial Expression — 0 1 2 3 4 5 __ (27)
The patient's face appears wooden, changes less than expected as emotional content of discourse changes

2 Decreased Spontaneous Movements — 0 1 2 3 4 5 __ (28)
The patient shows few or no spontaneous movements, does not shift position, move extremities, etc

3 Paucity of Expressive Gestures — 0 1 2 3 4 5 __ (29)
The patient does not use hand gestures, body position etc. as an aid in expressing his ideas

4 Poor Eye Contact — 0 1 2 3 4 5 __ (30)
The patient avoids eye contact or 'stares through' interviewer even when speaking

5 Affective Nonresponsivity — 0 1 2 3 4 5 __ (31)
The patient fails to smile or laugh when prompted

6 Inappropriate Affect — 0 1 2 3 4 5 __ (32)
The patient's affect is inappropriate or incongruous not simply flat or blunted

7 Lack of Vocal Inflections — 0 1 2 3 4 5 __ (33)
Tha patient fails to show normal vocal emphasis patterns, is often monotonic

8 Global Rating of Affective Flattening — 0 1 2 3 4 5 __ (34)
This rating should focus on overall severity of symptoms, especially unresponsiveness, eye contact, facial expression, and vocal inflections

ALOGIA

9 Poverty of Speech — 0 1 2 3 4 5 __ (35)
The patient's replies to questions are restricted in amount, tend to be brief, concrete, and unelaborated

10 Poverty of Content of Speech — 0 1 2 3 4 5 __ (36)
The patient's replies are adequate in amount but tend to be vague, overconcrete, or overgeneralised, and convey little in information

11 Blocking — 0 1 2 3 4 5 __ (37)
The patient indicates, either spontaneously or with prompting, that his train of thought was interrupted

12 Increased Latency of Response — 0 1 2 3 4 5 __ (38)
The patient takes a long time to reply to questions; prompting indicates the patient is aware of the question

13 Global Rating of Alogia 0 1 2 3 4 5 __ (39)
The core feature of alogia are poverty of speech and poverty of content

AVOLITION - APATHY

14 Grooming and Hygiene 0 1 2 3 4 5 __ (40)
The patient's clothes may be sloppy or soiled, and he may have greasy hair, body odor, etc.

15 Impersistence of Work or School 0 1 2 3 4 5 __ (41)
The patient has difficulty seeking or maintaining employment, completing school work, keeping house, etc. If an inpatient, cannot persist at ward activities such as OT, playing cards, etc.

16 Physical Anergia 0 1 2 3 4 5 __ (42)
The patient tends to be physically inert. He may sit for hours or not initiate spontaneous activity

17 Global Rating of Avolition-Apathy 0 1 2 3 4 5 __ (43)
Strong weight may be given to one or two prominent symptoms if particularly striking

ANNEDONIA - ASOCIALITY

18 Recreational Interests and Activities 0 1 2 3 4 5 __ (44)
The patient may have few or no interests. Both the quality and quantity of interests should be taken into account

19 Sexual Activity 0 1 2 3 4 5 __ (45)
The patient may show a decrease in sexual interest and activity, or enjoyment when active

20 Ability to Feel Intimacy and closeness 0 1 2 3 4 5 __ (46)
The patient may display an inability to form close or intimate relationships, especially with opposite sex and family

21 Relationships with Friends and Peers 0 1 2 3 4 5 __ (47)
The patient may have few or no friends and may prefer to spend all his time isolated

22 Global Rating of Anhedonia - Asociality 0 1 2 3 4 5 __ (48)
This rating should reflect overall severity, taking into account the patient's age, family status, etc

ATTENTION

23 Social Inattentiveness 0 1 2 3 4 5 __ (49)
The patient appears uninvolved or unengaged, he may seem 'spacy'

24 Inattentiveness During Mental Status Testing 0 1 2 3 4 5 __ (50)
Tests of 'serial 75' (at least five subtractions) and spelling 'world' backwards:
Score 2 = 1 error, score 3 = 2 errors, score 4 = 3 errors

25 Global Rating of Attention 0 1 2 3 4 5 __ (51)
This rating should assess the patient's overall concentration clinically and on tests

Sources: Interview ___ (73) Staff: ___ (74) Family: ___ (75) Friends ___ (76) Other: ___ (77)

Reliability: 1 2 3 4 5 ___ (78) Form No: ___ (79) ___ (80)

