Drug Dosing in Obese Surgical Patients

by

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DECLARATION OF ORIGINALITY

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STATEMENT OF ETHICAL CONDUCT

The research associated with this thesis abides by the Australian codes on human and animal experimentation, the guidelines by the Australian National Ethics and Institutional Biosafety Committees of the University. All research including surgical patients and anaesthetists was conducted under the approval of the Tasmanian Health and Medical Human Research Ethics Committee (Approval numbers H0015795 and H0017165).

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July 2019

STATEMENT OF CO-AUTHORSHIP

Given that this thesis is presented as a sequence of papers, either published or submitted, a statement of co-authorship is provided for each chapter. Due to this thesis format some content repetition is expected.

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All publications listed resulted from work described in this thesis.

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Located in Chapter 2: *Candidate was the primary author; who in conjunction with authors 2, 3 and 4 conceived and designed the study. Candidate undertook all data collection, analysis and drafting of the manuscript. Authors 2, 3 and 4 provided input into the writing of the research article.*

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ABSTRACT

Obesity has become a global health problem, reaching epidemic proportions in developed countries. Nearly 13% of the world's population is considered obese. Obesity contributes to the development of numerous health issues, including type 2 diabetes, coronary heart disease, osteoarthritis, respiratory problems such as obstructive sleep apnoea, and certain forms of cancer. Obesity is also linked with several physiological alterations, such as increased adipose tissue mass, increased cardiac output, elevated liver enzymes and renal hyperfiltration. These physiological changes contribute to alterations in the pharmacokinetic parameters of various drugs, including their volume of distribution and clearance. Despite the increasing prevalence of obesity and its associated drug dosing challenges, obese subjects are usually not included in clinical trials during the process of drug development. Therefore, the dosing information available in current monographs of medications may not be generalisable to the obese patient population. The situation is further worsened by the lack of universally accepted dosing guidelines for obese patients.

The overall aim of the thesis was to determine current drug dosing practices in obese elective surgical patients and examine clinical outcomes in relation to dosing in this patient group. Owing to the challenges of evaluating drug dosing in some real-life obese patient settings, such as limited documentation of weight and height, presence of acute illnesses and lack of follow-up information in out-patients, intensive care unit patients and general medical patients, the author chose to study elective surgical patients, who generally have better documentation, follow-up and no acute illness. Four studies using different methodologies, including a systematic review of the published literature, two retrospective studies and a cross-sectional survey, were performed to address the overall aim of the thesis.

In the first part of the thesis, the author identified the current level of published evidence for drug doses used in obese elective surgical patients. Clinical studies of drug dosing in this patient group were selected if they had a non-obese control or comparative dosing scalar group. Thirty-three studies of six surgically related drug classes were identified: antibiotics (n=5), anticoagulants (n=7), anaesthetics (n=6), muscle relaxants (n=10), neuromuscular reversal agents (n=3) and analgesics (n=2). A variety of dose scalars and/or recommendations was observed for the different drugs. The standard 2g intravenous dose of cefazolin appeared effective in the prevention of surgical site infection (SSI) in obese individuals. Stratified dosing of enoxaparin, using body mass index (BMI), was effective for venous thromboembolism

prevention. Lean body weight was proposed as a suitable weight scalar for induction of anaesthesia with propofol, whereas total body weight was suggested for maintenance of anaesthesia with propofol and the depolarizing muscle relaxants. Ideal body weight was reported as an appropriate dosing scalar for the non-depolarizing muscle relaxants and neuromuscular reversal agents. Ideal body weight and ideal body weight plus a correction factor of 40% were reported as suitable weight scalars for post-operative analgesia with morphine. However, no drug dosing recommendation achieved an "Excellent" (level 1) rating for quality of evidence. Methodologically strong clinical outcome studies are needed to provide empirical evidence for current dosing recommendations of these drugs.

The American Society of Health System Pharmacists' guidelines and the Australian Medicines Handbook recommend an increased 3g intravenous dose of cefazolin for surgical patients ≥ 120kg as antibiotic prophylaxis. Therefore, in the second part of the thesis, the author aimed to compare the prevalence of SSIs in obese and non-obese patients (BMI ≥ 30kg/m^2 and < 30kg/m^2), and those weighing ≥ 120kg and < 120kg, who received the standard 2g dose of cefazolin preoperatively. A 5-year retrospective 1:1 case control study of cefazolin dosing was conducted in patients who underwent elective surgical procedures (general, gynaecological and orthopaedic) from 2012 to 2016 at the Royal Hobart Hospital. The 90-day prevalence of SSI was investigated. At the study site, in contrast to the aforementioned guidelines, the standard antibiotic prophylaxis practice was 2g cefazolin administered at the induction of anaesthesia. One hundred and fifty-two obese patients met the inclusion criteria and were matched with non-obese controls. Baseline characteristics were similar between groups, except for an increased prevalence of diabetes in the obese group (35.5% vs 13.2%; p<0.001), as well as an American Society of Anaesthesiologists Score of 3 (61.8% vs 17.1%; p<0.001). The prevalence of SSI in the obese group was almost double that of the non-obese group (8.6% vs 4.6%; p=0.25), and in patients weighing ≥ 120kg (n=102) compared to those weighing < 120kg (n=202) (9.8% vs 5.0%; p=0.17). With the sample size studied, the prevalence of SSI was not significantly increased in obese patients, or those weighing ≥ 120kg, who received cefazolin 2g prophylactically; however, trends toward an increase prevalence were evident. There is a clear need for large scale randomised controlled trials to examine whether a 2g or 3g cefazolin dose is adequate to prevent SSI in obese individuals. In the interim, changing local practice to use the higher dose, in line with the guidelines above, might be advisable.

Guidelines such as those of the American Society for Metabolic and Bariatric Surgery, the American College of Chest Physicians and, the National Institute for Health and Care

Excellence have suggested the use of chemoprophylaxis for venous thromboembolism (VTE), but no information on type, dose and duration was provided. In the third part of the thesis, the author performed a retrospective clinical study of enoxaparin use in obese surgical patients undergoing weight loss procedures (primary and revisional laparoscopic adjustable gastric banding), from 2013 to 2017 at the Royal Hobart Hospital and Hobart Private Hospital. The incidence of VTE and major bleeding was investigated during a 90-day follow-up period. The study included 112 and 100 patients who had undergone primary and revisional (24 band procedures and 76 port procedures) laparoscopic adjustable gastric band surgery, respectively. The majority of patients (97%) had a mild risk of VTE development according to an assessment tool from the Cleveland Clinic, USA. Despite the low VTE risk, the majority of patients received enoxaparin. All primary procedure patients received prophylactic enoxaparin, compared to 79% and 20% of revisional patients who underwent band and port procedures, respectively ($p<0.001$). Most of these patients received 40mg enoxaparin once daily. The overall VTE incidence after 90 days was 0.9% (2/212), and no major bleeding events were observed. With no procedure-specific thromboprophylaxis guidelines for bariatric surgery, and with its use based solely on the discretion of the surgeon, thromboprophylaxis may not always achieve such low VTE and bleeding incidences. Further research to provide procedure and technique-specific thromboprophylaxis evidence may improve outcomes.

The Association of Anaesthetists of Great Britain and Ireland and the Society for Obesity and Bariatric Anaesthesia's combined guidelines have suggested the use of dosing scalars other than total body weight specific for every anaesthetic drug, to improve anaesthesia outcomes. However, these dosing recommendations are based on small-scale pharmacokinetic studies and no level 1 evidence is available to support these recommendations. In the final part of the thesis, the author conducted a cross-sectional survey to determine anaesthetists' drug dosing practices for class-III obese (BMI $\geq$ 40 kg/m^2) surgical patients, explore if they had experienced increased incidences of adverse events related to drug dosing with these patients, and assess which resources they consulted for dosing advice in this population. After validation, an invitation and web link to an electronic survey was emailed to 1000 randomly selected members of the Australian and New Zealand College of Anaesthetists. There were 230 completed responses (response rate 23%). Anaesthetists frequently reported dosing class-III obese patients in keeping with current recommendations, but substantial heterogeneity in dosing practices between respondents was observed. Lean body weight was most frequently used for dosing propofol, non-depolarising muscle relaxants, sugammadex and opioids;

whereas, total body weight was most frequently used for suxamethonium. Increased incidences of adverse events related to drug dosing in class-III obese patients were commonly reported. Many anaesthetists did not use any published drug dosing resources. Until higher level drug dosing evidence is available for class-III obese patients, anaesthetists should consider current recommendations as well as exercising increased attention with dosing and clinical observation of patients.

In conclusion, it was observed that obese patients were dosed mainly based on the clinical judgment of surgeons and anaesthetists. Dosing based on clinicians' experience and personal judgement may not always achieve optimal patient outcomes. Therefore, there is a need for more evidence to guide dosing for this patient group. Obese patients are not yet identified as a special population, unlike geriatric patients, paediatric patients and pregnant women. However, the extent of physiological and associated pharmacokinetic changes are similar to these groups. There is a need for large-scale clinical studies and randomised clinical trials to identify optimal doses of drugs commonly used in these patients. Results of the studies in this thesis may serve as baseline information in the development of more robust and widely acceptable obesity-specific drug dosing guidelines.

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ABBREVIATIONS

AAG	α_1-acid glycoproteins
AAGBI	Association of Anaesthetists of Great Britain and Ireland
ABW	Adjusted body weight
ACOG	American College of Obstetricians and Gynaecologists
ACS-NSQIP	American College of Surgeons-National Surgical Quality Improvement Programme
AMH	Australian Medicines Handbook
ANZCA	Australian and New Zealand College of Anaesthetists
ASA	American Society of Anaesthesiologists
ASHP	American Society of Health-System Pharmacists
ASMBS	American Society for Metabolic and Bariatric Surgery
AUD	Australian Dollars
BD	twice daily
BIS	bispectral index score
BMI	body mass index
BSA	body surface area
CAD	coronary artery disease
CBW	corrected body weight
CDC	Centre for Disease Control and Prevention
CHF	congestive heart failure
CHEST	American College of Chest Physicians
CPAP	continuous positive airway pressure
CrCl	creatinine clearance
CSE	combined spinal epidural
CTN	Clinical Trials Network
CVS	cardiovascular system
CYP 450	cytochrome P450
DM	diabetes mellitus
DVT	deep vein thrombosis
ED_{95}	effective dose
eGFR	estimated glomerular filtration rate
GFR	glomerular filtration rate

HPH	Hobart Private Hospital
HTN	hypertension
IBW	Ideal body weight
ICD	International Classification of Disease
IDSA	Infectious Diseases Society of America
Cl_{int}	intrinsic clearance
IU	International Units
LAGB	Laparoscopic adjustable gastric banding
LBW	Lean body weight
LMWH	low molecular weight heparin
LOC	loss of consciousness
LOS	length of stay
MAStARI	Meta-Analysis of Statistics Assessment and Review Instrument
MeSH	Medical Subject Headings
MIC	minimum inhibitory concentrations
NAFLD	non-alcoholic fatty liver disease
NHMRC	National Institute for Health and Care Excellence
OA	osteoarthritis
OD	once daily
OR	odds ratios
OSA	obstructive sleep apnoea
PE	pulmonary embolism
PIH	post induction hypotension
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
Q 12 h	every 12 hours
RHH	Royal Hobart Hospital
RSI	rapid sequence induction
SBP	systolic blood pressure
SCD	sequential compression devices
SHEA	Society for Healthcare Epidemiology of America
SIS	Surgical Infection Society
SNIIRM	French National Health Care System
SOBA	Society for Obesity and Bariatric Anaesthesia

SSI	surgical site infection
TBW	Total body weight
TED	thromboembolic deterrent
TG	Australian Therapeutic Guidelines
TIVA	total intravenous anaesthesia
TOF	train of four
UFH	unfractionated heparin
UGT	uridine diphosphate glucuronosyltransferase
USA	United States of America
USD	United States Dollars
Vd	volume of distribution
V_{ss}	volume of distribution at steady state
V_z	volume of distribution during elimination phase
VTE	venous thromboembolism
WHO	World Health Organisation
95% CI	95% confidence intervals

CHAPTER ONE: Introduction

Obesity is defined as abnormal or excessive fat accumulation that presents a risk to health (1). The aetiology of obesity involves an underlying imbalance between the energy ingested from food and energy utilised. The excess energy is stored in fat cells that leads to an increase in both the number and size of the cells, which results in a higher percentage of body fat when compared to non-obese individuals (2, 3). The World Health Organization (WHO) defines a crude population measure of obesity as the Body Mass Index (BMI). The BMI is "a person's weight (in kilograms) divided by the square of their height (in metres)" (4). A person with a BMI of $\geq 30 kg/m^2$ is considered obese and those with a BMI of $\geq 40 kg/m^2$ are considered morbidly obese (4).

Obesity has become a global health problem reaching epidemic proportions. Thought initially to be only a problem of developed nations, a recent increase in the number of obese people in developing and under-developed countries confirms obesity as an international health concern (5). Obesity is the 6^{th} most significant risk factor contributing to overall disease burden, which includes diabetes mellitus (DM), cardiovascular system (CVS) problems, osteoarthritis (OA), obstructive sleep apnoea (OSA), and certain forms of cancer (6, 7). Life expectancy has been shown to be reduced by an average of 7 years due to obesity (8). Furthermore, obesity is linked to 2.8 million annual deaths worldwide (9).

According to the Centre for Disease Control and Prevention (CDC), obesity-related health costs in the United States of America (USA) amounted to USD $147 billion in 2008 (10). According to the Australian Institute of Health and Welfare, the obesity-related health costs in Australia were AUD $8.6 billion in 2011-2012, of which direct health costs (pharmaceutical products, medical consultations, referral to allied health practitioners, and hospital admissions) accounted for $3.8 billion and indirect health costs (due to absenteeism, unemployment and lost work productivity) for the remaining $4.8 billion (11).

1. 1 Prevalence of obesity

The worldwide prevalence of obesity tripled between 1975 to 2016 (12). According to the WHO, 13% (over 650 million people) of the world's adult population was obese in 2016; 15% of women and 11% of men (12). Figure 1 and Figure 2 show the worldwide prevalence of obesity in women and men, respectively, in the year 2016. The highest prevalence of obesity in both females and males was observed in the USA (37.0% and 35.5%) and Saudi Arabia

(42.3% and 30.8%) (13). The lowest prevalence in both women and men was observed in India (5.1% and 2.7%) and China (6.5% and 5.9%) (13).

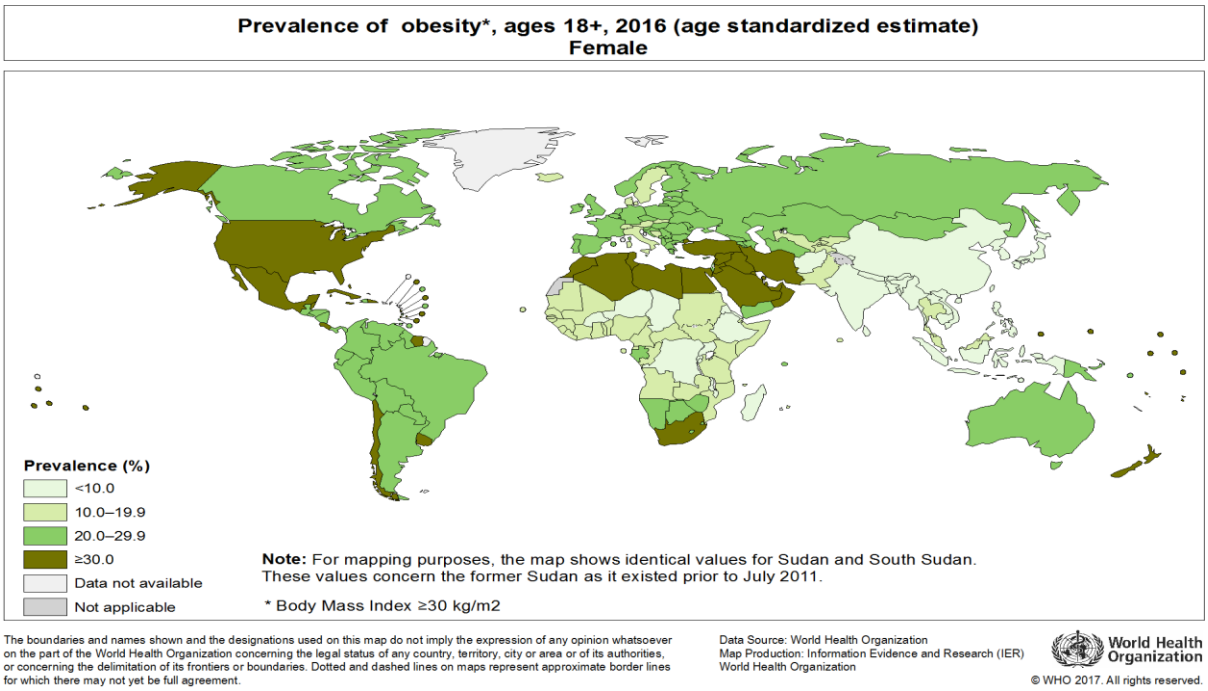

Figure 1. Worldwide prevalence of obesity in 2016 in females. This figure is reproduced from the WHO website (13)

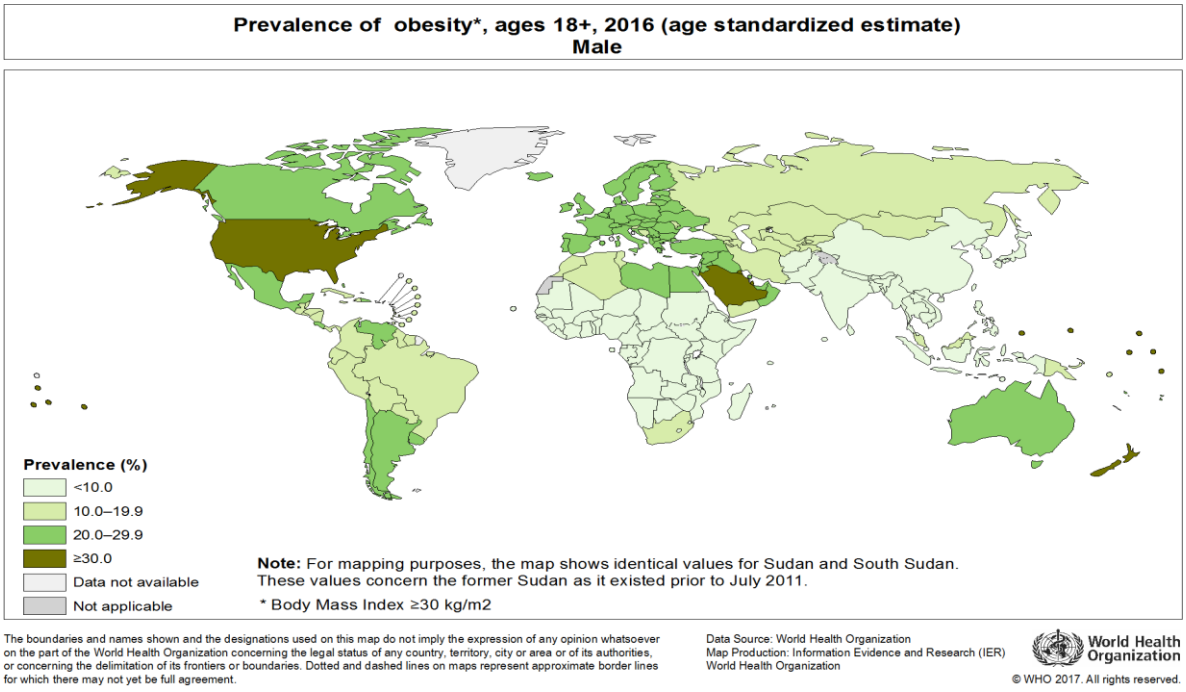

Figure 2. Worldwide prevalence of obesity in 2016 in males. This figure is reproduced from the WHO website (13)

1.2 Causes of obesity

Obesity appears to be the result of a combination of reduced physical activity, high caloric intake and genetic susceptibility (14). Drugs and endocrine abnormalities may also contribute to the development of obesity.

1.2.1 Physical inactivity

Reduced physical activity has been noted as a major contributor to obesity, in part due to technological advancements in manufacturing industries which have resulted in reduced manual labour (15). Concurrently, there has been a significant increase in the number of electronic tools/appliances used in everyday household work. For example, in the USA the percentage of houses with a washing machine rose to 79% in 2001 compared to 7% in 1960 (16). Also, leisure time activities have shifted away from walking, running and playing outdoors to watching television, internet surfing and playing computer games (17).

1.2.2 Higher caloric intake

The underlying cause of obesity is excessive calorie intake compared to calorie utilisation (12). According to the Pew Research Centre report, the average American consumed 2,481 calories daily in 2010, compared to 2,025 calories in 1970 (18). One of the main reasons for this increased caloric intake was the introduction of calorie dense food ('junk food') at cheap prices (compared to fresh fruits and vegetables) (19). Furthermore, their prices have not increased at the same rate as fresh produce. Between 1985 to 2000, for instance, the prices of fresh fruits/vegetables and dairy products increased by 118% and 56%, respectively, compared to sugar/sweets, fats/oils and carbonated drinks, which only rose 46%, 35% and 20%, respectively in the USA (20).

1.2.3 Genetic susceptibility

Genetic disorders and inheritance also play an important role in obesity development. Based on genetic variations, obesity is classified into 3 subgroups: i) monogenic obesity (due to a single gene mutation, mainly positioned in the leptin/melanocortin pathway in the central nervous system), ii) syndromic obesity (due to discrete genetic defects or chromosomal abnormalities at several genes, and can be X-linked or autosomal), and iii) polygenic obesity (a complex interaction between multiple genes and environmental factors) (21). The heritability of obesity is reported to be 40-80% (22).