REPRINTS: Nancy C Andreasen M.D., Dept Of Psychiatry Unviersity of Iowa
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Study number	ID	Age (years)	Weight (kg)	Sex	Renal dysfunction	Duration of condition (years)	Duration of FPZ therapy (years)
1	1101	50	95	Male	No	30	•
2	1093	44	113	Male	No	20	10
3	1620	47	84	Female	No	25	3
4	1716	54	•	Female	No	30	2
5	1199	56	76	Male	No	15	15
6	1019	58	66	Male	No	30	15
7	1020	55	89	Male	No	18	5
8	1062	32	•	Male	No	14	14
9	1044	34	•	Male	No	13	13
10	1052	37	80	Male	No	•	7
11	1087	34	50	Male	No	16	•
12	1033	26	86	Male	No	10	4
13	23275	39	80	Male	No	18	9
14	30089	67	63	Female	No	14	17
15	21701	60	77	Male	No	•	3
16	24288	55	91	Female	No	31	3
17	29870	48	66	Female	No	30	17
18	24535	35	68	Male	No	17	5
19	32676	50	57	Male	No	27	6
20	23673	67	100	Male	Yes	33	21
21	21571	66	89	Male	Yes	3	3
22	20450	33	83	Male	No	15	3
23	21456	46	56	Female	No	12	3
24	27086	66	95	Male	Yes	40	7

Study number	Current FPZ dose (mg/month)	Cumulative FPZ dose (12 months)	Positive symptom score	Negative symptom score	Total symptom score	Parkinsonism	Tardive dyskinesia
1	33.3	•	6	8	14	No	No
2	12.5	224.0	7	14	21	No	No
3	100.0	2000.0	9	17	26	No	No
4	50.0	675.0	4	14	18	No	No
5	100.0	1200.0	3	9	12	No	Yes
6	25.0	350.0	5	13	18	No	No
7	18.8	275.0	1	13	14	No	No
8	33.3	350.0	8	12	20	No	No
9	37.5	450.0	7	12	19	No	No
10	150.0	2175.0	19	9	28	No	No
11	100.0	1300.0	•	•	•	No	No
12	50.0	5500	0	8	8	No	No
13	37.5	450.0	6	4	10	No	No
14	75.0	975.0	6	15	21	No	No
15	25.0	325.0	11	5	16	No	No
16	50.0	650.0	2	12	14	No	No
17	50.0	600.0	8	5	13	No	No
18	100.0	1300.0	6	20	26	No	No
19	25.0	425.0	2	7	9	No	No
20	66.7	460.0	11	12	23	Yes	No
21	25.0	300.0	4	9	13	No	No
22	66.7	850.0	9	13	22	No	No
23	37.5	444.0	1	7	8	No	No
24	16.7	213.0	5	11	16	No	No

Study number	FPZ plasma level (ng/mL)	Liver dysfunction	Anticholinergic	Current FPZ dose (mg/kg/month)	all SAPS	all SANS	Antipsychotic	Within therap. range
1	0.60	No	Yes	0.35	•	•	Yes	Yes
2	1.00	No	Yes	0.11	•	•	No	Yes
3	<0.10	No	Yes	1.19	•	•	Yes	No
4	0.30	No	No	•	•	•	Yes	Yes
5	1.10	No	Yes	1.32	5	35	No	Yes
6	0.40	No	No	0.38	•	•	No	Yes
7	4.30	No	Yes	0.21	•	•	Yes	No
8	2.80	No	No	•	26	38	No	No
9	0.50	No	No	•	22	36	No	Yes
10	27.90	No	No	1.88	118	35	Yes	No
11	1.20	No	Yes	2.00	•	•	Yes	Yes
12	0.60	No	No	0.58	•	•	No	Yes
13	0.20	No	No	0.47	42	12	No	Yes
14	13.70	No	Yes	1.19	17	45	Yes	No
15	0.10	No	No	0.32	66	16	Yes	No
16	<0.10	No	No	0.55	11	47	Yes	No
17	0.50	No	No	0.76	34	14	No	Yes
18	0.40	Yes	Yes	1.47	25	79	Yes	Yes
19	0.30	No	No	0.44	8	14	No	Yes
20	0.90	No	Yes	0.67	51	48	No	Yes
21	0.20	No	No	0.28	9	24	No	Yes
22	0.70	No	No	0.80	35	47	Yes	Yes
23	0.20	No	No	0.67	6	22	No	Yes
24	0.20	No	No	0.17	5	36	No	Yes