1.2.4 Drug-induced obesity

Drugs can cause weight gain mainly by altering body functions such as increasing appetite, reducing mobility, lowering blood glucose levels, and altering hormonal levels. For example, tricyclic antidepressants (e.g. amitriptyline, nortriptyline) and anticonvulsants (e.g. valproic acid, lithium) cause an increase in appetite, which can lead to overeating (23). Antihypertensive drugs such as metoprolol and atenolol can cause reduced cardiac output and fatigue, which may result in reduced physical activity (23). Oral hypoglycaemics such as sulfonylureas can cause an increase in insulin release, which results in lower blood glucose levels and a subsequent increase in appetite (23). Antihistamines (cetirizine and fexofenadine) and corticosteroids can cause weight gain by increasing appetite (24, 25). Antipsychotic agents such as clozapine and olanzapine are linked to significant weight gain (26). Several mechanisms have been proposed for antipsychotics associated weight gain, such as: i) their action on dopamine (D2 and D3), muscarinic (M3), serotonin (5HT2A) and histamine (H1) receptors, ii) antipsychotic-induced imbalance between adipokines such as higher leptin level and lower adiponectin level, iii) changes in levels of gherlin hormone, which acts on the hypothalamus to enhance food intake and adipose cells deposition, and iv) the impact of antipsychotics on glucose and lipid metabolism which results in higher insulin resistance, as well as increased release of low density lipoprotein and triglycerides from adipocytes (27-30). Excessive alcohol consumption is also linked with weight gain (31). The proposed mechanisms for alcohol-induced weight gain are: inhibition of leptin and glucagon-like peptide-1 hormones, which can induce appetite (32) and, energy consumed as alcohol ("empty calories") is additive to that from other dietary sources, resulting in overall higher calories intake (33).

1.2.5 Endocrine abnormalities

Endocrine abnormalities, such as hypothyroidism and Cushing's syndrome, also cause weight gain in different ways. Thyroid hormones regulate the basal metabolic rate. Deficiency of these hormones (hypothyroidism) lowers the basal metabolic rate, which is characterised by reduced resting energy expenditure, reduced gluconeogenesis, reduced lipolysis, and increased blood cholesterol level, with weight gain (34). Cushing's syndrome is characterised by higher plasma cortisol levels (35). Cortisol plays a significant role in the breakdown of carbohydrates, fats and proteins. Higher cortisol levels promote gluconeogenesis, which causes hyperglycaemia and simultaneously increases insulin resistance, which results in hyperinsulinaemia (35). These metabolic changes result in fat accumulation at the face, neck, trunk and abdomen.

1.3 Measures of body weight and obesity

Obesity can be measured by using direct or in-indirect methods of body composition assessment, as shown in Table 1.

Table 1. Measures of body composition and obesity

Direct methods	In-direct methods
Underwater weighing.	Body mass Index.
Bioelectric impedance analysis.	Waist circumference.
Dual energy X-ray absorptiometry.	Skinfold measurement.

Direct body composition measurement techniques are more accurate compared to in-direct techniques, and unlike in-direct methods, they provide a comprehensive analysis of the body's composition. However, these techniques are not readily available to use in routine clinical practice because they require advanced equipment and skilled professionals. Therefore, direct methods are mainly used in research settings (36).

Among the indirect methods, BMI is the preferred measurement method for obesity in clinical settings (37). BMI is calculated by dividing a person's total body weight (TBW) in kilograms by the square of their height in metres (kg/m^2) (4). Depending on their calculated BMI, individuals can be grouped as either underweight, normal weight, overweight or obese. Obese individuals are further subdivided into class-I obesity, class-II obesity, and class-III or morbid obesity (Table 2). BMI has various advantages over other body composition measurement methods, as it: i) is non-invasive, ii) is relatively cheap to conduct compared to direct body composition measurement techniques, iii) is highly sensitive and specific, iv) is easy to use in routine clinical practice, and v) has well defined cut-off points based on strong reference data (37). BMI is considered the standard for categorisation of obesity in clinical practice; however, caution is required when interpreting the BMI of men and women with greater than normal muscle mass (38).

Table 2. BMI classification

Classification	BMI Range
Underweight	< 18.5kg/m^2
Normal weight	18.5 – 24.9kg/m^2
Overweight (pre-obesity)	24.9 – 29.9kg/m^2
Obesity class-I	30.0 – 34.9kg/m^2
Obesity class-II	35.0 – 39.9kg/m^2
Obesity class-III (morbid obesity)	≥ 40kg/m^2

Other in-direct methods of body composition measurement (which are mainly relevant when considering medicine dosing in a person using drugs with narrow therapeutic indices), such as ideal body weight (IBW), lean body weight (LBW) and adjusted/corrected body weight (ABW/CBW), are discussed in Chapter 2 in detail.

1.4 Consequences of obesity

Obesity may lead to a number of serious consequences, as presented in Figure 3. These will be discussed further in the following sub-sections.

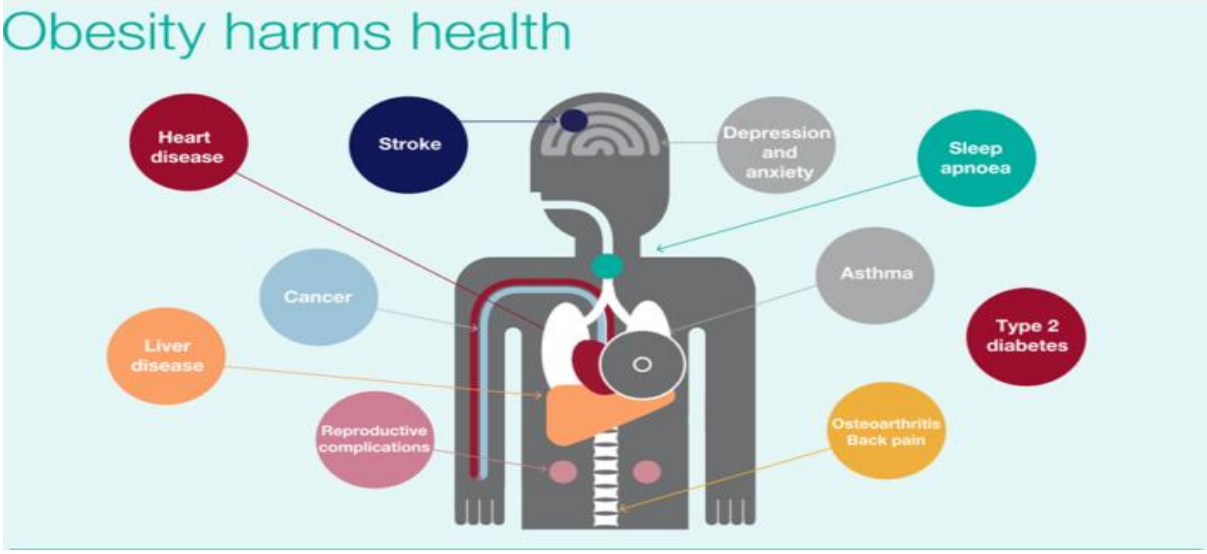

Figure 3. Consequences of obesity (39)

1.4.1 Depression and anxiety

Mental illness is an important issue linked to obesity (40). A large metanalysis of 15 studies (n=58,745) reported that the incidence of depression is 1.5 times higher in people with obesity compared to normal weight individuals (41). Similarly, another recent meta-analysis showed that obese people were 1.3 times more likely to suffer from anxiety symptoms, such as fatigue, restlessness, tenderness and muscle tension, compared to non-obese individuals (42). Psychologists have identified that obesity is considered a "stigma" because it is conceptualised as a form of physical abnormality (43). Although the exact mechanism of depression and anxiety remains unclear, biased behaviour towards obese people and social isolation are the most likely contributing factors (40).

1.4.2 Sleep apnoea

It is estimated that 58% of sleep apnoea occurrence is linked to obesity (44). Obese individuals suffer from decreased nocturnal oxygen saturation as well as increased incidences of snoring and increased maximal nocturnal sound intensity (45). The underlying cause is a reduction in residual lung volume due to elevated abdominal pressure on the diaphragm and fat deposition in the pharyngeal area and neck circumference; this causes narrowing or collapse of the pharyngeal airway and is more profound during sleep or while lying down (46).

1.4.3 Asthma

According to the American Thoracic Society report of 2010, obese individuals are 1.1 to 3.5 times more likely to develop asthma compared to non-obese individuals (47). Several mechanisms have been proposed to identify the association of obesity with asthma; however, the exact pathophysiology remains unclear (48). One proposed mechanism is the impact of obesity on lung physiology (49). Higher adiposity results in greater restriction around the abdomen and chest wall area, which can result in reduced lung capacity and most noticeably, low expiratory reserve volume; this leads to airway closure at or above functional residual capacity (50). A second potential mechanism is the effect of obesity-associated higher leptin hormone levels on the leptin receptors located on airway epithelial cells. Leptin works as a pro-inflammatory mediator. Higher amounts of plasma leptin levels can cause airways hyperresponsiveness, which can potentially impact the onset of asthma (51). Lastly, both obesity and asthma are inflammatory conditions. Therefore, higher inflammatory markers such as TNF-α, interlukin-6 and C-reactive protein in obesity can potentially worsen the asthma condition (52).

1.4.4 Type 2 diabetes

Obese individuals are 5 times more likely to have type 2 diabetes compared to normal weight individuals (53). The development of type 2 diabetes in obesity is caused by increased insulin resistance and β-cell dysfunction (54). Obesity is linked with enhanced secretion of free fatty acids from the enlarged or greater number of adipose tissues (54). These fatty acids are taken up by muscles and liver cells, and used as a source of energy instead of glucose (55). Metabolites of these fatty acid impair the insulin signalling pathway, and lead to insulin resistance which results in the development of type 2 diabetes (55). Secondly, an increase in adipose tissue is potentially associated with β-cells dysfunction; however, the exact underlying mechanism remains elusive (56). β-cells are responsible for maintaining insulin levels

according to the body's glucose levels by facilitating cellular glucose uptake. Failure to regulate glucose levels results in the development of type 2 diabetes (54).

1.4.5 Osteoarthritis

Obese individuals are 14 times more likely to develop osteoarthritis (OA) compared to normal weight individuals (57). Development of OA in obesity is related to excessive weight burden on joints, altered biochemical patterns and hormonal dysregulation (58). The proposed pathogenesis of OA in the ankle and knee is directly linked to the trauma associated with the burden of excess body weight during everyday activities (58). However, this association is not that simple because obesity-linked OA also affects non-weight bearing joints such as wrist joints, which is likely due to metabolic disorders (59). Furthermore, a direct association has been identified between metabolic disorders (hypertension, hypercholesterolemia and blood glucose) and knee OA, independent of obesity (60). This association reinforces the argument that OA related to obesity is related to associated metabolic disorders. The third proposed mechanism is the effect of proinflammatory leptin hormone on leptin receptors located in bone, cartilage and synovium (61). Obesity is characterised by higher levels of circulating leptin hormone, thereby potentially resulting in increased inflammation at receptor sites, which could lead to the development of OA (58).

1.4.6 Reproductive complications

Obesity has a profound impact on reproductive health, especially in women (62). Obese women are at increased risk of menstrual dysfunction, infertility and pregnancy-related complications compared to normal weight women (62). The risk of amenorrhoea increases by two fold with every unit increase in BMI (63). Several cohort studies have reported twice the incidence of anovulatory infertility in obese compared to normal weight women (64-66). Also, obese women are at higher risk of miscarriages, gestational diabetes and preeclampsia during pregnancy (62). A Danish cohort study reported that the hazard ratio for miscarriage is 1.23 in obese compared to non-obese women (67). Another large Canadian cohort study (n=226, 000) reported that obese women have two and three times higher risks of gestational diabetes and preeclampsia, respectively, compared to non-obese controls (68). Other pregnancy-related complications, such as pre-term birth, longer duration of labour and macrosomic foetus, are also higher in obese compared to non-obese women (62). In addition to affecting women, obesity can also negatively affect the reproductive health of men. For example, obese men are at higher risk of abnormalities such as erectile dysfunction and decreased testosterone levels

(62). The pathological mechanisms of obesity on these reproductive complications are complex, not fully elucidated and out of the scope of this thesis.

1.4.7 Liver diseases

Individuals with a BMI > 32kg/m^2 and BMI > 45kg/m^2 are 3 and 7 times more likely to develop gallstones, respectively, compared to normal weight individuals (69). Obesity is also associated with an increased amount of fat in the liver. Non-alcoholic fatty liver disease (NAFLD) is the term used to describe the liver abnormalities associated with obesity, such as elevated liver enzymes, hepatomegaly, cirrhosis, steatosis, steatohepatitis and fibrosis (70). An Italian analysis of liver biopsy specimens found that the incidence of steatosis was 4.6 times higher in obese compared to normal weight individuals (71). Gallstone formation (cholelithiasis) is associated with excess body weight due to higher cholesterol turnover (72). Cholesterol production is related to body fat: with every kg of extra body fat, an extra 20 mg of cholesterol is synthesised. Extra cholesterol is excreted in bile acid and increases the risk of cholesterol precipitation in the gallbladder, resulting in gallstones (72).

1.4.8 Cancer

Recent research has shown that every 5 kg/m^2 increase in BMI causes a 10% increase in cancer mortality (73). The risk of neoplasm of the prostate, rectum and colon is higher in obese men, while obese women have a higher risk of gallbladder and reproductive system cancers compared to their nonobese counterparts (74, 75). A large US study (n=1,444,920) in 2007 reported that 4% and 7% of newly-diagnosed cancers in men and women, respectively, might be attributed to obesity (76). Several pathological mechanisms have been proposed for different cancer types attributed to obesity, including ones that involve insulin and insulin-like growth factors, altered sex hormones, higher adipokines, and genetic susceptibility (73). However, the exact pathological mechanisms that link obesity and cancer are not fully understood (77).

1.4.9 Heart Diseases

Obesity can contribute to several forms of heart disease, such as hypertension (HTN), congestive heart failure (CHF) and coronary artery disease (CAD) (78). The risk of HTN is 6 times higher in obese compared to non-obese individuals (79). The exact mechanism of obesity-induced HTN is unclear; however, it is proposed that enhanced activity of both the renin-angiotensin and sympathetic nervous systems, as well as physical compression of the kidneys, may result in increased pressure on kidneys and higher sodium reabsorption, thus

contributing to increased blood pressure (80). With every unit increase in BMI, the risk of CHF increases by 5% and 7% for men and women, respectively (79). The increase in body weight causes an increase in cardiac weight which in turn leads to higher cardiac output (81). However, cardiac weight as a percentage of body weight in obese individuals is less compared to normal weight people. This leads to increased cardiac work, which may cause cardiomyopathy and CHF (81). Finally, with every unit increase in BMI, the risk of CAD is increased by 3.6 times (82). Obesity is associated with high cholesterol levels and low levels of high-density lipoprotein (HDL), which together can contribute to plaque formation in arteries and the development of CAD (83).

1.4.10 Stroke

Obesity is an established risk factor for stroke development. With every unit increase in BMI, a risk of stroke is increased by 6% (84). The higher incidence of stroke in obesity is explained by several indirect mechanisms, including the presence of hypertension, diabetes, atrial fibrillation, obstructive sleep apnoea and accelerated atherosclerosis (85-88). All these conditions can lead to the rupture or occlusion of arteries that result in the occurrence of stroke (89).

1.5 Physiological changes in obesity

Obesity leads to several physiological changes in the body such as both increases in adipose and lean tissue masses, enhanced cardiac output, and altered hepatic and renal functions, as summarised in Table 3 and discussed in further detail in the following subsections (90).

Table 3. Obesity-related physiological changes

Organ	Physiological changes attributed to obesity
Adipose tissue	Higher adipose tissue mass. Blood flow per gram of adipose tissues is lower compared to normal weight individuals.
Lean mass	Higher lean mass compared to normal weight individuals. Lower lean mass to adipose mass ratio.
Heart	Higher cardiac output.
Blood	Overall higher blood volume. Higher splenic, hepatic and renal blood flow.
Liver	Higher liver fat content. Altered liver enzyme activity.
Kidney	Increased kidney mass. Altered GFR. Enhanced tubular function.

GFR (Glomerular filtration rate)

1.5.1 Adipose tissues and lean mass

Adipose tissue is a connective tissue, mainly disseminated subcutaneously and in the intra-abdominal viscera. Excessive accumulation of adipose tissue mass leads to obesity (91). Increased adipose tissue mass is characterised by two patterns: hypertrophy and hyperplasia of adipose cells (91). Obese individuals have a higher amount of fat mass as well as lean mass; however, the percentage of lean mass calculated per kg of body weight is lower compared to non-obese individuals (91).

1.5.2 Cardiac function and blood flow

In obese individuals the body's blood requirement increases; therefore, heart size increases (1 mm in diameter with every 1.3kg increase in weight) to supply extra blood per beat; the amount of blood ejected by the heart with each beat is known as the stroke volume (92). The increase in stroke volume associated with obesity leads to an increase in cardiac output, which in turn leads to a higher cardiac oxygen demand (93). Despite the higher cardiac output seen in obese individuals, their cardiac performance is decreased due to an negative imbalance between cardiac oxygen supply and demand (94). Also, blood flow per gram of adipose tissue is significantly lower in obese due to the disproportionate increase in adipose tissue mass compared to non-obese individuals (95). The blood flow to the liver is also higher in obese individuals (96).

1.5.3 Hepatic changes

Obesity is associated with higher liver fat content and altered liver enzyme activity (97). Free fatty acids from adipose tissues cause NAFLD (97). The fatty liver infiltration is believed to be responsible for the alteration in liver enzyme activity (96). Furthermore, obesity is associated with an elevation in specific liver enzymes (aspartate aminotransferase, alanine aminotransferase) (98). Similarly, the impact of obesity on cytochrome P450 (CYP450) enzymes is isozyme-specific (99). Studies have shown that obesity mainly causes reduction in the activity of CYP450 3A4 (100) and, conversely, elevation of CYP450 2E1 (101) activity.

1.5.4 Renal changes

Obesity possibly affects renal function by altering the glomerular filtration rate (GFR) of obese individuals (102). It is hypothesised that higher GFR values in obese individuals is due to increased kidney mass; however, the exact physiological basis of this alteration is not well understood (103). Conversely, it is reported that GFR may also decrease in the long-term in

these individuals, possibly due to obesity-related comorbidities such as chronic kidney disease (104). It is also proposed that the increase in visceral adipose tissue compresses the kidneys physically, which leads to an increase in intrarenal pressure and higher tubular reabsorption (105). However, clinical evidence to prove this hypothesis is very weak. On the contrary, a case control study of lithium pharmacokinetics in healthy obese and non-obese subjects suggested that tubular reabsorption is decreased in obese individuals (106).

1.6 Drug pharmacokinetic changes in obesity

Drug pharmacokinetic changes attributed to obesity-related physiological alterations are outlined in Figure 4.

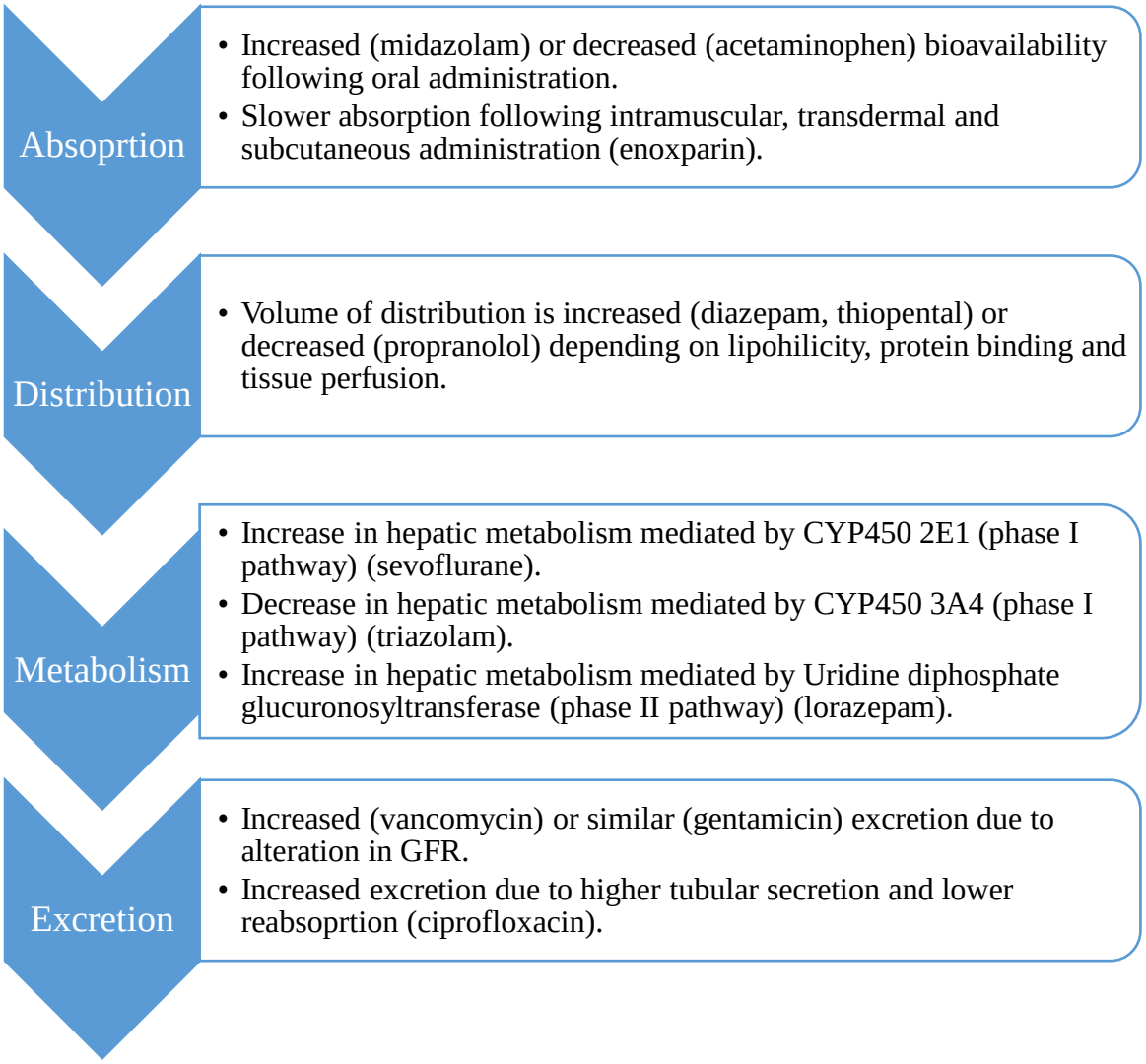

Figure 4. Impact of obesity on the pharmacokinetic handling of drugs

1.6.1 Absorption

Drug absorption denotes the mechanism by which drug leaves the administration site (oral or parenteral) and enters into the circulation. Obesity is associated with significantly higher splanchnic blood flow, accelerated gastric emptying time and higher cardiac output, all of which may alter the rate and extent of oral drug absorption (104).