APPENDICES 5 - 10

PART II - CARDIOPULMONARY BYPASS STUDY

Appendix 5: Drugs tested in specificity

Appendix 6: CPB consent form

Appendix 7: CPB patient information sheet

Appendix 8: CPB blood collection form

Appendix 9: CPB patient data file

Appendix 10: CPB physiological monitoring screen printout

Drugs tested in specificity

aspirin	ketoconazole
atenolol	ketorolac
bisacodyl	lactulose
budesonide	metformin
bumetanide	metoclopramide
carbamazepine	metoprolol
cephalexin	morphine
cimetidine	naproxen
clonazepam	nifedipine
cyclizine	nystatin
dexamethasone	paracetamol
diazepam	phenytoin sodium
diclofenac	potassium chloride
digoxin	prednisolone
diltiazem	ranitidine
docusate sodium	senna
enalapril	simvastatin
glibenclamide	sodium valproate
glyceryl trinitrate	temazepam
haloperidol	tiaprofenic acid
isosorbide mononitrate	

ROYAL HOBART HOSPITAL
CONSENT TO PARTICIPATE IN A RESEARCH PROJECT

I,.....
of.....
have been invited to participate in a research project entitled:
Pharmacokinetics of Drugs used in Coronary Surgery.
The aim of this project is to study drug use in cardiopulmonary bypass.
In relation to this project I have been informed of the following points:

1) Approval has been given by the Ethics Committee of the Royal Hobart Hospital.
2) The results which will be obtained may not be of any direct benefit to my medical management.
3) The procedure will involve some blood samples being taken for analysis.
4) The results of any test or information regarding my medical history will not be published in any way that could reveal my identity.
5) I have been given adequate opportunity to ask questions about this project and my involvement, and I know that if I have other questions in the future I may contact Rachel Miller on (002) 202202 between the hours of 9am and 5pm.
6) I will be given a copy of this form to keep.
7) I understand that I can refuse to take part in this study, or withdraw from it at any time without affecting my medical care or my relationship with the hospital and my doctors.

After considering all of these points, I accept the invitation to participate in this project.

SIGNATURE.....
Witness's signature.....
Witness's name (print).....
Address.....
Date.....

STATEMENT BY RESEARCHER

I have explained this trial and the implications of participation in it to this patient, and believe that he/she understands it, and that this consent is based on adequate information.

SIGNATURE..... NAME.....

Patient Information Sheet

Pharmacokinetics of Drugs used in Coronary Surgery

- A number of drugs are used in Cardiopulmonary Bypass.
- The physiological status of patients is altered by Cardiopulmonary Bypass and this may affect the way the body handles the drugs.
- We are conducting a study to examine this and would like you to participate in the study as a subject.
- All this will involve is taking some blood samples for analysis.
- It won't involve any alterations to your therapy or management; it is essentially an observational study.
- The results could benefit patients undergoing Cardiopulmonary Bypass in the future.
- If you have any questions, don't hesitate to ask.

Rachel Miller
c/- Sister in charge
Cardiac ward

Pharmacokinetics of Drugs used in Coronary Surgery

Rachel Miller
School of Pharmacy ph 202202

Patient ID..... Date.....