However, few studies have evaluated the impact of obesity on oral drug absorption, and in those that have, the majority reported no significant differences in the rate and extent of oral absorption of the studied drugs (midazolam, propranolol, cyclosporine, dexfenfluramine, trazodone and moxifloxacin) in obese compared to non-obese individuals (107-112). However, a later prospective observational study of midazolam pharmacokinetics reported higher bioavailability in morbidly obese individuals (113). The difference between the earlier and later midazolam studies was the subjects' mean weight (<120kg vs 144kg); therefore, it is possible that the bioavailability increases only in morbidly obese patients (104). On the contrary, two case control studies of acetaminophen and levothyroxine both reported significantly lower bioavailability in obese compared to non-obese individuals, following oral administration (114, 115).

The systemic absorption of drugs administered via intramuscular, transdermal and subcutaneous routes may be affected by obesity because of the significant increase in subcutaneous fat associated with obesity (99). Once again, however, there are very few studies evaluating the impact of obesity on drugs administered via these routes. A study of subcutaneous enoxaparin compared the rate and extent of absorption in obese and non-obese individuals (116). The time to reach maximum activity was 1 hour longer in obese subjects vs non-obese; however, no difference in extent of activity was observed between the groups (116). Another randomised study of subcutaneous rapid-acting insulin absorption in type 1 diabetes mellitus obese and non-obese patients reported no difference in the absorption rate and extent of activity (117).

Overall, the current evidence of impact of obesity on absorption following oral and parenteral drug administration is limited.

1.6.2 Distribution

Volume of distribution (Vd) is the theoretical volume that would be needed to contain the total amount of administered drug at the same concentration as that of blood plasma. Vd comprises

the amount of drug in both the blood and tissues. If more drug is confined to blood (the central compartment), the drug will have a smaller Vd. If more drug is distributed to tissues (the peripheral compartment), it will have larger Vd (118). The most significant challenge to measuring Vd in a multicompartment model (i.e. blood and tissues) is the infinite number of volumes of distribution after drug administration (119). The two mostly commonly reported are volume of distribution at steady state (V_{ss}) and volume of distribution during elimination phase (V_z). V_{ss} is highly sensitive to changes in the drug distribution and is only valid at a single point in time and only if the drug is given as a continuous intravenous infusion; whereas, V_z is valid at all the times after the distribution equilibrium has been achieved (120). Therefore, V_z provides more reliable information regarding the extent of drug distribution. However, Vd information alone is not enough to determine the actual extent of distribution because the Vd of drugs depends on their lipophilicity, plasma protein binding and polarity (121). This information can only be provided by the direct measurement of drug concentration in a tissue, which is not possible in pharmacokinetic studies. Lack of this specific information complicates the issue of drug optimisation in obese individuals (122). Nevertheless, important factors which can potentially affect drug distribution in obese patients are discussed below.

Firstly, the lipophilicity of drugs affects their distribution in obese individuals because of the higher adipose tissue mass in obese individuals. As a general rule, the Vd of lipophilic drugs tends to be higher in obese individuals compared to hydrophilic drugs. For instance, diazepam (123) and thiopental (124) have higher Vd in obese subjects, and hydrophilic drugs such as gentamicin and tobramycin have lower Vd in obese individuals (125). However, this rule is not free of exceptions. For instance, cyclosporine and digoxin (both lipophilic drugs) showed decreased Vd in obese individuals when dosed based on TBW (126, 127). Similarly, the Vd of vancomycin (hydrophilic) showed a strong linear increase with increase in TBW (128). Therefore, lipophilicity alone cannot predict a change in Vd.

Protein binding is another important factor which can affect the distribution of drugs, as changes in the concentration of tissue or plasma proteins can potentially impact the movement of drugs into different tissues (104). The major plasma proteins responsible for binding of basic drugs and acidic drugs are α_1-acid glycoproteins (AAG) and albumin, respectively. Studies have reported that albumin protein concentrations are unaltered in obesity (99). Therefore, drugs such as thiopental and phenytoin which are bound mainly by albumin show no significant changes in Vd in obese individuals (124, 129). Whereas, studies of AAG have reported both increased and decreased concentrations in obesity (99). Therefore, the Vd

of AAG-bound drugs may be higher or lower in obese individuals. For instance, propranolol which is primarily bound to AAG has a smaller Vd in obese individuals because they have higher AAG concentrations compared to normal weight individuals (130).

Drug tissue penetration is another vital factor affecting drug distribution; it depends on the physiochemical properties of the drug, the rate of blood flow to the tissue, and finally on drug protein binding (121). Tissue penetration is of particular importance in cases of localised infection and perioperative prophylaxis (104). A prospective observational study reported lower subcutaneous cefazolin concentrations in obese compared to normal weight individuals (131). Another case control study of ciprofloxacin has similarly shown lower drug concentrations in the interstitial fluid of skeletal and subcutaneous tissues in obese compared to normal weight patients, despite higher plasma concentrations in the obese, thereby, suggesting TBW-based dosing be used to yield adequate tissue-site concentrations in obese patients (132).

To summarise, the effect of obesity on the Vd of drugs varies significantly in the case of lipophilic drugs, AAG bound drugs and drugs with higher tissue penetration (104).

1.6.3 Metabolism

Drug metabolism is the chemical alteration of drug by the body, typically by enzymes. The liver is the major organ involved in drug metabolism. While lean liver volume may be greater in obese individuals, the increase in lean liver volume has no reported influence on intrinsic drug clearance (Cl_{int}) (133). As previously stated, however, in obesity, NAFLD can affect both the concentration and level of activity of liver enzymes, which together can affect the drug metabolism process (104). Drug metabolism is divided into three phases.

Phase 1 metabolism of drugs (oxidation, hydrolysis and reduction) is typically done by the CYP450 enzyme system, which accounts for 75% of the metabolism of marketed drugs (90). Important isozymes include CYP450 3A4 and CYP450 2E1, which account for 50% and 5% of phase 1 metabolism, respectively (90). CYP450 2E1 is of particular importance because of its association with NAFLD (99). A study measuring CYP450 2E1 activity by estimating the conversion of chlorzoxazone to 6-hydroxychlorzoxazone (a marker of CYP450 2E1 activity) found enhanced activity in obese individuals compared to non-obese control subjects (134). Similarly, anaesthetic drugs such as sevoflurane, halothane and enflurane, all of which undergo metabolism via CYP450 2E1, showed significantly increased Cl_{int} in obese individuals (90). Conversely, a study of CYP450 3A4 activity measurement by estimating the formation of *N*-

methylerythromycin and 6β-hydroxycortisol from erythromycin and cortisol, respectively, showed reduced activity of CYP450 3A4 in obese individuals (100). As a result, substrate drugs of CYP450 3A4, such as midazolam, triazolam, carbamazepine, alprazolam, ciclosporin and alfentanil, have significantly lower Cl_{int} in obese individuals compared to their nonobese counterparts (96).

Phase 2 metabolism includes conjugation reactions such as acetylation, sulfation, glucuronidation and methylation. Uridine diphosphate glucuronosyltransferase (UGT) enzymes are responsible for 50% of phase 2 metabolism (135). UGT substrate drugs such as lorazepam (metabolised by glucuronidation), oxazepam (metabolised by glucuronidation), and acetaminophen (metabolised by glucuronidation and sulfation) have shown increased Cl_{int} in obese compared to normal weight individuals (136, 137). However, no difference in Cl_{int} was observed in obese individuals for drugs which are metabolised by other enzymes, such as N-acetyltransferase (procainamide) (138).

Limited evidence suggests that non-hepatic metabolism in adipose tissue may also play an important role in drug kinetics. For instance, a study of insulin metabolism by adipose tissues reported a 5 to 6-fold higher breakdown of insulin in the fat tissues of obese compared to lean individuals (139). Glutathione transhydrogenase (an enzyme which cleaves insulin) is present in adipose tissues; therefore, the authors concluded that the higher insulin breakdown was attributed to the higher adipose tissue mass present in obese individuals (139). Another case control study of obese and normal weight adults reported an increase in the conversion of prednisolone to prednisone in obese compared to normal weight individuals (140). The authors hypothesised that 11-hydroxysteroid dehydrogenase (an enzyme which converts prednisolone to prednisone), present in adipose tissues and in higher levels in the adipose tissue mass in obese individuals, is responsible for this increased conversion (140).

In summary, the existing literature suggests that the impact of obesity on phase 1 metabolism is isozyme-specific, such that the activity of CYP450 2E1 seems to be higher and CYP450 3A4 seems to be lower. Similarly, obesity alters various phase 2 metabolic pathways in different patterns and to different levels.

1.6.4 Excretion

Drug excretion is the removal of intact or chemically altered drug (metabolites) from the body. The kidneys are the primary excretory organs in the body, and their excretory function can be divided into three processes: glomerular filtration, tubular secretion and tubular reabsorption

(141). In clinical practice, GFR is estimated using serum creatinine (an end product of muscle breakdown). In this situation, estimated GFR is calculated by putting the creatinine value in the formula, along with various patient variables such as age, race, gender and body weight (104). The available formulae to calculate GFR have their own limitations (beyond the scope of this thesis). For instance, estimated GFR (eGFR) which is based on IBW can underestimate renal function due to the higher absolute lean mass in obese compared to non-obese individuals. Conversely, estimated creatinine clearance (CrCl), which is based on TBW, can over-estimate renal function due to the lower lean:fat mass ratio in obese compared to lean individuals (142). Furthermore, the distinction between glomerular and tubular processes overall in renal excretion is difficult to assess in routine clinical practice (104).

Different studies of GFR estimation in obese versus nonobese individuals report dissimilar findings. For instance, a case control study reported no difference in GFR and renal tissue perfusion in obese and normal weight individuals (143). Conversely, another longitudinal follow-up study reported higher GFR in obese compared to normal weight individuals (144). In line with these reported discrepancies in renal function studies, drug clearance studies have also reported erratic findings, such as increased or similar renal clearance in obese compared to non-obese individuals (145, 146). Vancomycin and gentamicin are examples of drugs which are excreted mainly by glomerular filtration (141). Vancomycin has been shown to have increased clearance in the obese (145), while no differences have been observed in the clearance of gentamicin in obese compared to non-obese individuals (146).

The impact of obesity on tubular function is difficult to measure because the majority of drugs are cleared by a combination of glomerular filtration and tubular reabsorption/secretion. For instance, lithium is excreted by both glomerular filtration and tubular reabsorption (104). A higher renal clearance of lithium was noted in obese patients compared to normal weight patients, with no difference in GFR observed; this suggests the increased clearance may possibly be due to decreased tubular reabsorption in obese patients (106). Likewise, ciprofloxacin, cimetidine and procainamide (cleared by tubular secretion and glomerular filtration) showed higher clearance in obese individuals without any proportionate increase in GFR, indicating possibly higher tubular secretion in obese individuals compared to their nonobese counterparts (138, 147, 148).

In conclusion, obesity may be associated with a higher GFR initially, but it may reduce with time because of other obesity-related comorbidities, such as chronic kidney disease (104). Tubular function seems to be enhanced in obesity (104).

1.6.5 Drugs requiring dose adjustment in obese

Examples of commonly used drugs which require dose adjustment in obese patients is presented in Table 4.

Table 4. Examples of drugs which require dose adjustment in obesity (38, 149)

Drug	Dose adjustment	Dose adjustment basis
Amikacin	ABW	Pharmacokinetic
Atracurium	LBW	Pharmacokinetic
Colistin	IBW	Pharmacokinetic
Dalteparin	TBW, dose capped	Pharmacokinetic
Daptomycin	TBW	Pharmacokinetic
Enoxaparin	TBW (VTE prophylaxis)	Pharmacokinetic
Fondaparinux	TBW (> 100 kg: 10 mg daily)	Pharmacokinetic
Gentamicin	ABW	Pharmacokinetic
Heparin	TBW (VTE treatment)	Pharmacokinetic
Morphine	LBW	Pharmacokinetic
Propofol	LBW (induction), ABW (infusion)	Pharmacokinetic
Rocuronium	LBW	Pharmacokinetic
Tinzaparin	TBW, dose capped (VTE treatment)	Pharmacokinetic
Tobramycin	ABW	Pharmacokinetic
Vancomycin	TBW	Pharmacokinetic
Vecuronium	LBW	Pharmacokinetic
Voriconazole	ABW or IBW	Pharmacokinetic

1.6.6 Additional factors affecting drug pharmacokinetics

In addition to obesity-related pharmacokinetic changes, other conditions such as fever and infection may lead to the false interpretation of pharmacokinetic changes attributed to obesity (150). Unplanned hospital admission is often accompanied by acute illnesses. A retrospective cohort study reported that 29% of unplanned admissions to a tertiary care hospital were due to fever, mainly because of infectious diseases (151). Fever and infection can affect drug pharmacokinetics in addition to obesity-related kinetic alterations.

Fever is associated with a number of systemic changes such as an increase in heart rate, higher renal blood flow, increase in splanchnic and hepatic blood flow, enzymatic changes, risk of haemorrhage, and delayed gastric emptying time due to altered gastric secretion and motility (152). Acute infection is characterised by decreased tissue perfusion (skin, muscles

and splanchnic organs), increased capillary permeability, alterations in serum protein (decrease in albumin and increase in AAG), and lower hepatic blood flow (153). These factors can all affect drug pharmacokinetics. For example, a cross-sectional study of ceftriaxone pharmacokinetics in typhoid fever patients reported a significantly larger Vd and higher clearance during the febrile compared to the afebrile period, possibly due to a combination of hypoalbuminaemia and increased capillary permeability during the febrile period (154). In another cross-sectional study, lower serum gentamicin concentrations were observed during the febrile period in healthy adults in which fever was induced using etiocholanolone (155). Similarly, a prospective study that evaluated the pharmacokinetics of gentamicin in addition to two other aminoglycosides (tobramycin and amikacin, all hydrophilic drugs and with little serum-protein binding) in patients suffering from acute infection found more than 20% increase in Vd of aminoglycosides in 60% of patients (156). Likewise, another prospective study reported a larger Vd for amikacin in sepsis patients (157). The possible reason for the larger Vd and lower plasma drug concentration is the increased capillary permeability that occurs during infection.

Other factors which can also alter the pharmacokinetic profiles of drugs are: formulation of administered product, physiochemical properties such as ionisation constant, individuals' gastrointestinal physiology, food consumption, concomitant medication use and environmental exposure to other xenobiotics (99). These factors should also be considered in drug dosing decision making for obese individuals.

1.7 Drug pharmacodynamic changes in obesity

While pharmacological research in obesity drug dosing has mainly focused on pharmacokinetic changes, this might not necessarily provide enough evidence for optimal drug dosing in this population. Genetic, nutritional and physiological changes in obesity may potentially affect the body's response to drugs via modifications in a receptor's affinity to a drug, as well as to its expression (141). Recent evidence has shown that pharmacodynamic changes play an important role in drug efficacy and toxicity (104). For instance, the greater amount of adipose tissue in obese individuals results in higher levels of leptin secretion; and increased leptin secretion reduces the differentiation and activity of macrophages on T-cells (158). Consequently, obese individuals have worse outcomes for several infectious diseases, including nosocomial infections, skin infections, periodontitis and H1N1 influenza infection

(159). Despite this, existing knowledge of obesity-affected drug pharmacodynamics is mainly limited to animal studies (99). Published studies using human subjects are limited to a handful.

A case control study reported a higher sedation mean score in obese compared to non-obese individuals after a second standard dose of triazolam, potentially due to increased psychomotor sensitivity (160). In another case control study, researchers reported that atracurium dosed based on weight, resulted in higher plasma drug concentrations in obese compared to normal weight patients; however, no difference in the duration of neuromuscular blockade was noted (161). The authors concluded that this difference may be attributed to either a desensitisation of acetylcholine receptors and/or an alteration in protein binding affinity in obese patients (161). A randomised controlled trial which measured the anaesthetic effect of propofol in gastrointestinal surgery patients reported an enhanced anaesthetic effect in obese compared to non-obese patients despite lower or equal serum propofol concentrations in obese patients (162). The authors reported that this was possibly due to an increase in central nervous system sensitivity to propofol in obese patients (162). Obesity-related insulin resistance has been thoroughly investigated as an underlying factor of type 2 diabetes mellitus in obese individuals (163). Obese patients exhibited hyperinsulinemia in the basal state and after a hyperglycaemic stimulus; thereby, resulting in higher dose requirements of exogenous insulin (163). The authors concluded that this insulin resistance is potentially a function of obesity, independent of pharmacokinetic parameters (163).

Overall, existing knowledge supports the hypothesis of some obesity-related changes in drug efficacy. However, these are just preliminary findings and further studies are required to fully elucidate the effects of obesity on the pharmacodynamics of drugs (104).

1.8 Obese elective surgical patients

It is generally understood that obese patients are more likely to undergo elective procedures, including general, cardiac, orthopaedic and liver surgeries, compared to their non-obese counterparts due to the health risks such as CAD, type 2 diabetes, osteoarthritis and NAFLD associated with obesity (164-167).

The physiological and associated pharmacokinetic and pharmacodynamic changes that can occur with obesity necessitate due consideration be given when choosing dosing strategies in obese people. Nevertheless, obese patients are not yet identified as a special population requiring special attention, unlike geriatric patients, paediatric patients and pregnant women, despite substantial physiological and associated pharmacokinetic/pharmacodynamic changes

(168). Therefore, no obesity-specific data is available at the drug development phase (168). Furthermore, studies conducted in clinical settings post-marketing are limited.

This situation gets more complicated in surgical patients because of the higher risk of harm and the common concurrent use of multiple high-risk medicines in this group of individuals. A large retrospective cohort study (n=19,844) reported that the incidence of harm (any unintended physical injury resulting from or contributed to by medical care that requires additional monitoring, treatment, or hospitalisation or that results in death) was 2.2 fold higher in surgical compared to non-surgical patients (169). Also, in the majority of surgical procedures at least four high risk medicines (aminoglycosides, potassium and electrolytes, narcotics and heparin) are used (170). In addition, being obese increases the risk of short and long term surgical complications such as longer operative time, renal failure, prolonged assisted ventilation, surgical site infection (SSI), venous thromboembolism (VTE) and mortality (171). Some of these surgical complications may be due to inappropriate drug use or dosing in these patients.

1.9 Drugs commonly used in surgery

Types of drugs used in surgical patients vary greatly and depend on the surgical procedure and the medical condition of the respective patients. The most commonly used drugs in the majority of surgical procedures are prophylactic antibiotics, prophylactic anticoagulants and anaesthetics.

Intravenous antibiotics are given to minimise the microbial burden of intra-operative contamination to a level that should not overwhelm the host defence. Commonly used antibiotics for SSI prophylaxis are cefazolin, vancomycin, gentamicin and metronidazole (172). Cefazolin is considered the first-line prophylaxis option for the majority of surgical procedures due to its good safety profile, low-procurement cost and good efficacy against the majority of gram positive and gram negative bacteria (173). Once-only administration just before surgical incision is recommended in the majority of elective surgical procedures, except for vascular surgery, which requires additional cefazolin doses for 48 hours post-surgery (174).

Subcutaneous anticoagulants are administered to surgical patients for the prevention of VTE. Commonly used anticoagulants for VTE prophylaxis in hospital are heparin, low molecular weight heparins (LWMH, such as enoxaparin, dalteparin, tinzaparin) and fondaparinux (175). Enoxaparin and dalteparin are the most commonly used agents (176). VTE prophylaxis therapy is started either pre-operatively or post-operatively ranging from once-

only use to extended use (including after hospital discharge) depending on VTE risk factors such as previous VTE, obesity, delayed mobilisation and type of surgery (177).

Anaesthetic drugs are administered to surgical patients to render them unconscious and to minimise painful stimuli. There are three types of anaesthesia: i) local ii) regional and iii) general. Local and regional anaesthesia is beneficial for minor procedures on the skin surface such as dental procedures and cataract surgery (178). General anaesthesia is required in procedures in which a) patients cannot be adequately anaesthetised with regional anaesthesia, b) prolonged deep sedation is required, c) the surgery is likely to result in significant blood loss and d) for non-cooperative patients (179). There are five major classes of anaesthetic drugs used in general anaesthesia: i) intravenous anaesthetics such as propofol and thiopental, ii) intravenous sedatives such as midazolam and ketamine, iii) intravenous narcotics such as fentanyl, alfentanil and remifentanil, iv) neuromuscular blocking drugs such as suxamethonium, atracurium and rocuronium, and v) inhalation anaesthetics such as nitrous oxide, isoflurane, and desflurane (179).

1.10 Drug dosing in obese surgical patients

In normal weight surgical patients, drugs are usually dosed either as a fixed dose or based on patients' total body weight (mg/kg). A fixed dosing regimen assumes that pharmacokinetic parameters remain unchanged with increasing body weight; whereas, dosing based on total body weight assumes a linear change in pharmacokinetic parameters with increasing body weight (180). Fixed doses may result in under-dosing and dosing based on total body weight may lead to over-dosing in obese patients (180).

Several pharmacokinetic studies have evaluated optimal dosing strategies for commonly used drugs in obese elective surgical patients, including prophylactic cefazolin (131, 181-189), prophylactic enoxaparin (190-194), propofol (195, 196), rocuronium (197), vecuronium (198), atracurium (161), fentanyl (199, 200) and remifentanil (201). However, these pharmacokinetic studies all had small sample sizes and where multiple studies exist for the same drug, reported inconsistent findings. In addition, pharmacokinetic findings are not always clinically relevant (202).