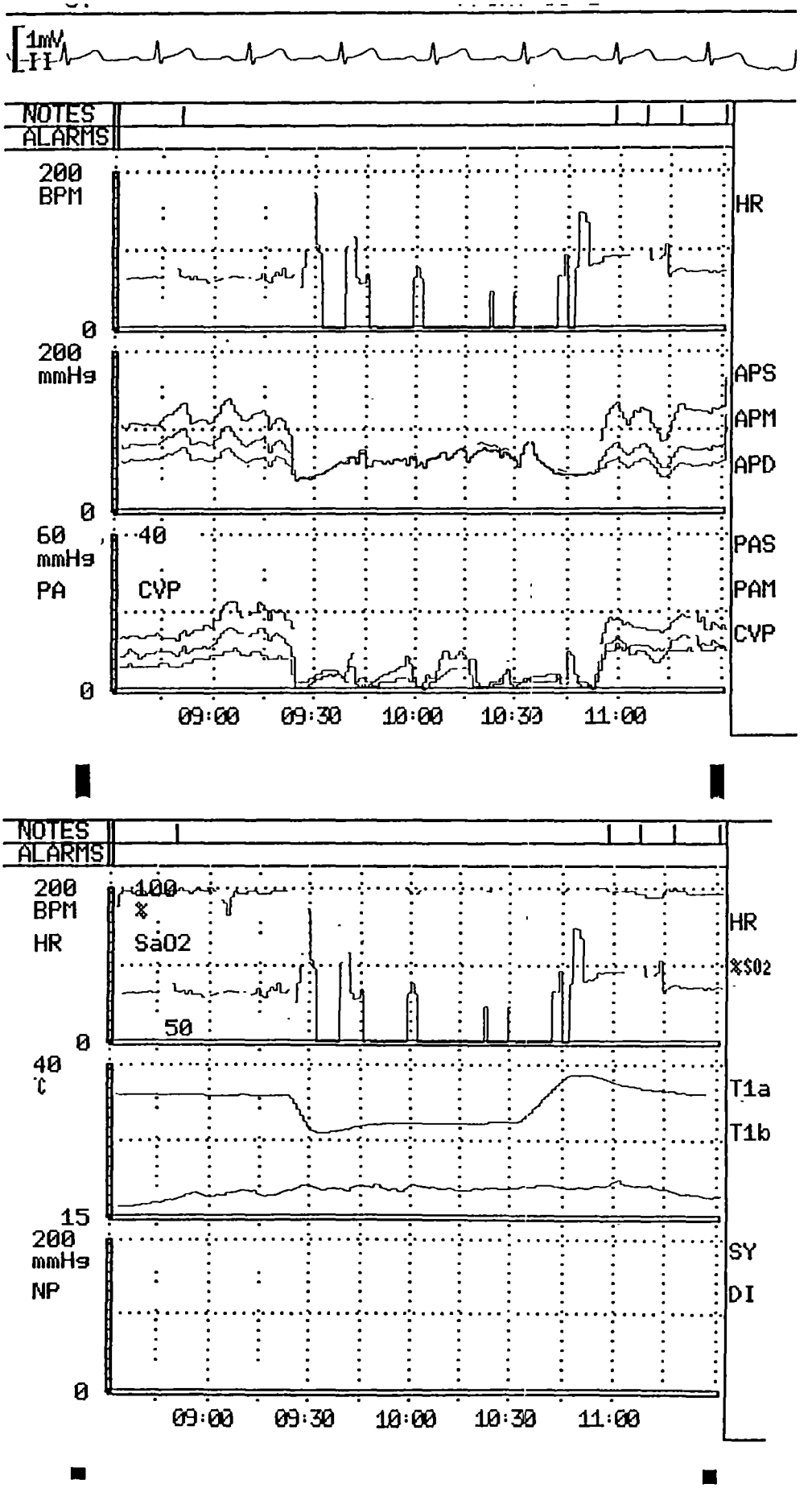
Blood Samples (7 mL into heparinised tubes)

No.	Event	Intended Time	Intended Time (clock)	Actual Time (clock)	Actual Time
1.	**Last fentanyl IV dose**	1 min after			
2.		5 min after			
3.		10 min after			
4.	**Start of bypass**	5 min after			
5.		30 min after			
6.		60 min after			
7.	**Just before rewarming**				
8.	**The end of bypass**	1 min before			
9.		1 hour after			
10.		2 hours after			
11.		3 hours after			

Study number	Age (years)	Sex	Weight (kg)	Serum creatinine (μmol/L)	Est creatinine CL (mL/min)	Alc. elimin. half-life (min)	Total fentanyl dosage (μg)
1	63	Male	86.5	116	70.5	222	3000
2	68	Male	78.0	81	85.1	233	2500
3	70	Male	72.0	139	44.5	235	2500
4	48	Male	86.8	84	116.7	68	3000
5	60	Male	81.2	84	94.9	180	2500
6	65	Female	71.4	103	54.2	225	2000
7	68	Male	85.0	136	55.2	166	3000
8	65	Male	70.6	113	57.5	220	2500
9	67	Male	66.6	108	55.3	219	2500
10	68	Male	98.5	112	77.7	222	3000
11	47	Male	68.8	85	92.4	159	2500
12	62	Male	67.6	84	77.1	177	2500
13	83	Male	92.1	88	73.2	193	2500
14	60	Female	63.0	77	68.3	247	2500
15	75	Female	76.0	62	83.2	173	2500
16	48	Male	83.8	97	97.6	167	2500