There are few international guidelines providing drug dosing recommendations for obese surgical patients, and where they exist, the majority of their recommendations are based on small-scale pharmacokinetic studies. Examples of these guidelines' recommendations are as follow. The collective guideline for surgical prophylaxis developed by the Infectious

Diseases Society of America (IDSA), American Society of Health-System Pharmacists (ASHP), Surgical Infection Society (SIS) and Society for Healthcare Epidemiology of America (SHEA), suggested an increased dose of cefazolin (3g intravenously) for patients weighing ≥ 120kg (203). Guidelines such as those of the American Society for Metabolic and Bariatric Surgery (ASMBS), the American College of Chest Physicians (CHEST) and the National Institute for Health and Care Excellence (NICE) suggested the routine use of prophylactic anticoagulant in obese patients but no dosing information is given (204-206). The Association of Anaesthetists of Great Britain and Ireland (AAGBI) and the Society for Obesity and Bariatric Anaesthesia's (SOBA) guidelines, state that dosing of anaesthetics based on total body weight (TBW) increases the risk of relative overdose and suggest some dosing strategies for obese patients (149, 207).

The pharmacokinetic basis of these guidelines and the limited amount of clinical outcome data available restricts the acceptability and applicability of recommendations in clinical settings (208). This leads to potential uncertainty among clinicians in making optimal drug dosing decision for obese patients.

1.11 Rationale of the thesis

Obesity-related pharmacokinetic changes (such as to Vd and clearance) and potential pharmacodynamic changes can result in drug toxicity and/or inadequate clinical response. For instance, higher CYP enzyme activity can convert a drug to its toxic metabolites or inactive medications or their metabolites at a faster rate in obese individuals, compared to their counterparts; this can raise both safety and efficacy concerns (141). Despite the increasing number of obese patients frequently presenting for elective surgical procedures, there is a lack of universally accepted dosing guidelines for this patient population. Also, no dosing information is available from the drug development phase meaning that the information available in drug monographs may not be applicable to the obese population (168). The situation is further complicated by the varied recommendations presented in the limited number of clinical studies of these drugs.

For antibiotic prophylaxis, cefazolin is the preferred agent in the majority of surgical procedures. The optimal dosing of prophylactic cefazolin is vital because under-dosing can result in SSI and over-dosing could lead to antimicrobial resistance and *Clostridium difficile* diarrhoea (209). The surgical prophylaxis guidelines which suggested higher than the standard 2g dose (i.e. 3g) for patients who weigh > 120kg were based on pharmacokinetic findings. Only

two clinical studies of prophylactic cefazolin dosing in obese elective surgical patients were identified (173, 202). These studies reported that a 2g prophylactic cefazolin dose was sufficient to provide antimicrobial coverage. The major limitation of these studies was the relatively low mean participant BMI (35kg/m^2 and 36kg/m^2), which may have under-represented morbidly obese patients (173, 202).

For anticoagulant prophylaxis, LMWHs are preferred agents because of their predictable anticoagulant activity (210). Similar to antibiotics prophylaxis guidelines, the majority of recommendations for prophylactic enoxaparin dosing guidelines are based on small-scale pharmacokinetic studies. Despite the relative safety of enoxaparin, suboptimal dosing can result in a VTE event or haemorrhage (210). Also, clinical studies of prophylactic enoxaparin dosing in obese surgical patients have reported inconsistent findings. Few studies have suggested that using only mechanical prophylaxis provides sufficient VTE prophylaxis and that prophylactic enoxaparin is not necessary in obese surgical patients (211-213). Conversely, other studies have suggested a higher than usual prophylactic enoxaparin dose is needed in obese patients (190, 214).

Drugs used in general anaesthesia which are easily reversible, and have fast onset and offset are preferred in obese patients: for instance, propofol (anaesthetic), suxamethonium (neuromuscular blocker), fentanyl (narcotic) and desflurane (inhalation anaesthetic) are widely used agents in obese patients (149). Even with the use of these agents, obese patients present a specific set of challenges and require tailored peri-operative dosing strategies (149). The majority of these drugs are usually titrated according to patients' response; however, a comprehensive knowledge for their initiation is essential to ensure the efficacy as well as safety of these drugs (149). Under or over-dosing of peri-operative drugs could lead to serious adverse outcomes, potentially including severe hypo- or hypertension, ineffective paralysis, incomplete reversal or opioid-induced hypoventilation (215, 216). Clinical practice studies of anaesthetic drugs have shown a wide range of dosing strategies are used in obese surgical patients. Small sample sizes and inconsistent findings from these studies form the basis of the majority of guidelines, thereby, limiting the generalisability of these guidelines to a wider population.

1.12 Aim of the thesis

Given the lack of strong clinical evidence for drug dosing strategies in obese patients, the overall aim of the thesis was to determine current drug dosing practices in obese elective

surgical patients, evaluate clinical outcomes in relation to dosing, and to generate recommendations for drug dosing practices for this group of patients.

The aims of the specific studies were as follows.

i) To gather the current drug dosing evidence for commonly used drugs in obese elective surgical patients.

ii) To evaluate the dosing practices for prophylactic antibiotics and the incidence of SSI in obese elective surgical patients.

iii) To evaluate the dosing practice for prophylactic anticoagulants and the incidences of VTE and major bleeds in obese elective surgical patients.

iv) To explore anaesthetists' dosing practices of anaesthetic drugs and to explore if they had experienced increased incidences of adverse events related to drug dosing in obese surgical patients.

1.13 Summary of chapters

To gather the current drug dosing evidence in obese elective surgical patients, the author conducted a systematic review of the literature (Chapter 2). Clinical studies of drug dosing in obese patients were selected if they had a non-obese control or comparative dosing scalar group Based on these studies, recommendations were made for dosing elective surgical obese patients. The National Health and Medical Research Council GRADE tool was used to assess the level of evidence for each recommendation of prophylactic antibiotics, prophylactic anticoagulants and anaesthetics (217).

To evaluate the drug dosing practices of prophylactic antibiotics, a 5-year (2012-2016) retrospective 1:1 case control study was conducted of obese (n=152) and non-obese (n=152) adults who underwent elective surgical procedures (general, gynaecological and orthopaedic) at a tertiary care hospital (Chapter 3). Patients' medical records were reviewed to obtain sociodemographic, drug dosing and clinical information. Inpatient, outpatient and emergency department notes were screened for up to 90 days postoperatively to identify documented SSIs.

To evaluate the drug dosing practices of prophylactic anticoagulants, a 5-year (2013-2017) retrospective study was conducted of obese patients who underwent primary and revisional weight loss surgical procedures in tertiary care hospitals (Chapter 4). Laparoscopic adjustable gastric band surgery was the only weight loss procedure performed at the study sites. The risk

of VTE in each patient was estimated using a post-discharge VTE risk assessment tool published by the Cleveland Clinic (218). The use (dose and duration) of chemoprophylaxis and the 90-day incidence of adverse outcomes (VTE and bleeding events) were identified using patients' clinical notes.

To understand anaesthetists' dosing practices of anaesthetics drugs in obese patients, a binational cross-sectional online survey of members of the Australian and New Zealand College of Anaesthetists (ANZCA) was conducted (Chapter 5). The survey consisted of questions regarding their drug dosing practices, relative incidence of adverse events related to drug dosing in obese versus nonobese patients, and the types of resources anaesthetists consult to guide drug dosing in class-III obese patients.

This thesis highlights the magnitude of potential drug dosing problems in obese surgical patients. The findings of different studies will provide a thoughtful insight to surgeons and anaesthetists about the quality of available drug dosing evidence and appropriate dosing strategies for obese surgical patients. This thesis may serve as baseline information in the development of more robust and widely acceptable obesity-specific drug dosing guidelines.

CHAPTER TWO: Peri-operative Medication Dosing in Adult Obese Elective Surgical Patients: A Systematic Review of Clinical Studies

Overview

This chapter presents a study that addresses the first objective of the thesis. It summarises the current clinical evidence of drug dosing strategies in obese electives surgical patients based on the clinical outcome studies.

This work is a reproduction of the following publication.

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2.1 Abstract

Background: Despite the increasing numbers of obese patients undergoing elective surgery, there is a lack of evidence-based dosing guidelines for peri-operative medications in obesity.

Objective: The objective was to systematically review the dosing and outcomes of peri-operative medications used in obese elective surgical patients.

Methods: Medical subject headings and general key words were used to systematically search multiple databases (PubMed, EMBASE, Cochrane Library and CINAHL). Studies of medications in obese surgical patients were included if they had a non-obese control or comparative dosing scalar group. The National Health and Medical Research Council GRADE tool was used to assess quality of evidence for each drug.

Results: Thirty-three studies of six drug classes were identified: anaesthetics (n=6), muscle relaxants (n=10), neuromuscular reversal agents (n=3), analgesics (n=2), antibiotics (n=5), and anticoagulants (n=7). A variety of dose scalars and/or recommendations was observed for various medications. Lean body weight was proposed as a suitable weight scalar for induction of anaesthesia with propofol whereas total body weight for maintenance of anaesthesia with propofol and depolarizing muscle relaxants. Ideal body weight was reported as an appropriate dosing scalar for non-depolarizing muscle relaxants and neuromuscular reversal agents. Both corrected body weight 40% and ideal body weight were reported as suitable weight scalars for post-operative analgesia with morphine. The standard 2 g dose of cefazolin appeared effective in the prevention of surgical site infection. Body mass index stratified dosing of enoxaparin was effective for venous thromboembolism prevention.

Conclusion: No drug recommendation achieved an "Excellent" quality of evidence. Limited data suggests that clinicians should consider each individual class of medication when selecting a dose for obese surgical patients. Routine use of fixed dosing regimens is likely to under- or overdose obese patients thus predisposing them to adverse drug events or treatment failure leading to patient harm.

Key Words: Anaesthetic drugs, Obese patient, Prophylactic drugs, Surgical procedures, Clinical outcomes

2.2 Introduction

The incidence of obesity is increasing at an alarming rate with more than 600 million who may be categorised as obese worldwide (219). Obese patients have been shown to have increased length of hospital stay, frequent readmissions, and to utilise greater healthcare resources than normal weight patients (220-222). Significant physiological changes in obesity lead to an altered pharmacokinetic profile of many medications (122). However, limited information is available to select the optimum dosing of medications in obese patients. This may result in under- or overdosing, consequently impacting efficacy, toxicity and clinical outcomes (180). Geriatric patients, paediatric patients and pregnant women are considered as special populations due to their significant physiological characteristics and thus require population specific data from the regulatory authority prior to drug approvals (168); no such requirements are applicable to obese patients in the presence of similar kinds of pharmacokinetic changes such as altered volume of distribution and clearance of drugs (223). Therefore, dose determining studies often exclude obese patients during the drug development phase (224). As such, doses of medications that are recommended for normal weight individuals are routinely used in obese patients potentially leading to poor patient outcomes (131, 183, 191, 192, 225).

Despite an increasing interest in obesity dosing research, most of the literature has focused on antimicrobial use (38, 226-230) with little attention directed towards other medication classes. Information about the dosing of commonly used medications in obese surgical patients such as anaesthetics, muscle relaxants, prophylactic antibiotics and anticoagulants is limited to narrative reviews and expert commentaries (208, 231-235). Given the significant number of medications that are routinely used in obese patients undergoing elective surgery, there are two crucial reasons why there is a need for a comprehensive systematic review of the relevant literature. Firstly, a review like this will provide evidence-based recommendations for dosing of routinely used medications. Secondly, it can identify specific gaps in our knowledge that can be used to design future research in this critical albeit neglected area of research.

2.3 Method

2.3.1 Study identification

A comprehensive search was performed using the PubMed, EMBASE, CINAHL and Cochrane databases during September 2016. The search was updated in May 2017 to include recently published articles. A combination of Medical Subject Headings (MeSH) and key words such

as "Therapeutic Uses"/ "Medication Use"/ "Drug Dosing"/ "Drug Therapy", "Obesity"/ "Obese"/ "Overweight", "Surgical Procedures, Operative"/ "Surgery"/ "Surgical Patient"/ "Medical Procedures" were used. No restrictions were applied to publication year, publication type and language during the systematic search. The search strategy details are provided in Appendix A. References from included studies and any published systematic reviews were screened to identify additional relevant studies.

2.3.2 Study selection

Following the removal of duplicates, the titles and abstracts of the remaining studies were screened to identify relevant studies. In cases where insufficient information was available to identify a study's suitability from its title and abstract, the full text was screened to clarify eligibility. One reviewer (ZH) independently evaluated the inclusion of each article; this was checked by a second reviewer (STRZ), and any disagreement regarding the inclusion was resolved through extensive discussion.

Following initial screening, the full text of the studies identified as potentially suitable for inclusion were reviewed. Studies were included if they were about medication outcomes in obese adults (≥18 years old) undergoing elective surgery and included a comparative group (a non-obese control and/or different dosing scalars trialled in obese groups). Studies conducted on animals, pharmacokinetic studies with no clinical outcomes, non-surgical or emergency surgery studies, studies not available in English, conference abstracts, short communications, letters to editors and reviews were excluded (Figure 5).

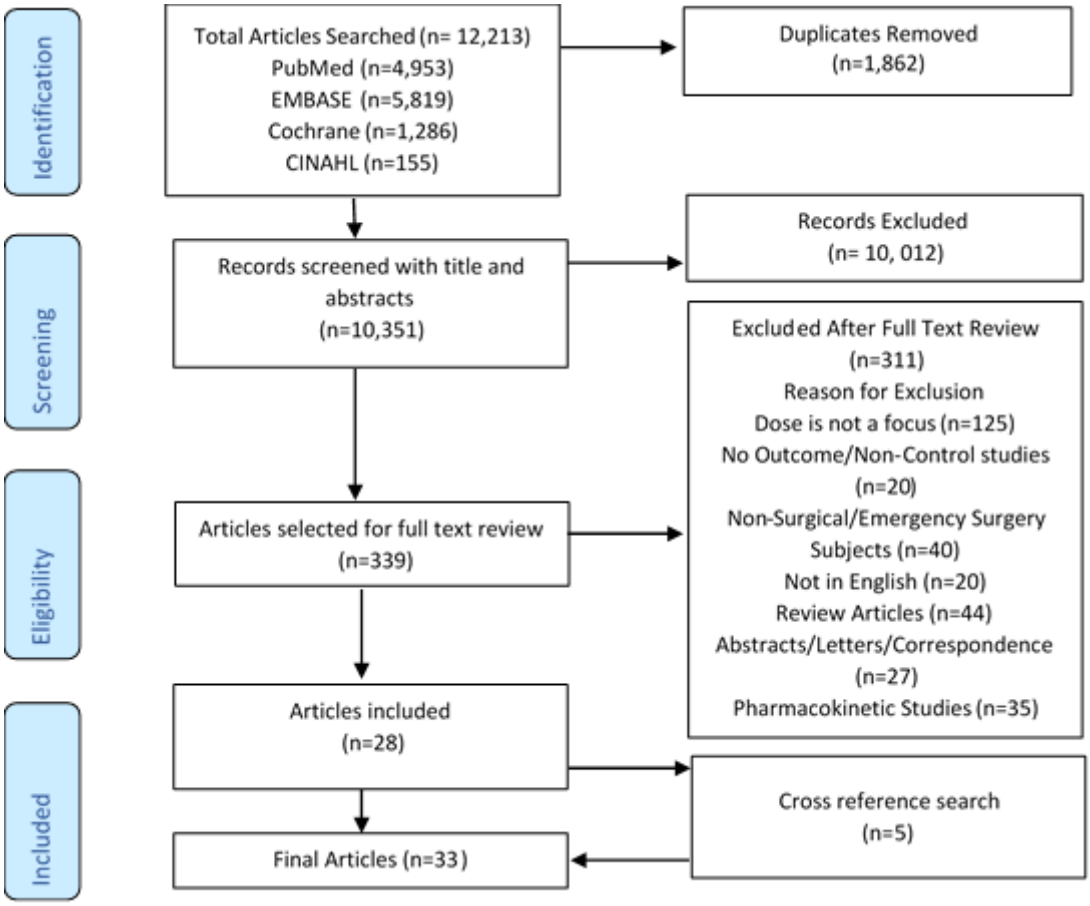

Figure 5. Flowchart of study selection

2.3.4 Data extraction and quality assessment

One reviewer (ZH) extracted the data from the included studies. A second reviewer (STRZ) did the verification of extracted data against the original studies. The following data were extracted: author, publication year, country of study, the number of subjects, subject characteristics (age range, weight or BMI range), type of surgery, study design, drug and dose, clinical outcomes, dose sufficiency and dosing scalar. Clinical outcomes were drug specific: dose requirements, loss of consciousness (LOC), and bispectral index score (BIS) for anaesthetics; recovery index and/or duration of action for muscle relaxants; reversal time and time to extubation for reversal agents; analgesic requirements and/or pain score for analgesics; incidence of surgical site infection (SSI) for antibiotics; and venous thromboembolism (VTE) and bleeding incidences for anticoagulants. The dosing scalars of total body weight (TBW), lean body weight (LBW), ideal body weight (IBW), corrected body weight 20% (CBW20), corrected body weight 40% (CBW40), corrected body weight 60% (CBW60) and body surface

area (BSA) used to achieve the associated desired clinical outcomes were investigated in this review. A detailed explanation of these dosing scalars is given in Table 5.

The systematic literature search is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Appendix B) (236). Meta-analyses were not performed due to the significant heterogeneity in study groups, methodology and outcome measures.

Risk of bias for each study was assessed using the Meta-Analysis of Statistics Assessment and Review Instrument (MAStARI) for the cohort (with control) and randomised studies (237). The MAStARI quality of each study was rated as weak, moderate or strong quality (Appendix C). The assessment of evidence level of each study and the dosing recommendation grading was done by using National Health and Medical Research Council GRADE tool (238). For the grading evaluation, risk of bias and internal consistency (evidence base and consistency) of different studies of every drug were considered (Table 7). The dosing recommendation of every drug was graded as A (Excellent), B (Good), C (low) and D (very low).

Table 5. Commonly used dosing scalars

Total Body Weight (TBW)	The actual weight in kg
Body Mass Index (BMI)	BMI is based on a height and weight ratio. BMI does not account for fat to muscle ratio. BMI equation is the same for male and female. BMI = (Weight in Kg/Height in meters^2)
Body Surface Area (BSA)	Similar to BMI, BSA is also based on height and weight. BSA is calculated the same way for males and females. BSA = [(TBW) × (height)/3600]$^{0.5}$
Ideal Body Weight (IBW)	IBW considers gender in addition to height. It does not account for fat to muscle mass ratio. IBW (kg) for male = 50 kg + 2.3 kg/each 2.54 cm over 152.5 cm IBW (kg) for female = 45.5 kg + 2.3 kg/each 2.54 cm over 152.5 cm
Corrected Body Weight (CBW)	Corrected body weight considers that obese individuals have increases lean mass compared to non-obese individuals. It is calculated by adding 20%, 40% and 60% of the difference between TBW and IBW to the person's IBW (which takes gender into account). CBW 20 (kg) = IBW + 0.2 (TBW - IBW) CBW 40 (kg) = IBW + 0.4 (TBW - IBW) CBW 60 (kg) = IBW + 0.6 (TBW - IBW)
Lean Body Weight (LBW)	LBW is the person's weight without fat mass. Many formulas are recommended to calculate LBW but Janmahasatian's* is most commonly used. LBW (kg) for male = (9270×TBW)/(6680+216×BMI) LBW (kg) for female = (9270×TBW)/(8780+244×BMI)

*Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clinical pharmacokinetics. 2005;44(10):1051-1065 [(239)]

2.4 Results

In total, 12,213 articles were identified using the initial search terms. After the initial search and search update, 28 articles met the inclusion criteria. Five additional relevant articles were identified by cross refrence search. A detailed description of each study is summarised in Table 6. Applying MAStARI, eighteen studies were rated as strong, thirteen as moderate and two of weak quality (Appendix C). The main reasons that compromised quality were missing accurate withdrawal reporting (the characteristics of patients who dropped out were not included in the final analysis), inconsistently reported outcome reliability (professionals involved in outcome measurement and/or the training of those professionals) and poor reporting of randomization procedures.

2.4.1 Anaesthetics

Six studies reported on the dosing of anaesthetics: three randomised studies investigated propofol for anaesthesia induction, one cohort study for anaesthesia maintenance, and two randomised studies were of bupivacaine dosing for combined spinal epidural (CSE) anaesthesia. The earliest report of propofol infusion in obese patients identified was by Ingrande and colleagues who compared dosing based on TBW (n=30) and LBW (n=30) in obese patients with TBW dosing in normal weight patients (n=30). A shorter time to loss of consciousness (65 sec vs. 94 sec) was observed, and a higher incidence of post induction hypotension (PIH) was noted in obese patients dosed as per TBW when compared to those dosed as per LBW (30% vs. 16%). There were no differences in LOC and PIH between obese patients dosed as per LBW and normal weight patients (240). Two more studies that did not employ a control normal weight group showed variable results (241, 242). The first study examined the effects of a single-bolus dose of propofol for induction in obese patients and found comparable BIS (48 vs. 52) and incidence of PIH (61% vs. 65%) when patients were dosed according to TBW (n=18) and CBW60 (n=20), respectively (241). The second study compared single boluses of 350 mg (n=10) and 200 mg (n=10) of propofol in obese patients and found that the higher dose resulted in more optimal mean BIS (31 vs. 53) (242). Only one study reported on the use of propofol for maintenance of anaesthesia in obese patients using doses based on CBW40. The obese group (n=8) dosed based on CBW40 were administered less propofol per kg compared to the non-obese group (n=10) who were dosed according to TBW (13.8 mg/kg vs. 21.6 mg/kg, $P<0.02$). This, resulted in a longer time to LOC (228 sec vs. 198 sec, P=NS) as well as a significantly shorter time to eye opening (10 min vs. 18 min, $P<0.05$) in the obese group (195).

Two randomized studies investigated the dose requirements of bupivacaine for combined spinal epidural (CSE) anaesthesia in obese and non-obese control groups (243, 244). The earlier study found that none of the patients in the obese (n=16) and control (n=24) groups who received more than 11.25 mg had incomplete sensory block within 15 minutes and/or required an additional dose. This study reported the comparable mean effective dose (ED_{95}) of obese and control groups as 11.9 mg and 12.8 mg (243). Likewise, another study reported similar mean times (17.4 min vs. 17.6 min) and doses (9.9 mg vs. 10.4 mg) to reach a maximum sensory block in their obese (n=54) and control (n=54) groups (244).

2.4.2 Muscle relaxants

Ten studies reported on the dosing of muscle relaxants in obese patients; nine studies were on non-depolarising, and one was on depolarising muscle relaxants. A cohort study of pancuronium dosing found higher doses were needed to achieve comparable muscle relaxation at 30 and 150-minute intervals in obese patients (n=7) compared to non-obese patients (n=7). Differences did not persist when the doses were normalised to BSA (245). Two separate cohort studies of vecuronium dosing based on 0.1 mg/kg TBW found obese patients (n=7, n=15) had a prolonged recovery index [time between 25-75% recovery of T_1] (33.0 min vs. 13.2 min, $P<0.01$) and prolonged recovery time [time between 25% recovery of T_1 and TOF ratio 0.9] (25.9 min vs. 6.9 min, $P<0.05$) respectively compared to normal weight patients (n=7, n=15) (246, 247). Three studies compared the dosing of atracurium in obese patients; two cohort studies had normal weight control groups (161, 246), whereas the third randomised did not include one (248). The randomised study found a significant difference in recovery time between obese patients who were dosed 0.5mg/kg based on either TBW (n=10) or IBW (n=9) (116.0 min vs. 60.0 min, $P<0.05$) (248). In contrast, the average recovery index reported in the first cohort study was comparable in obese (n=7) and normal weight (n=7) groups when a dose of 0.5mg/kg based on TBW was used (246). Similarly, the cohort study by Varin and co-workers used a lower dose of 0.2mg/kg based on TBW and found no differences in recovery time between obese (n=9) and normal weight (n=9) patients (161).

Four studies compared the dosing of rocuronium in obese patients (197, 249-251). Two studies (one randomised and one cohort) employed a normal weight control group (197, 249), whereas the other two randomised studies compared various dosing scalars (250, 251). The earlier randomised study compared the same dosing of rocuronium based on TBW (n=6) in obese and normal weight (n=6) patients, as well as 0.6 mg/kg based on IBW (n=6) in obese

patients (249). No significant differences were found in recovery index, and the authors suggest that IBW based dosing can be safely used in obese patients (249). Similar findings were reported by another randomised study where authors did not find any significant differences in recovery time when obese patients were dosed based on IBW (n=17), CBW20 (n=17) or CBW40 (n=17) (250). In contrast, the cohort study did not find any difference in recovery index between obese (n=6) and normal weight (n=6) patients (12.6 min vs. 12.8 min) when dosed at 0.6 mg/kg based on TBW (197). The randomised study of rocuronium for rapid sequence induction (RSI) found a shorter duration of paralysis when obese patients were dosed by LBW (n=20) compared to CBW40 (n=20) (35.0 min vs. 60.0 min, P<0.01) (251). The only randomised study of succinylcholine dosing reported that TBW (n=15) based dosing (1 mg/kg) in obese patients resulted in an appropriate recovery index (8.5 min vs. 7 min vs. 5 min, P<0.05) and excellent intubation conditions (86% vs. 46% vs. 26%, P<0.05) compared to LBW (n=15) and IBW (n=15) dosing groups (252).

2.4.3 Reversal agents

Three studies explored the dosing of sugammadex in obese patients. Two studies (one randomised and one cohort) investigated *moderate* neuromuscular block (253, 254) and one cohort study of *deep* neuromuscular block (255). The randomised study of moderate reversal found that the same dose of sugammadex (2 mg/kg) based on IBW (n=25) resulted in a prolonged reversal time (189 sec) when compared to the same dose based on IBW+40% (n=25) in obese patients (112 sec) (253). Whereas, a cohort study of moderate reversal found that dosing sugammadex (2 mg/kg) based on IBW (n=20) or TBW (n=20) resulted in similar reversal times (151 sec vs. 121 sec) (254). For reversal of *deep* neuromuscular block, a cohort study reported the undesirable prolonged reversal time of 115 sec when dosing (4 mg/kg) based on IBW (n=33) and a shorter than expected recovery time when giving the same dosing based on TBW (n=31) (87 sec). This study suggested that a dose of 4 mg/kg based on IBW + (35 to 50%) appeared suitable for deep block reversal in obese patients (255).

2.4.4 Analgesics

Two studies (one cohort and one case control) investigated the dosing of morphine in obese compared to normal weight patients (256, 257). Earlier cohort study reported the higher total morphine dosing rate during 36 to 72 hours post-operative was observed in obese (n=14) cohort compared to non-obese (n=32) cohort (1.84 mg/h vs. 1.65 mg/h). The differences in dosing rate was not significant (0.024 mg/kg/h vs. 0.028 mg/kg/h, P=NS) when normalised for IBW (256).

A later case control study found that obese patients (n=61) required higher morphine doses than non-obese patients (n=76) during 30 minutes post-operative (16.7 mg vs. 13.9 mg). The difference in the dose requirements became non-significant in both cohorts when adjusted for CBW40 (0.21 mg/kg vs 0.21 mg/kg, P=NS) (257).

2.4.5 Antibiotics

Cefazolin is the most common prophylactic antibiotic in elective surgery and was the focus of the majority of studies. Four studies (one randomised and three case control) examined the effect of obesity on cefazolin dosing and the associated incidence of SSIs. Surprisingly, none of the studies found any significant difference in SSI incidence when comparing higher doses with routinely recommended doses. One study included a non-obese control group (173), and three studies evaluated different doses in obese patients (187, 202, 258). A randomised study reported no difference in SSI incidence in obese patients who received either a 2 g (n=11) or 4 g (n=9) dose (187). The non-obese control group study reported a similar incidence of SSI in obese (n=99) and non-obese (n=96) patients administered a 2 g prophylactic dose of cefazolin (7% vs 5.2%, P=NS) (173). Similarly, two case control studies evaluating different cefazolin doses found a similar SSI incidence in obese patients following the administration of 3 g (n=160, n=284) and 2 g (n=175, n=152) doses of cefazolin (202, 258). In contrast to cefazolin, a cohort study of cefoxitin reported a higher incidence of SSI in obese patients (n=14) who received a 2 g prophylactic dose compared to non-obese patients (n=13) who received a 1 g prophylactic dose (21.4% vs 0%) (259).

2.4.6 Anticoagulants

Seven studies evaluated the dosing of prophylactic anticoagulants in obese patients: one randomised study each on nadroparin (260) and parnaparin (261) and five studies (one randomised, two cohort, two case control) on enoxaparin (190, 194, 262-264). A randomized study reported that a 5700 IU (n=30) dose of nadroparin not adjusted for BMI showed fewer bleeding events than 9500 IU (n=30) in obese patients (0% vs. 6.6%, statistical significance not reported) with no difference in VTE incidence (0% vs. 0%) (260). Another randomised study reported no differences in VTE or bleeding incidence when obese patients received either a 6400 IU dose (n=119) or 4250 IU dose (n=131) of parnaparin (261).

Enoxaparin is the most widely studied anticoagulant in obese patients. A randomised controlled trial measured the effects of enoxaparin 40 mg daily (n=44), 60 mg daily (n=44) and 40 mg twice daily (n=47) on the incidence of VTE and bleeding (194). The study found no

statistically significant differences in any outcome despite a relatively higher incidence of bleeding in the twice-daily arm when compared to the once daily dosing arms (194). The earlier cohort study reported that enoxaparin 40 mg twice daily (n=389) resulted in fewer VTE complications (0.5% vs. 5.4%) and less bleeding events (0.2% vs. 1.08%) compared to 30 mg twice daily (n=92) (262). The later cohort study of BMI (kg/m^2) startified dosing reported that 40 mg twice daily for patients with BMI 30-50 kg/m^2 (n=124) and 60 mg twice daily for patients with BMI > 50 kg/m^2 (n=99) resulted in effective VTE prophylaxis without increasing bleeding events (190). Similary, a case control study reported that BMI (kg/m^2) stratified dosing for obese patients [i.e. 30 mg BD for BMI < 40 (n=11), 40 mg BD for BMI 41-49 (n=145), 50 mg BD for BMI 50-59 (n=9) and 60 mg BD for BMI > 59 (n=5)] appeared effective without increasing the bleeding risk (263). Whereas, the second case control study reported that a 40 mg enoxaparin daily dose (n=200) resulted in significantly fewer bleeding events when compared to 40 mg twice daily (4% vs. 15%, $P<0.05$) dose (n=100), with no difference in VTE incidence (264).

Table 6. Summary of studies

Author (year) /Country	No of participants/ Body weight (range in Kg)	Surgery/Drug/Study Design	Outcome measure(s)	Result(s)	Conclusion
Anaesthetics					
Servin et al. (1993)/France [(195)]	10 Control (50-96) 8 Obese (97-160)	General/Orthopaedic Propofol/ Prospective, Cohort	Dose of propofol, loss of consciousness (LOC), time of eyes opening after anaesthesia compared in control (G 1) and obese dosed according to and CBW40 (G 2) respectively (21 mg/kg/h 5 min, 12 mg/kg/h 10 min, 6 mg/kg/h for rest of surgery)	Dose of propofol (mg/kg) G1 vs G2 = 21.6 mg/kg vs 13.8 LOC (sec) G 1 vs G2 = 198 vs 228 (P=NS) Time to eye opening (min) G 1 vs G2 = 18.4 vs 10.4 (P<0.05)	Dose based on CBW40 in obese patients resulted in longer time for LOC and shorter time in eye opening. TBW based dose appeared to be suitable for maintenance of anaesthesia.
Van Kralingen et al. (2010)/Netherlands[(242)]	20 Obese (98-176)	Bariatric surgery Propofol/ Prospective, Randomized	Bispectral index (BIS), Systolic Blood Pressure (SBP), Intubation conditions and additional dose requirements in two group of patients G 1 (n=10) = 200 mg TBW G 2 (n=10) = 350 mg TBW	BIS score (mean) G1 vs G2 = 53 vs 31 (P=0.01) Mean SBP (mm/hg) G1 vs G2 = 162 vs 122 (P=0.01) Good intubation conditions (%) G 1 vs G2 = 80 vs 100 Additional dose (n) G1 vs G2 = 2 vs 0	Varied and higher BIS values and SBP were observed in 200 mg group. Induction dose of 350 mg of propofol appeared to be beneficial over 200 mg in obese.
Ingrande et al. (2011)/USA[(240)]	30 Control (54-66*) 60 Morbidly Obese (105-156*)	General/Orthopaedic/Ear,Nose,Throat/Gynaecological Propofol/ Prospective, Randomized	Dose of propofol required for LOC in three groups G 1 (n=30) = Control (100 mg/kg/h TBW) G 2 (n=30) = Obese (100 mg/kg/h TBW) G 3 (n=30) = Obese (100 mg/kg/h LBW)	Total dose administered (mg) G1 vs G2 vs G3 = 155 vs 245 vs 183 TBW normalized dose (mg/kg) G1 vs G2 vs G3 = 2.57 vs 1.84 vs 1.41 LBW normalized dose (mg/kg) G1 vs G2 vs G3 = 3.62 vs 3.69 vs 2.76 Time to LOC (sec) G1 vs G2 vs G3 = 86 vs 65 vs 94 (P = 0.0001)	Higher propofol dose requirement and shorter time to LOC was observed in obese group when dosed based on TBW. A strong relationship was observed between LBW with total propofol dose and time to LOC across all three groups.

				Hypotension n (%) G1 vs G2 vs G3 = 3 (10%) vs 9 (30%) vs 5 (16%)	
Lam et al. (2013)/Taiwan**(241)**	38 Obese (89-134*)	Bariatric surgery Propofol/ Prospective, Randomized	Comparison of upper and lower levels of BIS, lowest systolic and diastolic blood pressure in 2 groups of patients G 1 (n=18) = 2 mg/kg TBW G 2 (n=20) = 2 mg/kg CBW60	Mean propofol dose (mg) G1 vs G2 = 217 vs 189 (P<0.05) Highest mean BIS values G1 vs G2 = 48 vs 52 (P=NS) Lowest mean BIS values G1 vs G2 = 32 vs 36 (P=NS) Lowest SBP (mmHg) G1 vs G2 = 89 vs 89 (P=NS) Lowest DBP (mmHg) G1 vs G2 = 50 vs 51 (P=NS)	Similar BIS and hemodynamic values were observed in TBW and CBW60 groups. CBW60 may be used for propofol induction of anaesthesia in obese patients.
Lee et al. (2009)/Canada**(243)**	24 Control (BMI = 19-23) 16 Obese (BMI = 31-45)	Caesarean section Bupivacaine/ Prospective, Randomized	Satisfaction Level and effective dose 95% (ED_{95}) for a complete sensory block (bilateral T_6 block) in control (G 1) and obese patients (G 2). Each group was further subdivided into 9, 9.75, 10.50, 11.25 and 12 mg.	Satisfaction Level (%) G1 vs G2 = 67 vs 87 Mean ED_{95} (mg) G1 vs G2 = 12.7 vs 11.9 (P = NS)	Similar proportion of patients achieved complete neuraxial block with equal doses in both groups. No dose alteration is required for obese patients.
Kim et al. (2012)/South Korea**(244)**	54 Control (51-59*) 54 Morbidly Obese (70-84*)	Orthopaedic Bupivacaine/ Prospective, Randomized	Peak bilateral sensory block, time to reach sensory block, the dose required (ED_{50}/ED_{90}) for operation success (no further dose required) were evaluated in control (G 1) and obese patients (G 2). Each group was further subdivided into 6 subgroups of nine patients each given 6, 7, 8, 9, 10 and 11 mg of bupivacaine dose.	Peak bilateral sensory block (mean) G1 vs G2 = $T_{7\ vs}$ T_7 (P=NS) Mean time to reach sensory block (min) G1 vs G2 = 17.6 vs 17.4 (P=NS) Mean ED_{50} (mg) G1 vs G2 = 6.9 vs 6.4 Mean ED_{90} (mg) G1 vs G2 = 10.4 vs 9.9 Operation Success (%) G1 vs G2 = 64 vs 74 (P=NS)	Same percentage of patients in both groups achieved complete neuraxial block at similar time duration with equal doses. No dose reduction is required in obese patients.

Muscle Relaxants					
Tsueda et al. (1978)/USA[245]	7 Control (59-71) 7 Obese (127-147)	Gastrectomy Gastric bypass Pancuronium/Prospective, Cohort	Dose requirements for ulnar nerve stimulation in control (G 1) vs obese (G 2) at different time intervals.	Dose requirement (mg) 30 min G1 vs G2 = 2.75 vs 3.66 (P<0.05) 60 min G1 vs G2 = 0.81 vs 1.17 (P=NS) 90 min G1 vs G2 = 0.57 vs 0.91 (P<0.05) 120 min G1 vs G2 = 0.45 vs 0.75 (P<0.05) 150 min G1 vs G2 = 0.43 vs 0.71 (P<0.05)	To maintain constant 90% depression of twitch height obese group required higher doses compared to normal weight group. BSA appeared to be a suitable dosing scalar for obese.
Weinstein et al. (1988)/ USA[246]	7 Control (48-77) 7 Obese (61-95)	Neurosurgery Vecuronium/ Prospective, Cohort	Recovery Index (25-75% recovery of T_1) compared in control (G 1) vs obese (G 2) following the administration of 0.1 mg/kg (TBW) dose	Recovery Index (min) G1 vs G2 = 13.2 vs 33.0 (P<0.01).	Delayed recovery was observed in obese group compared to normal weight groups when doses based on TBW. IBW seemed to be an appropriate dosing scalar for obese.
Suzuki et al. (2006)/Japan[247]	15 Normal Weight (49-57*) 15 Overweight (61-70*) 15 Obese (77-92*)	Gynaecological surgery Vecuronium/ Prospective, Cohort	Recovery time (TOF ratio 0.9) after the administration of vecuronium 0.1mg/kg TBW compared in 3 groups of patients G 1 = Normal weight G 2 = Overweight G 3 = Obese	Recovery time (min) G1 vs G2 vs G3 = 6.9 vs 14.6 vs 25.9 (P<0.05)	Slow recovery was observed in obese group compared to normal and overweight groups when doses based on TBW. IBW based dosing appeared appropriate in obese patients.
Weinstein et al. (1988)/ USA[246]	7 Control (48-77) 7 Obese (61-95)	Neurosurgery Atracurium/ Prospective, Cohort	Recovery Index (25-75% recovery of T_1) compared in control (G 1) vs obese (G 2) following the administration of 0.5 mg/kg (TBW) dose.	Recovery Index (min) G1 vs G2 = 9.3 vs 9.7 (P=NS)	Obese and normal weight groups had similar recovery when dosed based on TBW. TBW is a suitable weight scalar for dosing in obese patients.
Varin et al. (1990)/Canada[161]	9 Control (54-70*)	Gastroplasty Atracurium/	Recovery Index (25-75% recovery of T_1) compared in control (G 1) vs obese (G 2) following the	Recovery Index (min) G1 vs G2 = 36.1 vs 38.5 (P=NS).	Similar recovery was observed in obese and normal weight groups when dosed based in TBW. TBW

	9 Obese (110-158*)	Prospective, Cohort	administration of 0.2 mg/kg (TBW) dose.		is a suitable weight scalar for dosing in obese patients.
Van Kralingen et al. (2011)/ Netherlands[(248)]	19 Obese (112-260)	Bariatric surgery Atracurium/ Prospective, Randomized	Recovery time (TOF ratio 0.9), intubation conditions and need for neostigmine in two groups G 1 (n=10) = 0.5 mg/kg TBW G 2 (n=9) = 0.5 mg/kg IBW	Recovery time (min) G1 vs G2 = 116.0 vs 60.0 (P<0.05) Neostigmine required (n) G1 vs G2 = 7 vs 0	Significant delay in recovery was observed in obese group who dosed based on TBW compared to IBW group. IBW resulted in desirable muscle relaxation without prolonged recovery time.
Pühringer et al.(1999)/ Austria[(197)]	6 Control (55-59*) 6 Obese (77-97*)	Gynaecological surgery Rocuronium/ Prospective, Cohort	Recovery Index (25 - 75 % recovery of T_1) compared following the administration of 0.6 mg/kg TBW dose in two groups G 1 = Control G 2 = Obese	Recovery Index (min) G1 vs G2 = 12.8 vs 12.6	Similar recovery was observed in both groups when dosed based on TBW. TBW seemed an appropriate dosing scalar.
Leykin et al. (2004)/Italy[(249)]	6 Control (56-70*) 12 Obese (98-135*)	Laparoscopic Gastric Banding Rocuronium/ Prospective, Randomized	Recovery Index (25 - 75 % recovery of T_1) compared in 3 groups G 1 = 6 obese (0.6 mg/kg TBW) G 2 = 6 obese (0.6 mg/kg IBW) G 3 = 6 control (0.6 mg/kg TBW)	Recovery Index (min) G1 vs G2 vs G3 = 16.6 vs 13.6 vs 11.3 (P = NS).	Delayed recovery was observed in obese group dosed based on TBW compared to IBW obese and normal weight groups. IBW seemed an appropriate dosing scalar for rocuronium dosing.
Meyhoff et al. (2009) /Denmark[(250)]	51 Obese (89-194)	Laparoscopic Gastric Banding, Gastric Bypass Rocuronium/ Prospective, Randomized	Recovery time (TOF ratio 0.9) compared in groups G 1 (n=17) = 0.6 mg/kg IBW G 2 (n=17) = 0.6 mg/kg CBW20 G 3 (n=17) = 0.6 mg/kg CBW40	Recovery time (min) G1 vs G2 vs G3 = 63.0 vs 75.0 vs 76.0	Delayed recovery was observed in obese groups dosed based on CBW20 and CBW40 compared to IBW based dose group. IBW appeared to be a suitable scalar for rocuronium dosing.
Sakızcı-Uyar et al. (2016)/Turkey[(251)]	40 Obese (73-151)	Laparoscopic Surgery Rocuronium/ Prospective Randomized	Duration of action (time between start of injection to 25% recovery of T1) compared in two groups underwent rapid sequence induction (RSI) G 1(n=20) = 1.2 mg/kg CBW G 2 (n=20) = 1.2 mg/kg LBW	Duration of action (min) G1 vs G2 = 60.0 vs 35.0 min (P<0.01)	Prolonged duration of action was observed in CBW dose group compared to LBW dose group. For RSI with rocuronium, LBW appeared to be a suitable dosing scalar.