Study number	Alcuronium dose (mg)	Haemoblobin (g/L)	Alcuronium dose/kg	Duration of bypass (min)	Number of grafts	Time induction to bypass (min)	Fentanyl dose/kg
1	20	14.2	0.23	105	3	87	34.70
2	20	15.4	0.26	109	4	84	32.05
3	20	14.9	0.28	93	2	87	34.70
4	20	15.2	0.23	94	2	91	34.60
5	30	14.8	0.37	85	3	86	30.80
6	20	13.4	0.28	96	3	72	28.00
7	20	13.6	0.23	124	3	82	35.30
8	20	14.3	0.28	114	2	95	35.40
9	20	15.2	0.30	94	2	87	37.50
10	30	14.7	0.30	81	3	85	30.45
11	20	14.6	0.29	67	1	79	36.30
12	20	15.2	0.30	69	3	98	37.00
13	20	12.5	0.22	121	4	79	27.10
14	20	11.5	0.32	62	2	106	39.70
15	20	12.6	0.26	102	4	93	32.90
16	20	14.9	0.24	57	2	78	29.80

Study number	BMI	Size of fent incr. (ng/mL	% drop in Hb on bypass	% drop in fent. conc. on bypass	% drop in alc. conc. on bypass	% decrease in binding
1	28.2	5.4	38.0	33.7	14.0	•
2	24.6	-0.3	52.6	84.3	21.0	•
3	24.0	-0.4	50.3	58.8	25.0	•
4	27.1	3.1	48.0	41.5	42.0	6.6
5	25.6	1.5	48.6	57.4	37.5	5.6
6	26.9	4.5	57.5	•	18.0	18.0
7	27.4	1.4	47.1	74.5	25.0	•
8	24.7	0.8	52.5	67.0	36.0	15.1
9	23.0	0.9	44.1	70.4	32.0	5.0
10	28.5	3.7	40.8	56.3	29.0	12.9
11	24.4	1.0	43.8	55.6	16.0	13.5
12	24.8	0.3	44.1	57.1	41.0	8.2
13	27.8	3.1	45.6	45.6	39.0	15.6
14	26.2	1.3	64.3	77.8	41.0	9.1
15	29.3	3.4	49.2	56.2	21.0	15.3
16	26.7	2.3	40.9	45.5	14.5	11.6


1mV
II
NOTES
ALARMS
200
BPM
HR
0
200
mmHg
APS
APM
APD
0
60
mmHg
PA
40
CVP
PAS
PAM
CVP
0
09:00
09:30
10:00
10:30
11:00
NOTES
ALARMS
200
BPM
HR
100
%
SaO2
50
HR
%SO2
0
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°C
T1a
T1b
15
200
mmHg
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0
09:00
09:30
10:00
10:30
11:00

APPENDICES 11 - 14

PART III - SUBCUTANEOUS FENTANYL STUDY

Appendix 11: Subcutaneous fentanyl consent form

Appendix 12: Subcutaneous fentanyl patient information sheet

Appendix 13: Subcutaneous fentanyl data collection form

Appendix 14: Subcutaneous fentanyl patient data file

CONSENT TO RESEARCH STUDIES AND PROCEDURES

Surname	Christian or given names	File No.
Service No.	Sex	Age

I, _____
(First/or Given names) (Surname)

have had explained to me by the investigator Fay Abbott / Professor Ian Maddocks
(or his/her representative)

the nature and effects of the Research Study: Fentanyl Pharmacokinetics with Subcutaneous Administrat
(Title of Study) in Palliative Care Patients.

I have been provided with a Patient Information Sheet about the study which I have read and understood.

I understand that the study involves the following procedures:

You will have one blood sample taken (one or two teaspoonsful) to measure the level of fentanyl. Also, we will record some data (age, sex, weight and liver function) from your medical record. This information will be completely confidential.

- I have understood and am satisfied with the explanations that I have been given and hereby consent to the participation in the above study.
- I understand that the results of these studies may be published, but my identity will be kept confidential.
- I understand that the procedure may not be of any benefit to myself, and that I may withdraw my consent at any stage without affecting my rights or the responsibilities of the investigator in any respect.
- I understand that representatives from the Hospital Research and Ethics Committee, from the sponsoring organisation for this study and/or from Government Drug Regulatory Authorities may need to access my medical record for information related to the study. I am happy to authorise access to my medical record for this purpose.
- I declare that I am over the age of 18 years.