Lemmens et al.(2006) /USA[252]	45 Obese (103-149*)	Laparoscopic Gastric Bypass Succinylcholine/ Prospective, Randomized	Max. neuromuscular block, recovery index and intubating conditions in 3 groups of 15 patients each G 1 (n=15) = 1 mg/kg IBW G 2 (n=15) = 1 mg/kg LBW G 3 (n=15) = 1 mg/kg TBW	Max block (%) G1 vs G2 vs G3 = 93 vs 99 vs 100 (P <0.05) Recovery index$_{50\%}$ (min) G1 vs G2 vs G3 = 5 vs 7 vs 8.5 (P < 0.05) Poor Intubating conditions (%) G1 vs G2 vs G3 = 33 vs 27 vs 0	Appropriate nerve block, optimal recovery and good intubation conditions were observed in TBW dose group compared to LBW and IBW groups. TBW appeared as an appropriate dosing scalar.
Reversal Agents					
Van Lancker et al.(2011)/Belgium[253]	100 Obese (104-134*)	Laparoscopic Bariatric Surgery Sugammadex/ Prospective, Randomized	Comparison of total dose and reversal time (TOF > 0.9), time to tracheal extubation in 4 groups of 25 patients each G 1 (n=25) = 2 mg/kg IBW G 2 (n=25) = 2 mg/kg IBW + 20% G 3 (n=25) = 2 mg/kg IBW + 40% G 4 (n=25) = 2 mg/kg TBW	Total dose (mg) G1 vs G2 vs G3 vs G4 = 119 vs 143 vs 162 vs 236 Reversal time (sec) G1 vs G2 vs G3 vs G4 = 188.9 vs 154.6 vs 112.5 vs 128.5 (P<0.001) Time to tracheal extubation (min) G1 vs G2 vs G3 vs G4 = 5.3 vs 5.1 vs 4.2 vs 5.4 (P=NS)	Optimal recovery was observed in 2 mg/kg IBW + 40% dose group compared to other dose groups. Dose of 2 mg/kg IBW + 40% appeared suitable for reversal of moderate block.
Sanfilippo et al.(2013)/Italy[254]	40 Obese (109-140*)	Laparoscopic Bariatric Surgery Sugammadex/ Prospective, Cohort	Comparison of reversal time (TOF ≥ 0.9) and time to tracheal extubation in two group of patients G 1 (n=20) = 2 mg/kg IBW G 2 (n=20) = 2 mg/kg TBW	Reversal time (sec) G1 vs G2 = 151 vs 121 (P =NS)	Shorter receovy was obersved in IBW dose group comapred to TBW dose group. Dose of 2 mg/kg IBW provided appropriate reversal for moderate block.
Badaoui et al.(2016)/France[255]	64 Obese (104-152*)	Laparoscopic Bariatric Surgery Sugammadex/ Prospective, Cohort	Comparison of total dose, reversal time (TOF ≥ 0.9) and time to tracheal extubation in two groups of patients G 1 (n=31) = 4 mg/kg TBW G 2 (n=33) = 4 mg/kg IBW	Total dose (mg) G1 vs G2 = 508 vs 359 (P<0.001) Reversal time (sec) G1 vs G2 = 87 vs 115 (P=NS) Time to tracheal extubation (min) G1 vs G2 = 9.3 vs 11.6 (P=NS)	No significant difference of recovery was observed in TBW and IBW dose groups. However, authors suggested Sugammadex dose of 4 mg/kg IBW + (35 to 50%) for effective reversal without any adverse events.
Analgesics					

Graves et al. (1983)/USA[256]	32 Control (50-88*) 14 Obese (98-147*)	General vs gastric bypass Morphine/ Prospective, Cohort	Comparison of morphine dosing rate in control (G 1) vs obese (G 2) subjects.	Dosing rate (mg/hr) G1 vs G2 = 1.65 vs 1.84 (P=NS). TBW normalized (mg/kg/hr) G1 vs G2 = 0.024 vs 0.015 (P<0.05) IBW normalized (mg/kg/hr) G1 vs G2 = 0.028 vs 0.024 (P=NS)	For effective post-operative pain control obese group required higher morphine dose compared to normal weight group. IBW appeared to be a suitable dosing scalar for morphine dosing.
Grodofsky et al.(2012)/ USA[257]	76 Control (BMI < 30) 61 Obese (BMI > 30)	Orthopaedic Surgery Morphine/Retrospective, Case Control	Comparison of morphine dose administered and during 30 min post-surgery in control (G 1) vs obese (G 2).	Mean morphine dose (mg) G1 vs G2 = 13.9 vs 16.7 (P<0.05) Dose adjusted for TBW (mg/kg) G1 vs G2 = 0.20 vs 0.16 (P<0.05) Dose adjusted for IBW (mg/kg) G1 vs G2 = 0.23 vs 0.27 (P<0.05) Dose adjusted for CBW40 (mg/kg) G1 vs G2 = 0.21 vs 0.21 (P=NS)	For effective post-operative pain control obese group required significantly higher morphine dose compared to normal weight group. CBW40 is an appropriate dosing scalar for morphine dosing in obese.
Antibiotics					
Toma et al.(2011)/ USA[259]	13 Control (50-70*) 14 Obese (97-155*)	Gynaecological/Colorectal Surgery Cefoxitin/ Prospective, Cohort	SSI incidence compared in two dosing groups G 1 = Control (1 g) G 2 = Obese (2 g)	SSI (n) G1 vs G2 = 0 (0%) vs 3 (21.4%)	Higher SSI rate was observed in obese group who received 2 g dose compared to 1 g normal weight group. Obese patients may need more than 2 g.
Stitely et al.(2013)/ USA**[187]**	20 Obese (94-141*)	Caesarean Section Cefazolin/ Prospective, Randomized	SSI incidence compared in two dosing groups G 1 (n=11) = 2 g (Mean BMI 42) G 2 (n=9) = 4 g (Mean BMI 41)	SSI (n) G1 vs G2 = 0 (0%) vs 0 (0%) (P=NS)	No difference in SSI rate was noted in 2 g and 4 g dose groups. The lower dose (2 g) appeared to be effective for obese patients.
Unger et al.(2014)/ USA[173]	96 Control (79-101) 99 Obese (102-182)	Cardiac, Orthopaedic and General Surgery Cefazolin/Retrospective, Case Control	Comparison of SSI incidence following the administration of 2 g prophylaxis dose in two groups G 1 = Control (Mean BMI 27) G 2 = Obese (Mean BMI 35)	SSI (n) G1 vs G2 = 5 (5.2%) vs 7 (7.0%) (P=NS)	No significant difference of SSI rate was observed in obese and non-obese patients who received 2 g dose. A 2 g dose appeared to be effective for obese patients.
Ahmadzia et	335 Obese (135 – 156*)	Caesarean Section Cefazolin/Retrosp	Comparison of SSI incidence in two dose groups	SSI (n) G1 vs G2 = 23 (13.1%) vs 21 (13.1%)	Similar SSI rate was observed in 2 g and 3 g dose groups. The 2 g dose

al.(2015)/ USA[258]		ective, Case Control	G 1 (n=175) = 2 g (Mean BMI 50) G 2 (n=160) = 3 g (Mean BMI 53)		appeared to be effective for obese patients.
Peppard et al.(2017)/ USA**(202)**	436 Obese (100-142*)	All types of surgery Cefazolin/Retrospective, Case Control	Comparison of SSI in two dose groups G 1 (n=152) = 2 g (Mean BMI 36) G 2 (n=284) = 3 g (Mean BMI 40)	SSI (n) G1 vs G2 = 11 (7.2%) vs 21 (7.4%)	Similar SSI rate was observed in 2 g and 3 g dose groups. The 2 g dose appeared to be effective for obese patients.
Anticoagulants					
Kalfarentzos et al.(2001)/ Greece[260]	60 Obese (107 – 161)	Gastric Bypass Nadroparin/ Prospective, Randomized	Thromboembolic events (VTE) and bleeding events compared in two dosing groups G 1 (n=30) = 5700 IU daily (until discharge) G 2 (n=30) = 9500 IU daily (until discharge)	VTE (n) G1 vs G2 = 0 (0%) vs (0%) Bleeding (n) G1 vs G2 = 0 (0%) vs 2 (6.6%)	No difference in VTE events was observed in 5700 IU dose group and 9500 IU dose group. The lower fixed dose (5700 IU) of nadroparin appeared effective.
Scholten et al.(2002)/ USA[262]	489 Obese (Mean BMI 50) *	Bariatric Surgery Enoxaparin/ Prospective, Cohort	Comparison of VTE and bleeding events assessed in two groups G 1 (n=92) = 30 mg BD (until discharge/mobile) G 2 (n=389) = 40 mg BD (until discharge/mobile)	VTE (n) G1 vs G2 = 5 (5.4%) vs 2 (0.5%) Bleeding (n) G1 vs G2 = 1 (1.08%) vs 1 (0.2%)	Higher VTE events were observed in 30 mg BD dose group compared to 40 mg BD dose group. A dose of 40 mg BD appeared effective.
Borkgren-Okonek et al.(2008)/ USA[190]	223 Obese (87 – 249)	Gastric Bypass Enoxaparin/ Prospective, Cohort	VTE and bleeding events compared in two groups (OD 10 days after discharge) G 1 (n=124) = 40 mg BD (BMI ≤ 50) G 2 (n=99) = 60 mg BD (BMI > 50)	VTE (n) G1 vs G2 = 1 (0.8%) vs 0 (0%) Bleeding (n) G1 vs G2 = 4 (3.2%) vs 1 (1.0%)	Similar VTE events were observed in BMI stratified groups who received 40 mg BD and 60 mg BD doses This BMI stratified dosing appeared effective.
Singh et al.(2012)/ USA**(263)**	170 Obese (Mean BMI 48)	Bariatric Surgery Enoxaparin/Retrospective, Case Control	VTE and bleeding events compared in three BMI stratified dosing groups G 1 (n=11) = 30 mg BD for BMI < 40	VTE (n) G1 vs G2 vs G3 vs G4 = 0 (0%) vs 0 (0%) vs 0 (0%) vs 0 (0%) Bleeding (n) G1 vs G2 vs G3 vs G4 = 0 (0%) vs 4 (2.7%) vs 0 (0%) vs 1 (20%).	No VTE event was observed in BMI stratified groups who received 30 mg BD, 40 mg BD, 50 mg BD and 60 mg doses. BMI stratified dosing of enoxaparin appeared effective.

			G 2 (n=145) = 40 mg BD for BMI41-49 G 3 (n=9) = 50 mg BD for BMI 50-59 G 4 (n=5) = 60 mg BD for BMI >59		
Javanainen et al.(2016)/Finland[264]	400 Obese (Mean BMI 49*)	Bariatric Surgery Enoxaparin/Retrospective, Case Control	VTE and bleeding events compared in three dosing groups G 1 (n=100) = 40 mg BD for 10 days (given BD on surgery day) G 2 (n=100) = 40 mg BD for 10 days (given OD on surgery day) G 3 (n=200) = 40 mg OD (given OD on surgery day)	VTE (n) G1 vs G2 vs G3 = 0 (0%) vs 0 (0%) vs 0 (0%) Bleeding (n) G1 vs G2 vs G3 = 15 (15%) vs 6 (6%) vs 9 (4.5%) (P<0.05)	No VTE event was observed in 40 mg OD dose group and 40 mg BD dose groups. Dose of 40 mg OD appeared effective in VTE prevention without increasing the risk of bleeding complications.
Steib et al. (2016)/France[194]	135 Obese (Mean BMI 49*)	Gastric Bypass Enoxaparin/ Prospective, Randomized	VTE and bleeding events compared in three dosing groups G 1 (n=44) = 40 mg OD G 2 (n=44) = 60 mg OD G 3 (n=47) = 40 mg BD	VTE complications (n) G1 vs G2 vs G3 = 0 (0%) vs 0 (0%) vs 0 (0%) Bleeding (n) G1 vs G2 vs G3 = 1 (2.2%) vs 2 (4.5%) vs 6 (12.7%)	. No VTE event was observed in 40 mg OD, 60 mg OD and 40 mg BD dose groups. A dose of 60 mg daily appeared effective for VTE prevention without increasing the risk of bleeding complications.
Imberti et al.(2014)/Italy[261]	250 Obese (Mean BMI 44)	Bariatric Surgery Parnaparin/ Prospective, Randomized	VTE and bleeding events compared in two dosing groups G 1 (n=131) = 4250 IU/day G 2 (n=119) = 6400 IU/day	VTE (n) G1 vs G2 = 3 (1.5%) vs 1 (0.8%) (P=NS) Bleeding (n) G1 vs G2 = 8 (6.1%) vs 6 (5.0%) (P=NS)	No significant difference in VTE events and bleeding complications were observed in low dose (4250 IU) and high dose (6400 IU) groups. Daily dose of 4250 IU appeared effective in obese patients.

* Approximation

Total Body Weight (TBW), Body Mass Index (BMI), Body Surface Area (BSA), Ideal Body Weight (IBW), Corrected Body Weight 20% (CBW20), Corrected Body Weight 40% (CBW40), Corrected Body Weight 60% (CBW60), Lean Body Weight (LBW), Systolic Blood Pressure (SBP), Bispectral Index (BIS), Loss of Consciousness (LOC), Once Daily (OD), Twice Daily (BD), Every 12 hours (Q12h), International Units (IU), Group (G), Venous Thromboembolism (VTE), Surgical Site Infection (SSI), Train of Four (TOF).

2.5 Discussion

An increasing incidence of obesity is expected to impact anaesthetists' and surgeons' clinical decision-making for patients undergoing elective surgical procedures. Despite the availability of commentaries and narrative literature reviews on the use of specific medication classes in obese surgical patients (208, 231, 232), there is a gap in our understanding of medication use in obese patients undergoing elective surgeries. A distinctive attribute of this review is its broad search strategy. To ensure that we are not missing any relevant studies, we employed a broader definition of search terms, chose an extra level of medical subject heading (MeSH) terms and used broader Emtree terms (Appendix A).

2.5.1 Anaesthetics

Studies on anaesthetics other than propofol and bupivacaine are lacking. While there were studies of thiopental, dexmedetomidine, and inhaled anaesthetics (208), these studies were pharmacokinetic studies or lacked a control group or dosing comparison across various weight categories.

Studies reporting induction doses of propofol in obese patients made conflicting recommendations. One study (240) recommended LBW whereas a second study (241) favoured CBW60 as the preferred dosing weight for propofol induction. Given the differences in outcome measures (Time to LOC in the first study vs. BIS in the second study), the different mean body weights (130 kg vs. 100 kg) and the different modes of administration (standard IV infusion vs. bolus dose), differences in dosing recommendations are expected. However, the presence of a control normal weight group and higher mean weight in the obese group in the first study provides greater justification for their recommendation. Additionally, the higher incidence of hypotension in the second study (83% vs. 23%) also favours the former study's findings to dose propofol according to LBW. The grade of evidence for induction of anaesthesia with propofol in obese patients was very low. Both studies had moderate risk of bias due to lack of clarity on randomisation, methodology and inconsistency in findings. Only one study was identified in the literature for maintenance of anaesthesia with propofol in obese patients; it suggested TBW as a suitable dosing scalar (195). The study was non-randomised and lack of clarity of outcome measures resulted in a low grade of evidence.

Despite the common belief that obese patients require low doses of bupivacaine, perhaps based on the reasoning that their high body lipid content may lead to the excessive spread of bupivacaine in cerebrospinal fluid (265, 266), authors found that similar doses were

needed to achieve appropiate neuraxaial block in obese patients when compared to normal weight patients (243, 244). The grade for evidence of bupivacaine dosing in obese patients for neuraxial block was good. Both studies had a moderate/low risk of bias and were consistent in findings.

2.5.2 Muscle relaxants

Despite its frequent use in clinical practice, we were able to find only one study of succinylcholine; it recommended the use of TBW for dose calculation in obese patients (252). The grade of evidence for succinylcholine dosing was low due to the lack of clarity on randomisation and blinding identified in that study.

The number of studies assessed the dosing of non-depolarising agents in obese patients Pancuronium is not a drug of first choice for obese patients due to its long duration of action compared to vecuronium and atracurium (208). The only study comparing the dosing of pancuronium in obese patients with normal weight controls found a higher total dose was needed to achieve desirable effects; nevertheless, differences were not significant when doses were normalised to BSA (245). The grade of evidence for pancuronium dosing was very low, because of unclear methodology and lack of reliability of outcomes measurement.

Two studies of vecuronium use in obese patients recommended dosing based on IBW as doses based on TBW resulted in prolonged recovery (246, 247). The grade of evidence for vecuronium dosing in obese patients was low, as both the studies were non-randomised and had a moderate risk of bias. However, the hydrophilic nature of vecuronium and potentially compromised hepatic elimination in obese patients (vecuronium is highly dependent on hepatic clearance) support the argument of IBW rather than TBW based dosing.

Three studies reported two different recommendations for atracurium dosing in obese patients (161, 246, 248). Earlier two studies found no differences in recovery index when atracurium was dosed using TBW (161, 246). On the contrary, a recent study reported a longer recovery time and an increase in the need for neostigmine reversal when atracurium was dosed as per TBW compared to IBW (248). The earlier two studies did not include an IBW based regimen and had a much lower maximum weight in the obese group when compared to the third study (max weight of 158 kg in earlier two studies vs. max weight of 260 kg in third study). The overall grade of evidence was very low, which is mainly due to the inconsistent findings of reported studies.

Similar findings were noted in studies examining the effect of obesity on rocuronium dosing. The study by Pühringer and colleagues included patients with a maximum weight of 97 kg and favoured TBW based dosing (197), whereas the two later studies that included patients with a maximum weight of 135 kg and 194 kg, respectively, favoured IBW dosing (249, 250). The grade of evidence for rocuronium dosing in obese patients was good because of the pseudo-randomised/randomised study designs and the low risk of bias in the later two studies. The only study of rocuronium dosing for RSI recommended LBW as an appropriate dosing scalar for obese patients (251). This study was truly randomised study with a low risk of bias, thus resulting in a good grade of evidence.

2.5.3 Reversal agents

Dosing studies of reversal agents in obese patients were available only for sugammadex. Several recent studies of sugammadex dosing in obese patients lacked a control group or dosing scalar and were not included in this review (255, 267, 268). For the reversal of moderate neuromuscular block, two studies reported slightly different findings. One study reported that a dose of 2 mg/kg based on IBW provided appropriate neuromuscular reversal (254), whereas another study found a dose of 2 mg/kg based on IBW + 40% provided more timely neuromuscular reversal compared to 2 mg/kg based on IBW (253). Authors of later study justified the reason for higher dose requirement was to rule out the possibility of recurarisation (253). The grade of evidence for sugammadex dosing for moderate block reversal in obese patients was low mainly due to the inconsistent findings of reported studies and the lack of any true randomisation study. The only identified study of deep block reversal with sugammadex in obese patients reported 4 mg/kg IBW + 35 to 50% as a suitable dosing scalar (255). The study was non-randomised and of moderate risk of bias. Therefore, the grade of evidence was very low.

2.5.4 Analgesics

Despite the potential limitations of morphine use in obese patients such as upper airway obstruction and risk of accumulation (269, 270), the dosing studies of opioids included in this review were limited to morphine (256, 257). Studies available for fentanyl, remifentanil and sufentanil were either pharmacokinetic modelling studies or lacked the control group necessitated by the inclusion criteria of this review (201, 271, 272). Two studies of morphine dosing in obese patients found IBW and CBW40 were appropriate dosing scalars (256, 257). The former study did not report the difference in total morphine dose in the obese and control

groups and their associated clinical outcome (pain/sedation score) (256), whereas, the limitation of the later study is the shorter 30 minutes post-operative follow-up time (257). Overall, a very low grade of evidence was assessed for morphine dosing in obese patients; both studies were non-randomised, of moderate risk and reported inconsistent findings.

2.5.5 Antibiotics

Cefazolin is the most widely used drug in surgical patients for SSI prophylaxis (273). Four studies of cefazolin dosing reported consistent findings that a standard 2 g dose provided appropriate antibiotic prophylaxis in obese surgical patients (173, 187, 202, 258). Overall, a good grade of evidence was assessed for prophylactic cefazolin dosing in obese patients. The studies were of moderate to low risk of bias and consistent in findings. However, the American Society of Health-System Pharmacists (ASHP) 2013 guidelines recommend a 3 g dose of cefazolin for patients weighing ≥ 120 kg (203). The dosing recommendations of ASHP are based only on small-scale pharmacokinetic studies. The findings of these pharmacokinetic studies are also inconsistent. For instance, some pharmacokinetic studies found that a 2g prophylactic dose of cefazolin may fail to provide the complete antimicrobial coverage in obese patients; therefore, a 3g dose is required for these patients (131, 181, 183). On the contrary, other pharmacokinetic studies reported that the 2g prophylactic dose of cefazolin provides sufficient antimicrobial coverage in obese surgical patients (185, 186, 189).

The only study of cefoxitin dosing which met the inclusion criteria for this review suggested that a dose higher than 2 g is required in obese patients for SSI prophylaxis (259). The study was non-randomised with a high risk of bias. Therefore, the grade of evidence for prophylactic cefoxitin dosing in obese patients was very low.

2.5.6 Anticoagulants

Dosing studies of anticoagulants in obese patients are mainly confined to low molecular weight heparins. Although one study of unfractionated heparin dosing in obese patients was identified, it did not report the comparison of outcomes in the two dosing groups (274). Regarding enoxaparin, Scholten and colleagues found that a dose of 40 mg twice daily provided effective VTE prophylaxis in obese patients (262). Two recent studies favoured the once daily dosing regimens of 40 mg and 60 mg respectively (194, 264). The possible reason for this difference in reported regimens is due the differences in the initiation of enoxaparin (initiated on the day of surgery in the Scholten and colleagues study and one day before surgery in the latter two studies. Two studies recommended BMI stratified dosing of enoxaparin. The former study

recommended the enoxaparin dose of 60 mg twice daily for patients with a BMI > 50 kg/m^2 and the later study favoured 60 mg twice daily for patients with a BMI > 59 kg/m^2 (190, 263). The overall grade of evidence of enoxaparin dosing in obese patients for VTE prophylaxis was low. Most studies were non-randomised and reported inconsistent findings. Similarly, the American College of Chest Physician Guidelines recommend using higher than the usual 40 mg once daily dose of enoxaparin for obese patients; however, optimal dose adjustment for obese patients remained unclear in these guidelines (275).

The only study of nadroparin reported that the standard dose of 5700 IU was sufficient to provide appropriate VTE prophylaxis in obese patients (260). The grade of evidence of nadroparin dosing was very low. This study lacked the clarity of randomisation and blinding. A randomised control study reported that a fixed dose of parnaparin (4250 IU) is effective in obese patients for VTE prophylaxis (261). The grade of evidence was good because the study was truly randomised and of low risk of bias.

Table 7. Dosing recommendations for obese surgical patients

Drug	Dosing strategies/Weight Scalar	Study Design (Quality of Study)	Level of Evidence	Evidence Base	Consistency	Dosing Recommendations	Recommendation Grade*
Propofol	Induction: LBW[240]	Pseudo-randomised (Moderate)	III-1	Poor	Satisfactory**	LBW	D
	Induction: CBW60[241]	Pseudo-randomised (Moderate)	III-1				
Propofol	Maintenance: TBW[195]	Cohort (Strong)	III-3	Satisfactory	NA	TBW	C
Bupivacaine	11 mg[243]	Pseudo-randomised (Moderate)	III-1	Good	Excellent	11 mg	B
	11 mg[244]	Randomised (Strong)	II				
Pancuronium	BSA[245]	Cohort (Weak)	III-2	Poor	NA	BSA	D
Vecuronium	IBW[246]	Cohort (Moderate)	III-2	Poor	Excellent	IBW	C
	IBW [247]	Cohort (Moderate)	III-2				
Atracurium	IBW[248]	Pseudo-randomised (Moderate)	III-1	Poor	Satisfactory**	IBW	D
	TBW[246]	Cohort (Moderate)	III-2				
	TBW[161]	Cohort (Strong)	III-2				
Rocuronium	IBW[249]	Pseudo-randomised (Strong)	III-1	Good	Good	IBW	B
	IBW[250]	Randomised (Strong)	II				
	TBW[197]	Cohort (Moderate)	III-2				
Rocuronium (RSI)	LBW [251]	Randomised (Strong)	II	Good	NA	LBW	B
Succinylcholine	TBW[252]	Pseudo-randomised (Strong)	III-1	Satisfactory	NA	TBW	C

Sugammadex (Moderate Block Reversal)	2 mg/kg IBW + 40% [253]	Pseudo-randomised (Strong)	III-1	Satisfactory	Satisfactory**	2 mg/kg IBW + 40%	C
	2 mg/kg IBW[254]	Cohort (Moderate)	III-2				
Sugammadex (Deep Block Reversal)	4 mg/kg IBW + 35 to 50%[255]	Cohort (Moderate)	III-2	Satisfactory	NA	4 mg/kg IBW + 35 to 50%	D
Morphine	IBW[256]	Cohort (Moderate)	III-2	Satisfactory	Poor	IBW or CBW40	D
	CBW40[257]	Case Control (Moderate)	III-2				
Cefazolin	2 g[187]	Randomised (Moderate)	II	Good	Excellent	2 g	B
	2 g[173]	Case Control (Moderate)	III-2				
	2 g[258]	Case Control (Strong)	III-2				
	2 g[202]	Case Control (Strong)	III-2				
Cefoxitin	> 2 g[259]	Cohort (Weak)	III-2	Poor	NA	> 2 g	D
Nadroparin	5700 IU[260]	Pseudo-randomised (Moderate)	III-1	Poor	NA	5700 IU	D
Parnaparin	4250 IU[261]	Randomised (Strong)	II	Good	NA	4250 IU	B
Enoxaparin	60 mg OD[194]	Pseudo-randomised (Moderate)	III-1	Good	Poor	Weight based or BMI stratified	C
	40 mg BD[262]	Cohort (Strong)	III-3				
	40 mg BD (BMI ≤ 50) 60 mg BD (BMI > 50)[190]	Cohort (Strong)	III-2				
	30 mg BD (BMI < 40) 40 mg BD (BMI41-49)	Case Control (Moderate)	III-2				

	60 mg BD (BMI 50-59) 60 mg BD (BMI >59)[263]						
	40 mg OD[264]	Case Control (Strong)	III-2				

*Recommendations Grades explanation is as follow;

A (Excellent) = Body of evidence can be trusted to guide practice

B (Good) = Body of evidence can be trusted to guide practice in most situations

C (Low) = Body of evidence provides some support for recommendation(s) but care should be taken in its application

D (Very low) = Body of evidence is weak, and recommendation must be applied with caution

** Satisfactory (some inconsistency reflecting genuine uncertainty around clinical question) = Reason(s) explained in discussion section

2.6 Strengths and limitations

The main strength of this review is the robust inclusion criteria. Another strong point of this review is the dosing recommendations (Table 7) with respective grades for each drug (based on the quality of individual studies, level of evidence, evidence base and consistency). Overall, this review provides a thoughtful insight for dosing of various medications in obese surgical patients.

There are certain limitations to this review. Firstly, the sample size in the majority of studies is small, and some drug recommendations (such as those of succinylcholine, heparins and pancuronium) were supported by only one study. Secondly, there were no studies identified for some common perioperative drugs, such as opiates other than morphine. Thirdly, differences in the outcome measures of studies of the same drug such as propofol (LOC, BIS), vecuronium and rocuronium (recovery index, recovery time), and differences in the mean weights of participants in various studies may have compromised the uniformity of our findings. Lastly, only full-length articles with control group and published in English were included in this review. Exclusion of conference abstracts, studies without control group and studies in languages other than English might have influenced the dosing recommendations and/or grade of evidence. The presence of these limitations and the "very low", to "low" quality evidence for the majority of drug doses limits the ability of decision makers to further individualise dosing recommendations.

2.7 Conclusion

Managing obese patients' needs special considerations because of obesity related physiological changes and altered dosing requirements for various medications used in surgery. Different studies of one drug reported varied dosing strategies for obese patients. The evidence for perioperative dosing recommendations of majority of anaesthetics and prophylaxis medications is not strong. Strong methodological clinical outcome studies with larger sample sizes are needed to provide empirical evidence for current dosing recommendations of these medications.

CHAPTER THREE: Prophylactic Cefazolin Dosing and Surgical Site Infections: Does the Dose Matter in Obese Patients?

Overview

This chapter presents a study addressing the second objective of the thesis. It is a retrospective case control study of adult elective surgical patients. Patients receiving 2g cefazolin were grouped as obese and non-obese, and by weight (≥ 120kg or < 120kg). The 90-day prevalence of SSI and potential contributing factors were investigated.

This chapter is a reproduction of the following publication.

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3.1 Abstract

Background: Most surgical prophylaxis guidelines recommend a 3g cefazolin intravenous dose in patients weighing ≥ 120kg. However, this recommendation is primarily based on pharmacokinetic studies rather than robust clinical evidence. This study aimed to compare the prevalence of surgical site infections (SSIs) in obese and non-obese patients (body mass index ≥ 30 kg/m^2 and < 30 kg/m^2), and those weighing ≥ 120kg and < 120kg, who received 2g cefazolin preoperatively.

Methods: A retrospective case control study was conducted in adult elective surgical patients. Patients receiving 2g cefazolin were grouped as obese and non-obese, and by weight (≥ 120kg or < 120kg). The 90-day prevalence of SSI and potential contributing factors were investigated.

Results: We identified 152 obese (median 134kg) and 152 non-obese control patients (median 73kg). Baseline characteristics were similar between groups, except for an increased prevalence in the obese group of diabetes (35.5% vs 13.2%; p<0.001) and an American Society of Anaesthesiologists Score of 3 (61.8% vs 17.1%; p<0.001). While not statistically significant, the prevalence of SSI in the obese group was almost double that in the non-obese group (8.6% vs 4.6%; p=0.25), and in patients weighing ≥ 120kg (n=102) compared to those weighing < 120kg (n=202) (9.8% vs 5.0%; p=0.17).

Conclusion: The prevalence of SSI was not significantly increased in obese patients, or those weighing ≥ 120kg, who received cefazolin 2g prophylactically; however, trends toward an increase were evident. Large scale randomised trials are needed to examine whether a 2g or 3g cefazolin is adequate to prevent SSI in obese (and ≥ 120kg) individuals.

Key Words: Antibiotic prophylaxis, Cefazolin, Elective surgery, Obese, Surgical site infection

3.2 Introduction

Obese patients undergo surgical procedures more frequently than their non-obese counterparts due to obesity-related health problems, such as osteoarthritis, cardiovascular disease, diabetes and cancer (149). Obesity is also associated with a number of surgical complications, including an increased risk of surgical site infection (SSI) (276). The repercussions of SSI include extended hospital stay, more frequent hospital readmissions, pain, anxiety and higher healthcare resource utilization (277). However, the administration of an appropriate antibiotic at an appropriate dose before surgery significantly reduces the risk of SSI (203).

Cefazolin remains the drug of choice for surgical prophylaxis in many procedures due to its favourable safety profile, low cost and targeted activity against the microorganisms commonly encountered during surgical procedures (203). In 2013, a collective guideline for surgical prophylaxis developed by the Infectious Diseases Society of America (IDSA), the American Society of Health-System Pharmacists (ASHP), the Surgical Infection Society (SIS) and the Society for Healthcare Epidemiology of America (SHEA), suggested an increased dose of cefazolin (3g intravenously) for patients weighing ≥ 120kg (203). Similarly, the Australian Medicines Handbook (AMH) recommends a 3g dose of cefazolin for patients > 120kg (278). The Australian Therapeutic Guidelines (TG) and the American College of Obstetricians Gynaecologists (ACOG) Practice Bulletin and also suggest the need for a higher prophylactic cefazolin dose for obese surgical patients, but do not specify the recommended dose or weight or BMI cut-off values (279, 280).

The dosing recommendations of those guidelines were based on small-scale and inconsistent pharmacokinetic studies (level-III according to the National Health and Medical Research Council levels of evidence) (217). Four pharmacokinetic studies found that a 2g prophylactic dose of cefazolin may be inadequate in morbidly obese patients undergoing bariatric procedures and caesarean section, due to the blood and/or tissue drug concentrations being below minimum inhibitory concentrations (MIC) (131, 181-183). These studies suggested the need for a higher (3g) dose in these patients. In contrast, six pharmacokinetic studies in similar surgical specialties found that a 2g dose did provide adequate antimicrobial coverage (concentration above MIC) in morbidly obese patients with similar weight ranges, suggesting no dose increment was required (184-189).

Given the lack of satisfactory evidence supporting 3g dosing in obese patients and a scarcity of clinical outcome studies, this study sought to ascertain whether an intravenous 2g

dose of cefazolin was comparatively effective in obese versus non-obese surgical patients, and in those who weighed above or below 120kg, based on the observed rate of SSI within 90 days of operation.

3.3 Method

A retrospective 1:1 case control study was conducted of obese (BMI ≥ 30 kg/m^2) and non-obese adults who underwent elective surgical procedures at the Royal Hobart Hospital (RHH) from 1 Jan 2012 - 31 Dec 2016. The prevalence of SSI at this institution was not known, so a duration-based (5-year) sampling method was used. The 500-bed RHH is the largest public teaching and referral hospital in the state of Tasmania, Australia. Ethical approval was obtained from the Tasmanian Health and Human Research Ethics Committee (H0015795). Informed consent from patients was not needed as data was collected retrospectively and de-identified upon collection.

Patients were included if they were at least 18 years of age and had received prophylactic cefazolin pre-operatively. The reasons for selecting elective cases were that more detailed documentation was available for these patients, they were more likely to have adequate pre-operative optimisation of medical comorbidities and a lower incidence of pre-operative bacterial colonisation compared to emergency cases (281, 282). Patients were excluded if they i) lacked follow-up within 90 days of surgery, ii) had an unplanned non-infective post-operative intensive care unit admission, iii) had a second operation during the same admission for causes other than infection, iv) required perioperative blood transfusion, v) were taking systemic immunosuppressive medication (corticosteroids, sirolimus, everolimus, cyclosporine, tacrolimus, azathioprine, mycophenolate, monoclonal antibodies or biologics e.g. abatacept, etanercept) at admission and/or discharge, vi) were receiving antibiotics immediately prior to admission, or vii) had missing requisite data (such as antibiotic type, dose, or surgical duration) in their medical record. Aside from BMI, the same inclusion and exclusion criteria were applied to obtain the non-obese (BMI < 30 kg/m^2) control patients.

A list of obese patients, based on the International Classification of Disease-10 (ICD-10), who underwent elective surgical procedures during 2012 to 2016, was obtained from the hospital's coding database. The list was then reviewed to identify patients who met the inclusion criteria. To include non-obese control patients, a list of similar elective surgical procedures from 2012-2016 was systematically screened, by including every fifth patient if

they met the study inclusion criteria, until we reached approximately equal numbers in every surgical speciality to that of obese group.

Patients' medical records were reviewed to obtain socio-demographic and clinical information, including gender, age, weight, height, body mass index (BMI), smoking status, diabetes status, length of stay (LOS), American Society of Anaesthesiologists (ASA) score (283), surgical wound class, duration of surgery, post-operative antibiotic use, surgical specialty and SSI incidence. Diabetes was identified based on a recorded diagnosis or use of any medication for diabetes management at admission or discharge. Wound class was categorised based on the Centre for Disease Control and Prevention Centre (CDC) criteria (284). Duration of surgery was calculated as the time between skin incision and skin closure. LOS was calculated from date of admission until date of discharge in patients who did not develop SSI during admission, or until date of SSI development for those who developed SSI during admission. Surgical procedures were grouped into a surgical specialty based on the department in which the patient underwent surgery "i.e." general surgery (such as laparoscopic adjustable gastric banding, laparoscopic cholecystectomy, incisional hernia repair), gynaecological surgery (such as caesarean section, hysterectomy, ovarian cystectomy) and orthopaedic surgery (such as hip and knee replacement, hip arthroplasty, ankle fracture). Prophylactic pre-operative cefazolin dose and post-operative antibiotic use (when not for SSI treatment) was recorded. Inpatient, outpatient and emergency department notes were screened for up to 90 days post-operatively to identify documented SSIs, which were classified into superficial, deep, and organ/space, in accordance with the CDC (284).

Continuous variables were expressed as median (interquartile range) and categorical variables as the count (percentage). Pearson's X^2 test and Fisher's exact test were used for categorical variables and the Mann Whitney-U test was used for continuous variables to compare the baseline variables and primary outcome. Logistic regression was used to identify the potential predictors of SSI. Variables (other than ASA score, post-operative antibiotic use and wound class) from the univariate analysis with a p-value ≤ 0.20 were included in the multivariate logistic regression model. ASA score was not included in the multivariate analysis because it depends on two other study variables, diabetes and body weight. Post-operative antibiotic use was also not included in the multivariate analysis because its use was limited to certain surgical specialties, such as orthopaedics, and given to only 14% of patients. Wound class was also not included in the multivariate analysis because of the very small number of patients with contaminated and dirty wounds. The regression analysis was presented as

unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI). A p-value of < 0.05 was considered significant in all the statistical analyses. Analyses were performed using SPSS version 22 (IBM Inc., Chicago, IL).

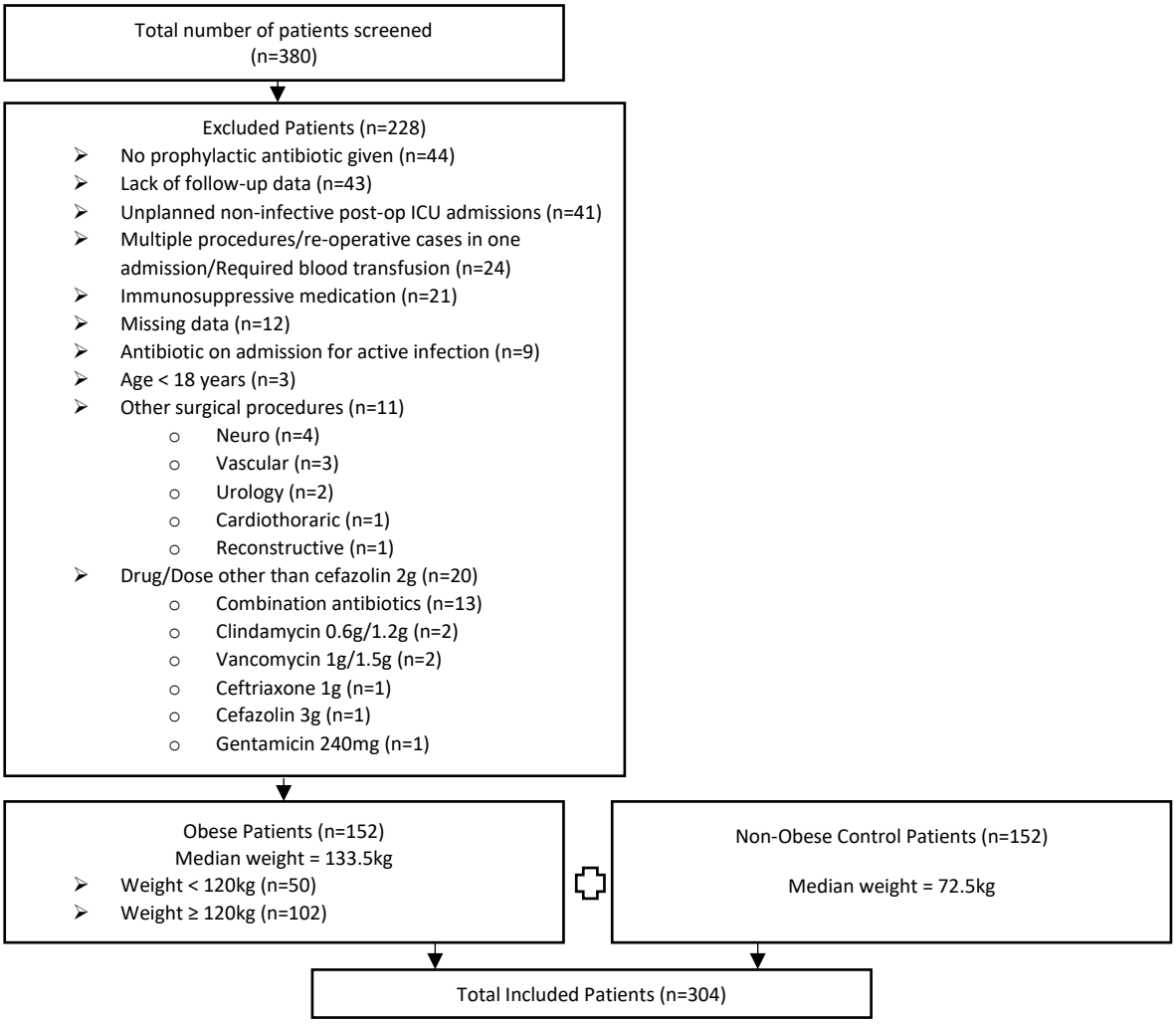

Figure 6. Flow chart of patient inclusion

3.4 Results

One hundred and fifty-two obese patients met the inclusion criteria for this study and were matched with non-obese controls (Figure 6). Patient characteristics are described in Table 8. There were differences between the obese and non-obese groups in median body weight (133.5kg vs 72.5kg, p<0.001), median BMI (47.0 kg/m^2 vs 26.7 kg/m^2, p<0.001), presence of diabetes (35.5% vs 13.2%, p<0.001) and ASA score (score 3 in 61.8% vs 17.1%, p<0.001). Overall, nearly two-thirds (64.5%) were general surgical patients and more than half had a clean surgical wound in each group (non-obese=58.6% and obese=61.8%). Less than 2% of

patients in either group were given prophylactic antibiotics when it was not recommended according to the Australian TG (279).

Table 8. Comparison of non-obese and obese patients

Variable	Non-obese (n=152)	Obese (n=152)	P-value
Gender (female), n (%)	110 (72.4)	113 (74.3)	0.80
(male), n (%)	42 (27.6)	39 (25.7)	
Age (years), median (IQR)	49.0 (30.0-61.0)	46.0 (31.2-54.0)	0.17
Weight (kg), median (IQR)	72.5 (65.0-82.0)	133.5 (115.0-148.0)	***<0.001***
BMI (kg/m^2), median (IQR)	26.7 (24.2-28.6)	47.0 (41.1-52.1)	***<0.001***
Current smoker, n (%)	43 (28.3)	37 (24.3)	0.52
Diabetes, n (%)	20 (13.2)	54 (35.5)	***<0.001***
ASA score			***<0.001***
1, n (%)	48 (31.6)	2 (1.3)	
2, n (%)	78 (51.3)	56 (36.8)	
3, n (%)	26 (17.1)	94 (61.8)	
Length of stay (days), median (IQR)	2.0 (0.0-3.0)	1.0 (1.0-4.0)	0.14
Duration of surgery (minutes), median (IQR)	60.0 (45.2-89.5)	55.5 (45.0-90.0)	0.95
Implants, n (%)	78 (51.3)	77 (50.7)	1.000
Surgical specialty			1.000
General, n (%)	98 (64.5)	98 (64.5)	
Gynaecological, n (%)	41 (27.0)	41 (27.0)	
Orthopaedic, n (%)	13 (8.6)	13 (8.6)	
Wound class			0.91
Clean, n (%)	89 (58.6)	94 (61.8)	
Clean-contaminated, n (%)	61 (40.1)	56 (36.8)	
Contaminated, n (%)	1 (0.7)	1 (0.7)	
Dirty, n (%)	1 (0.7)	1 (0.7)	
Antibiotic prophylaxis recommended (as per TG[279])			0.65
Yes, n (%)	149 (98.0)	150 (98.7)	
Post-op antibiotic use			0.34
None, n (%)	135 (88.8)	126 (82.9)	
IV, n (%)	14 (9.2)	20 (13.2)	
Oral, n (%)	3 (2.0)	6 (3.9)	
Post-op antibiotic duration (hour)			
IV, median (IQR)	20.0 (16.0-24.0)	24.0 (18.0-24.0)	0.36
Oral, median (IQR)	120.0 (48.0-160.0)	180.0 (120.0-240.0)	0.55

Statistically significant values (p<0.05) under the column of p values are shown in italics to highlight such significance.

Thirteen (8.6%) obese and 7 (4.6%) non-obese patients developed SSIs (p=0.25; Table 9). Similarly, the observed rate of SSI was 9.8% in patients weighing ≥ 120kg (n=102) compared to 5.0% in those weighing < 120kg (n=202) (p=0.17). Three patients (2 obese and 1 non-obese) developed a SSI during their admissions and 17 (11 obese and 6 non-obese) developed SSI post-discharge. Four of the SSIs were classified as deep (2 obese and 2 non-obese) and 16 as superficial (11 obese and 5 non-obese).

Patients who developed a SSI had a significantly higher ASA score, longer duration of surgery and longer hospital LOS compared to patients who did not develop a SSI (Table 9).