Signature: _____

Date: _____

Signature of Witness: _____

Date: _____

Printed Name of Witness: _____

FENTANYL PHARMACOKINETICS WITH SUBCUTANEOUS ADMINISTRATION IN PALLIATIVE CARE PATIENTS

PATIENT INFORMATION

Fentanyl is a drug often used with other drugs to help relieve pain. This study is involved with measuring the levels of fentanyl in the bloodstream of patients who have been on this drug for at least one day. Hopefully from this study in the Palliative Care Unit, information will be gathered which may improve the use of this drug.

As a patient in the Palliative Care Unit you are being asked to take part in this research. This would involve having one blood sample taken (five to ten mL or one to two teaspoonful) to measure the level of fentanyl. Also, we will record some data (age, sex, weight, and liver function) from your medical record. This information will be completely confidential. If you have any questions please feel free to ask. If you agree to participate but change your mind during the process, you can withdraw at any time. Your decision to take part or not in this study will not affect your medical treatment or any therapy you may currently be receiving. Should you be interested in the results of the study they will be made available to you upon its completion.

Should you require further details about the study, either before, during or after the study, you may contact the investigators, Fay Abbott (Pharmacy Department) or Professor Ian Maddocks. This study has been reviewed by the Research and Ethics Committee at the Repatriation General Hospital. Should you wish to discuss the study with someone not directly involved in particular in relation to matters concerning policies, information about the conduct of the study or your rights as a participant, or should you wish to make a confidential complaint, you may contact Ms Debra Rowett (RGH 2769666).

UNIVERSITY OF TASMANIA AND REPATRIATION GENERAL HOSPITAL, DAW PARK

FENTANYL STUDY

Study number

Age Sex M/F Date

Weight (kg)

Diagnosis

Renal function

	Recent result
Date	Serum creatinine (mmol/L)

Liver function

Bilirubin	Normal/Abnormal/Unknown
ALT	Normal/Abnormal/Unknown
GGT	Normal/Abnormal/Unknown
AP	Normal/Abnormal/Unknown

Serum albumin

History of chronic liver disease?

Fentanyl details

Date of commencement of fentanyl therapy

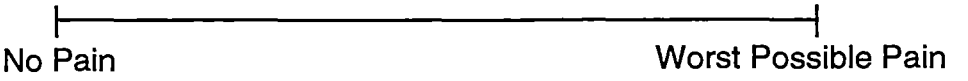
Current dosage regimen

Period of time on this dosage

Time of blood sampling

Other drug therapy

Please rate your current level of pain by marking a cross on the line



Study number	Age (years)	Sex	Diagnosis	Weight (kg)	Renal function	Liver function	Fentanyl dosage (µg/24 hours)
1	75	Male	GU	60	normal	abnormal	5000
2	84	Male	GU	55	abnormal	normal	1200
3	75	Female	Lung	60	normal	normal	1700
4	86	Male	Skin	55	normal	abnormal	2000
5	69	Female	Breast	30	normal	normal	3000
6	71	Female	GI	70	•	•	1000
7	66	Male	GI	55	normal	abnormal	800
8	67	Female	Lung	50	normal	abnormal	800
9	83	Male	GU	80	normal	abnormal	600
10	82	Male	Lung	65	normal	normal	1500
11	72	Male	Lung	75	normal	normal	800
12	84	Male	GU	50	abnormal	normal	3500
13	80	Female	Lung	45	normal	normal	1000
14	65	Female	GU	•	normal	abnormal	300
15	67	Male	GU	•	normal	normal	3000
16	75	Male	GI	75	abnormal	abnormal	750
17	66	Female	GU	85	normal	abnormal	100
18	79	Male	GI	60	normal	abnormal	1000
19	54	Female	Breast	•	normal	normal	2000
20	80	Male	Lung	75	normal	normal	300

GU - Genitourinary
GI - Gastrointestinal

Study number	Fentanyl dosage (µg/kg)	No. of other drugs	Fentanyl plasma level (ng/mL)	% free	Pain score	Albumin (g/L)	Cardiac failure
1	83.3	10	9.00	21.2	0	21	No
2	21.8	11	0.75	33.6	3.0	23	No
3	28.3	8	1.50	23.4	1.2	27	No
4	36.4	10	2.20	33.6	0	26	No
5	100.0	4	2.50	19.7	0	39	No
6	14.3	5	0.50	•	0	•	No
7	14.5	8	0.40	44.1	3.3	20	No
8	16.0	4	0.25	35.1	5.8	24	No
9	7.5	10	0.60	•	0	25	No
10	23.1	8	1.20	33.7	1.0	24	No
11	10.7	13	1.40	24.3	1.2	30	No
12	70.0	9	4.40	17.8	4.5	31	Yes
13	22.2	11	0.60	30.1	0	19	Yes
14	•	8	0.20	41.7	4.4	24	No
15	•	7	5.10	•	0	21	No
16	10.0	7	0.30	•	0	27	Yes
17	0.9	3	0.10	•	0	28	No
18	16.7	15	1.00	32.0	0	32	No
19	•	6	5.10	•	1.1	20	Yes
20	4.0	13	0.20	44.4	0	22	No

Study number	Chronic liver disease	Level to dose ratio	Presence of pain	Duration of fentanyl therapy (days)	Free level (ng/mL)	Free level to dose ratio
1	No	1.80E-3	No	157	1.90	3.80E-4
2	No	6.25E-4	Yes	2	0.25	2.10E-4
3	No	8.80E-4	Yes	30	0.35	2.10E-4
4	No	1.10E-3	No	11	0.75	3.80E-4
5	No	8.30E-4	No	13	0.50	1.70E-4
6	No	5.00E-4	No	4	•	•
7	No	5.00E-4	Yes	4	0.20	2.50E-4
8	No	3.10E-4	Yes	•	0.10	1.25E-4
9	No	1.10E-3	No	4	•	•
10	No	8.00E-4	Yes	1	0.40	2.70E-4
11	No	1.75E-3	Yes	13	0.35	4.40E-4
12	No	1.30E-3	Yes	11	0.80	2.30E-4
13	No	6.00E-4	No	9	0.20	2.00E-4
14	No	6.70E-4	Yes	3	0.10	3.30E-4
15	No	1.70E-3	No	7	•	•
16	No	4.00E-4	No	4	•	•
17	No	1.00E-3	No	4	•	•
18	Yes	1.00E-3	No	13	0.30	3.00E-4
19	No	2.50E-3	Yes	12	•	•
20	No	6.70E-4	No	3	0.10	3.30E-4

APPENDICES 15 - 16

PART IV - NEBULISED MORPHINE STUDY

Appendix 15: Nebulised morphine consent forms

Appendix 16: Nebulised morphine nurses information sheet and timing schedule

NEBULISED MORPHINE vs SALINE FOR DYSPNOEA IN PALLIATIVE CARE PATIENTS

CONSENT FORM

The aim of this study is to investigate the role of nebulised morphine in the management of breathlessness in palliative care patients.
Morphine is a commonly used drug for the relief of pain. It has also been used to ease breathing difficulties; however, its effectiveness for this purpose has not been proven. Hopefully from this study, information will be gathered which may be useful in improving the use of this drug for breathing difficulties.
As a patient in the Palliative Care Unit you are being asked to take part in this research. This would involve receiving nebulised saline then nebulised morphine and being asked to assess the degree of difficulty of breathing. Also respiratory function before and after the dose will be measured. In addition, we will record some data from your medical record. This information will be completely confidential.

If you agree to participate in this research, please sign this form, indicating your consent, on the following understanding.

1. This research study has been approved by the Royal Hobart Hospital Ethics Committee.

2. I have read this information and I comprehend the general purposes, methods, demands and possible risks, inconvenience or discomforts of the study.

3. If I do not volunteer to participate in the research study, I will still receive appropriate treatment for my condition.

4. In giving my consent I acknowledge that my participation in this study is voluntary and that I may withdraw at any time, without my treatment being affected.

5. I agree that research data gathered for the study may be published provided that I cannot be identified as a subject.

Thank you.
Further information can be obtained from Dr Dunne, or Rachel Miller or Greg Peterson at the University of Tasmania (phone: 202190)

Signature : Date :

Statement by the **investigator** :
I have explained this project and the implications of participation in it to this volunteer and I believe that the consent is informed and that he/she understands the implications of participation.

Signature of investigator : Date :

NEBULISED MORPHINE vs SALINE FOR DYSPNOEA IN PALLIATIVE CARE PATIENTS

AGREEMENT FORM FOR RELATIVES

The aim of this study is to investigate the role of nebulised morphine in the management of breathlessness in palliative care patients.
Morphine is a commonly used drug for the relief of pain. It has also been used to ease breathing difficulties; however, its effectiveness for this purpose has not been proven. Hopefully from this study, information will be gathered which may be useful in improving the use of this drug for breathing difficulties.
As a relative of a patient in the Palliative Care Unit you are being asked to allow them to take part in this research. This would involve receiving nebulised saline then nebulised morphine and being asked to assess the degree of difficulty of breathing. Respiratory function before and after the dose will also be measured. In addition, we will record some data from your relative's medical record. This information will be completely confidential.
If you agree for them to participate in this research, please sign this form, indicating your agreement, on the following understanding.

1. This research study has been approved by the Royal Hobart Hospital Ethics Committee.

2. I have read this information and I comprehend the general purposes, methods, demands and possible risks, inconvenience or discomforts of the study.

3. If I do not volunteer my relative to participate in the research study, they will still receive appropriate treatment for their condition.

4. In giving my agreement I acknowledge that my relative's participation in this study is voluntary and that I may withdraw them at any time, without their treatment being affected.

5. I agree that research data gathered for the study may be published provided that my relative cannot be identified as a subject.

Thank you.
Further information can be obtained from Dr Dunne, or Rachel Miller or Greg Peterson at the University of Tasmania (phone: 202190)

Relative's signature : Date :

Statement by the **investigator**:
I have explained this project and the implications of participation in it to this volunteer's relative and I believe that the agreement is informed and that he/she understands the implications of participation.

Signature of investigator : Date :

Nebulised morphine vs saline for dyspnoea in palliative care patients

Dyspnoea, or difficulty in breathing, occurs in up to 70% of patients with terminal cancer at some point during the course of their illness and is a very difficult symptom to manage.

Nebulised morphine is now commonly used in palliative care units to manage dyspnoea although its benefit has not clearly been proven, or indeed studied in any clinical trials.

The present trial is designed to determine the effect of low dose nebulised morphine on the intensity of dyspnoea in terminally ill cancer patients.

All patients at the Whittle Ward with dyspnoea due to advanced cancer will be asked to participate in the study. It is hoped that approximately 15-20 patients will be recruited over the course of the study. All patients (or their relatives) who agree to participate will be required to fill out a consent form.

A baseline assessment of the intensity of dyspnoea will be made using a visual analogue scoring system.

A baseline measurement of FEV_1 and FVC will be taken using a bedside spirometer.

After daily baseline assessment, patients will receive 3 mL 0.9% normal saline, morphine 2.5 mg or morphine 5 mg on three consecutive days delivered by a nebuliser four times a day. Dyspnoea will again be measured at 1 hour after each dose. Also at 1 hour after the second dose, another reading of respiratory function will be taken.

MORPHINE vs SALINE NEBULISER STUDY: TIME SCHEDULE

Day 1: Saline (0.9%) 3 mL

- 8.30 - 9.00am Baseline dyspnoea and respiratory function
- 9.00am First dose given via nebuliser
- 10.00am Dyspnoea measured
- 1.00pm Second dose given via nebuliser
- 2.00pm Dyspnoea and respiratory function measured
- 5.00pm Third dose given via nebuliser
- 6.00pm Dyspnoea measured
- 9.00pm Fourth dose given via nebuliser
- 10.00pm Dyspnoea measured

Day 2: Morphine 2.5 mg in saline (3 mL)

- 8.30 - 9.00am Baseline dyspnoea and respiratory function
- 9.00am First dose given via nebuliser
- 10.00am Dyspnoea measured
- 1.00pm Second dose given via nebuliser
- 2.00pm Dyspnoea and respiratory function measured
- 5.00pm Third dose given via nebuliser
- 6.00pm Dyspnoea measured
- 9.00pm Fourth dose given via nebuliser
- 10.00pm Dyspnoea measured

Day 3: Morphine 5mg in saline (3 mL)

- 8.30 - 9.00am Baseline dyspnoea and respiratory function
- 9.00am First dose given via nebuliser
- 10.00am Dyspnoea measured
- 1.00pm Second dose given via nebuliser
- 2.00pm Dyspnoea and respiratory function measured
- 5.00pm Third dose given via nebuliser
- 6.00pm Dyspnoea measured
- 9.00pm Fourth dose given via nebuliser
- 10.00pm Dyspnoea measured

LIST OF PUBLICATIONS

Miller RS, Peterson GM, McLean S, Westhead TT, Gillies P (1995) Monitoring plasma levels of fluphenazine during chronic therapy with fluphenazine decanoate. *Journal of Clinical Pharmacy and Therapeutics,* **20**: 55-62.

Miller RS, Peterson GM, Abbott F, Maddocks I, Parker D, McLean S (1995) Plasma concentrations of fentanyl with subcutaneous infusion in palliative care patients. *British Journal of Clinical Pharmacology* (in press).