Table 9. Relationship of SSI with patient and clinical characteristics

Variables	Prevalence of SSI (categorical variable) or median and IQR (numerical variable)	P-value
Gender (female), n (%) (male), n (%)	15 (6.7) 5 (6.2)	1.00
Age (years), median (IQR)	SSI: 48.5 (28.7-54.0) No SSI: 47.0 (31.0-57.0)	0.86
Weight (kg), median (IQR)	SSI: 118.0 (74.5-139.2) No SSI: 94.5 (72.2-131.7)	0.18
BMI (kg/m^2), median (IQR)	SSI: 40.7 (28.3-51.8) No SSI: 29.8 (26.5-46.9)	0.21
BMI category Obese, n (%) Non-obese, n (%)	 13 (8.6) 7 (4.6)	0.25
Weight category Weight < 120kg, n (%) Weight ≥ 120kg, n (%)	 10 (5.0) 10 (9.8)	0.17
Current smoker Yes, n (%) No, n (%)	 6 (7.5) 14 (6.3)	0.90
Diabetes Yes, n (%) No, n (%)	 9 (12.0) 11 (4.8)	0.06
ASA score 1, n (%) 2, n (%) 3, n (%)	 1 (2.0) 5 (3.7) 14 (11.7)	***0.02***
Length of stay (days), median (IQR)	SSI: 4.0 (1.2-5.7) No SSI: 1.0 (1.0-3.0)	***0.001***
Duration of surgery (minutes), median (IQR)	SSI: 80.0 (56.2-101.2) No SSI: 56.5 (45.0-89.5)	***0.02***
Implants Yes, n (%) No, n (%)	 8 (5.2) 12 (8.0)	0.43
Surgical specialty General, n (%) Gynaecological, n (%) Orthopaedic, n (%)	 13 (6.6) 6 (7.3) 1 (3.8)	0.94
Wound class Clean, n (%) Clean-contaminated, n (%) Contaminated, n (%) Dirty, n (%)	 10 (5.5) 9 (7.7) 0 (0.0) 1 (50.0)	0.15
Post-op antibiotic use (other than for treating SSI) No, n (%) IV, n (%)	 14 (5.4) 5 (14.7)	0.067

Oral, n (%)	1 (11.1)	
Post-op antibiotic duration (hours)		
Oral, median (IQR)	SSI: 120.0 (84.0-240.0) No SSI: 120.0 (66.0-240.0)	0.90
IV, median (IQR)	SSI: 16.0 (16.0-48.0) No SSI: 24.0 (16.0-24.0)	0.64

Statistically significant values (p<0.05) under the column of p values are shown in italics to highlight such significance.

In the multivariate analysis, however, no variable showed a significant independent association with SSI (Table 10).

Table 10. Logistic regression for variables associated with SSI (n=304)

Variable	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Weight Category (Weight ≥ 120kg)	2.08 (0.83-5.19)	***0.11***	1.78 (0.69-4.59)	0.23
Diabetes	2.70 (1.07-6.80)	***0.04***	2.31 (0.88-6.06)	***0.09***
Length of stay	1.18 (1.03-1.35)	***0.01***	1.13 (0.97-1.33)	0.11
Duration of surgery	1.00 (0.99-1.01)	***0.09***	1.00 (0.99-1.01)	0.43

Statistically significant values (p<0.05) under the column of p values are shown in italics to highlight such significance.

3.5 Discussion

The dose of prophylactic antibiotic is an important factor in SSI prevention, and pharmacokinetic studies provide baseline information about dose and timing. However, pharmacokinetic findings may not always be translated into clinical outcomes (202). Our findings showed no statistically significant difference in SSI prevalence between obese and non-obese patients, or those who weighed above and below 120kg, who received a 2g prophylactic cefazolin dose preoperatively. However, there were approximately two-fold increases in SSI prevalence in obese compared to non-obese patients, and in those who weighed ≥ 120kg compared to those who weighed < 120kg. The lack of statistically significant differences could be due to our relatively small sample size.

To date, no outcome study has shown the superiority of using a dose of prophylactic cefazolin exceeding 2g in obese surgical patients. A retrospective outcome study was conducted of obese (mean BMI=35 kg/m^2; n=99) and non-obese (mean BMI=27 kg/m^2; n=96) patients across various surgical specialties, who received a 2g cefazolin prophylactic dose (173). No significant difference in 30-day SSI prevalence was noted between the obese and non-obese groups (7.0% vs 5.2%, p=0.56) (173). Likewise, a recent retrospective study of 2g (mean BMI=36 kg/m^2; n=152) or 3g (mean BMI=40 kg/m^2; n=284) prophylactic cefazolin dosing in obese patients of various surgical specialties reported a very similar 90-day SSI prevalence in the two dosing groups (7.2% vs 7.4%, p=0.95) (202). Our obese cohort had a higher median

BMI (47 kg/m^2) compared to patients in the aforementioned studies (35 kg/m^2 and 36 kg/m^2) who received a 2g cefazolin dose. This is a possible explanation for the larger difference in SSI prevalence in the obese patients versus control patients in our study compared to the previous studies (173, 202).

Appropriate prophylactic antibiotic administration is just one measure of the multifactorial approach used in the prevention of SSI. Therefore, stringent inclusion criteria on patient selection were applied so that the effect of cefazolin dosing could be independently estimated. We excluded patients with factors that can potentially alter the pharmacokinetic properties of antibiotics (such as non-infective unplanned post-operative admissions due to acute illness (150)) or effect the wound healing process (such as peri-operative blood transfusion and taking immunosuppressive medications (285)). Furthermore, non-modifiable risk factors, such as older age, smoking, diabetes, LOS, duration of surgery, pre-existing implanted medical devices and wound class, were considered in the statistical analyses.

Patients with diabetes, an ASA score of 3, longer surgery duration and longer LOS tended to have higher SSI occurrence in our study. These are well-established known risk factors for SSI development (286). Other SSI risk factors reported in the literature, such as smoking, advanced age and non-clean surgical wounds (286) in obese patients, did not show a significant association with SSI.

This study has some limitations. Firstly, it was not a prospective randomised controlled trial. The retrospective study design meant we had to rely on the notes available in patients' medical records. For instance, we were not able to record the exact timing of prophylactic cefazolin dose administration. However, from the anaesthetic chart reviews we could ascertain that the doses were always administered in theatre, anywhere from immediately before induction until shortly after incision. As mentioned, the sample size of the study was relatively small. One possible reason for the small number of patients identified in our case group is that obesity was coded sporadically in hospital records as a comorbidity (ICD-10 list). Also, we excluded patients who underwent vascular, urologic, cardiothoracic and reconstructive surgery due to their limited numbers, which might compromise the generalisability of findings to these surgical specialities.

3.6 Conclusion

While no statistically significant difference in SSI prevalence was observed in non-obese and obese patients, or those who weighed above and below 120kg, who received a 2g prophylactic

cefazolin dose, trends towards an increase were evident. There is a clear need for large scale randomised controlled trials to examine whether a 2g or 3g cefazolin dose is adequate to prevent SSI in obese individuals.

CHAPTER FOUR: Prophylactic Enoxaparin Use and Outcomes in Obese Patients Undergoing Laparoscopic Adjustable Gastric Band Surgery

Overview

This chapter presents a study addressing the third objective of the thesis. This is a retrospective study of adult obese patients who underwent primary and revisional (band and port) Laparoscopic adjustable gastric band procedures. The incidence of VTE and major bleeding was investigated during a 90-day follow-up period.

This work is a reproduction of the following submitted manuscript.

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4.1 Abstract

Background: There is a lack of clear guidance for the prophylactic use of anticoagulants for patients undergoing laparoscopic adjustable gastric banding (LAGB) surgery.

Aim: This study aimed to evaluate the risk of venous thromboembolism (VTE), prophylactic use of enoxaparin and clinical outcomes in patients undergoing primary and revisional LAGB procedures.

Methods: A retrospective study evaluated the prophylactic use of enoxaparin in adult patients who underwent primary and revisional (band and port) LAGB procedures. The incidence of VTE and major bleeding was investigated during a 90-day follow-up period. Descriptive and inferential statistics were used for data analysis.

Results: We included 112 and 100 patients who had undergone primary and revisional (24 band procedures and 76 port procedures) LAGB surgery, respectively. The majority of patients (97%) had a mild risk of VTE development using a post-discharge VTE risk calculator tool published from the Cleveland Clinic. All primary procedure patients received prophylactic enoxaparin, compared to 79% and 20% of revisional patients who underwent band and port procedures, respectively ($p<0.001$). The overall VTE incidence was 0.9%, with no significant difference between patients who did or did not receive chemoprophylaxis (0.7% and 1.5%, respectively; $p=0.58$). No major bleeding events were observed.

Conclusion: Chemoprophylaxis may not be required in all patients undergoing low-risk LAGB surgery unless there are additional risk factors, such as the presence of super-super-morbid obesity or concomitant hormone replacement therapy. More studies are needed on the prophylactic use and dosing of enoxaparin in patients undergoing LAGB procedures to provide high-level evidence.

Key Words: Dose; Enoxaparin; LAGB; Obese; Prophylaxis; Surgery

4.2 Introduction

Bariatric surgery is considered the most effective treatment in the management of morbid obesity and prevention of obesity-related complications (287). The number of obese patients undergoing bariatric surgery has increased more than 10-fold in the past two decades (288). One of the main reasons for this increase has been the development of laparoscopic techniques, which offer an excellent safety profile (287). However, venous thromboembolism (VTE) remains a significant cause of morbidity and mortality during the post-operative period (289). The incidence of VTE ranges from 0.2% to 3.5% in bariatric patients undergoing laparoscopic surgery (289).

Mechanical prophylaxis methods, such as thromboembolic deterrent (TED) stockings and sequential compression devices (SCD), and chemoprophylaxis, such as unfractionated heparin (UFH) or low molecular weight heparin (LMWH), are often used to prevent VTE in patients undergoing bariatric surgery. The routine use of mechanical prophylaxis is recommended by various guidelines, such as those of the American College of Chest Physicians (CHEST), the American Society for Metabolic and Bariatric Surgery (ASMBS), and the National Institute for Health and Care Excellence (NICE) (205, 290, 291). However, studies have reported inconsistent findings regarding the potential need, choice of drug, dosing regimen, and duration for VTE chemoprophylaxis. Generally, there is consensus that enoxaparin is more effective in VTE prevention compared to UFH, without increasing the bleeding risk in bariatric surgical patients (292). Yet, controversy regarding the use and dose of enoxaparin exists in the literature; recommendations have ranged from its use not being essential (mechanical prophylaxis alone is enough) (211, 212) to the use of high-dose enoxaparin (60 mg twice daily) (190, 214). Similarly, some studies have reported that an extended duration of chemoprophylaxis for 10 days or 2 weeks post-discharge resulted in less VTE complications compared to in-hospital use only (190, 293, 294).

The ASMBS position statement published in 2013 reported there was no level 1 evidence regarding the type, dose and duration of chemoprophylaxis to be used in bariatric surgical patients (290). The CHEST guidelines published in 2012 recommended the use of LMWH or UFH in bariatric surgical patients who have moderate (grade 2B) or high (grade 1B) VTE risk; however, no information regarding the dose and duration of chemoprophylaxis was provided (295). The NICE guidelines published in 2018 suggested the use of chemoprophylaxis (LMWH or fondaparinux sodium) in all patients with low bleeding risk, and for it to be

continued while the patient had significantly reduced mobility (291). Importantly, these guidelines did not distinguish between types of bariatric procedure (gastric bypass, sleeve gastrectomy, gastric banding) and surgical techniques (open vs. laparoscopic) in regard to VTE prophylaxis.

In light of this variation and uncertainty, we retrospectively examined current local practice for chemoprophylaxis in patients undergoing primary and revisional bariatric surgery (laparoscopic adjustable gastric banding; LAGB). We estimated the risk of VTE in each patient using a post-discharge VTE risk assessment tool published by the Cleveland Clinic (218). We determined the use (dose and duration) of chemoprophylaxis and the incidence of adverse outcomes (VTE and bleeding events). Finally, we identified the factors associated with the use of chemoprophylaxis.

4.3 Methods

Ethical approval for this study was obtained from the Tasmanian Health and Human Research Ethics Committee (H0015795). The need for consent from patients was waived by the committee due to the retrospective nature of the study and the collection of non-identifiable patient information.

A retrospective study was conducted of adult (age ≥ 18 years) obese patients (BMI ≥ 30 kg/m^2) who underwent primary and revisional bariatric surgery at the Royal Hobart Hospital (RHH) and the Hobart Private Hospital (HPH), from 1 Jan 2013 to 31 Dec 2017. The sole primary bariatric procedure at our study sites was LAGB. Revisional procedures were done for adjustment, replacement, or removal of bands, as well as adjustment, replacement, or removal of ports. Patients were excluded from the study if they were on regular anticoagulant or vitamin K therapy, underwent a concurrent surgical procedure (e.g. hysterectomy), or had an established congenital or acquired bleeding disorder, varicose veins, renal impairment with an estimated glomerular filtration rate < 60 mL/min/1.73m^2, prior heparin-induced thrombocytopaenia, haemorrhagic stroke within the previous 3 months, other surgery within the previous 3 months, or if relevant information was missing. Patients had been advised to stop taking any non-steroidal anti-inflammatory drugs and aspirin five days preoperatively.

A list of patients who had undergone primary and revisional LAGB during the study period was obtained from hospital coding databases. Patients' medical records were reviewed to confirm eligibility and to collect demographic and clinical information, including age, gender, body mass index (BMI), length of hospital stay (LOS), duration of surgical procedure,

American Society of Anaesthesiologists (ASA) score (283), return to operating room, incidents of dyspnoea at rest, smoking status, presence of diabetes mellitus, hypertension, congestive heart failure, paraplegia or obstructive sleep apnoea, history of VTE, oral contraceptive or hormone replacement therapy (HRT) use, details of mechanical prophylaxis, use of prophylactic anticoagulant (including dose and duration), and the occurrence of VTE (deep vein thrombosis and/or pulmonary embolism; DVT and/or PE) or major bleeding complications within 90 days following the procedure. Colour doppler ultrasound and CT pulmonary angiography techniques were used for diagnosis of VTE at our study sites. To define major bleeding, we used the criteria of the International Society on Thrombosis and Haemostasis: fatal bleeding; bleeding in vital organs (intracranial, intraspinal, retroperitoneal, intraarticular, pericardial, intraocular); bleeding at a surgical site requiring reoperation; and bleeding associated with a reduction in haemoglobin of at least 2 g/dL or requiring transfusion of at least 2 units of packed red cells/whole blood (296).

Categorical variables were expressed as count (percentage) and continuous variables as median (range). Fischer's exact test and Pearson's X^2 test were used for categorical variables to compare primary and revisional procedures. The Kruskal-Wallis test was used for continuous variables to compare demographic and clinical variables and prophylactic anticoagulant usage for primary and revisional procedures. Univariate logistic regressions were used to identify variables associated with enoxaparin use. Subsequently, variables with a p-value less than 0.15 in the univariate analyses, procedure type and VTE risk were considered in a multivariate regression analysis.

We also compared outcomes for our primary procedure cohort with the American College of Surgeons-National Surgical Quality Improvement Programme (ACS-NSQIP) and the French National Health Care System (SNIIRM) (218, 297). Only the primary LAGB procedure cohort was compared because the published data do not include revisional procedures. The one proportion sample test was used to compare our incidence of VTE and major bleeding with these data.

4.4 Results

Out of 262 screened patients, 212 met the inclusion criteria (Figure 7). One hundred and twelve underwent primary LAGB and 100 had revisional (24 band and 76 port) procedures. Socio-demographic and clinical characteristics of the patients are presented in Table 11. Patients in both cohorts were predominantly female. The primary procedure cohort had a significantly

higher mean weight and BMI. Primary and revisional band procedure patients had longer hospital lengths of stay (median of 1 day vs. 0 days, p<0.001) compared to the port procedure patients. Almost all patients in the primary (95%), revisional band (100%) and revisional port procedures (99%) categories had mild risk of VTE (218).

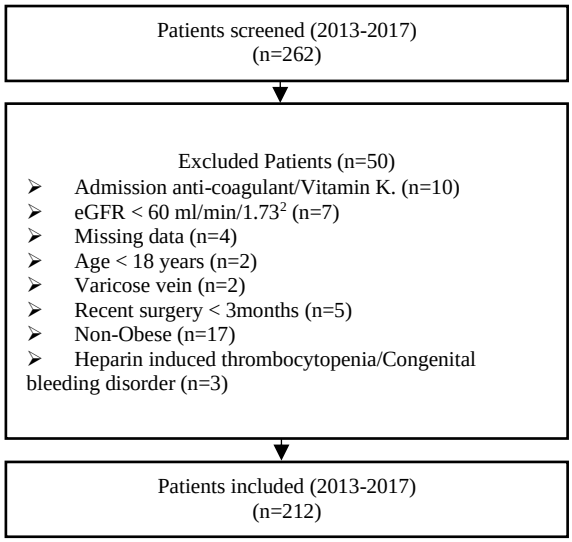

Figure 7. Flow diagram of patient inclusion

Mechanical prophylaxis was used during hospital stay in 100% of patients undergoing primary procedures compared to 96% and 84% for revisional band and port procedures, respectively. All patients in the primary procedure cohort were given the combination of TED, SCD and enoxaparin, compared to 75% in the revisional band procedures and just 18% of patients in the revisional port procedures cohorts (p<0.001). Overall, 69% of patients received chemoprophylaxis. The use of prophylactic enoxaparin was significantly higher in the primary and revisional band procedure cohorts compared to the revisional port procedure cohort (100% and 79%, vs. 20%; p<0.001). The majority of patients in the primary and revisional (band and port) cohorts received 40 mg enoxaparin once daily (Table 12). All patients in the primary procedure cohort received prophylactic enoxaparin post-discharge, typically for 10 days, compared to 54% of revisional band procedure and just 5% of revisional port procedure patients. The multivariate logistic regression model showed that patients who stayed longer in hospital (typically those who had undergone primary LAGB and band procedures) were more likely to receive chemoprophylaxis (Table 13); that is, enoxaparin use was higher in patients who had an overnight stay in hospital.

Table 11. Socio-demographic and clinical variables (n=212)

Variable	Primary Procedures (n=112)	Band Procedures (n=24)	Port Procedures (n=76)	P-value
Gender				***0.003***
Female, n (%)	86 (76.8)	16 (66.7)	70 (92.1)	
Age (years), median (range)	47.0 (18.0-69.0)	49.5 (25.0-71.0)	46.0 (24.0-67.0)	
Weight (kg), median (range)	135.5 (87.0-210.0)	112.0 (88.0-178.0)	120.0 (79.0-181.0)	***<0.001***
BMI (kg/m^2), median (range)	48.9 (36.2-75.3)	38.6 (34.5-62.5)	45.0 (32.4-64.9)	***<0.001***
TED/SCD				
Yes, n (%)	112 (100.0)	23 (96.0)	64 (84.2)	***<0.001***
Length of hospital stay, n (%)				***<0.001***
Day procedure only	0 (0.0)	7 (29.7)	62 (81.6)	
1 day	103 (92.0)	10 (41.7)	11 (14.5)	
2 days	6 (5.4)	5 (20.8)	1 (1.3)	
3 days	3 (2.7)	0 (0.0)	2 (2.6)	
4 days	0 (0.0)	2 (8.3)	0 (0.0)	
Days, median (range)	1 (1-3)	1 (0-4)	0 (0-3)	
Duration of surgery (minutes), median (range)	48.5 (30.0-113.0)	64.0 (25.0-145.0)	45.0 (20.0-92.0)	***<0.001***
ASA score				
1, n (%)	0 (0.0)	1 (4.2)	1 (1.3)	
2, n (%)	36 (32.1)	9 (37.5)	22 (28.9)	
3, n (%)	76 (67.9)	13 (54.2)	53 (69.7)	
4, n (%)	0 (0.0)	1 (4.2)	0 (0.0)	
Congestive heart failure				
Yes, n (%)	2 (1.8)	1 (4.2)	0 (0.0)	
Paraplegia				
Yes, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Return to operating room				
Yes, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Dyspnoea at rest				
Yes, n (%)	6 (5.4)	1 (4.2)	0 (0.0)	
Smoker				
Yes, n (%)	26 (23.2)	7 (29.2)	19 (25.0)	
Diabetes mellitus				***0.004***
Yes, n (%)	43 (38.4)	9 (37.5)	13 (17.1)	
Hypertension				
Yes, n (%)	50 (44.6)	7 (29.2)	22 (29.0)	
VTE history				
Yes, n (%)	3 (2.7)	1 (4.2)	0 (0.0)	
Obstructive sleep apnoea				

Yes, n (%)	32 (28.6)	4 (16.7)	18 (23.7)	
Oral contraceptive/Hormone replacement therapy Yes, n (%)	7 (6.2)	1 (4.2)	2 (2.6)	
VTE risk Mild, n (%) Moderate, n (%) High, n (%)	 107 (95.5) 4 (3.6) 1 (0.9)	 24 (100.0) 0 (0.0) 0 (0.0)	 75 (98.7) 1 (1.3) 0 (0.0)	

Only statistically significant values (p<0.05) are shown under the p-value column.

There was one VTE occurrence in each of the primary and revisional port procedure cohorts. Both patients were taking HRT. One patient (210 kg; BMI 75.3 kg/m^2) who underwent primary LAGB was diagnosed with a DVT 35 days post-operatively. This patient had received 40 mg enoxaparin at induction and 40 mg enoxaparin daily for 10 days post-discharge. The other patient (118 kg; BMI 49.1 kg/m^2) had undergone a port adjustment and was diagnosed with PE 2 months post-operatively, after reporting 4 weeks of shortness of breath. This patient had received only mechanical prophylaxis during hospital stay and no chemoprophylaxis. There was no significant difference in the overall occurrence of VTE between the primary and revisional procedure cohorts (0.9% vs. 1.0% respectively; p-value = 1.00). No major bleeding event was observed in either cohort. Similarly, there was no statistically significant difference in the overall 90-day VTE incidence between the cohorts who received and did not receive chemoprophylaxis (0.7% vs. 1.5%, respectively; p-value = 0.58).

Table 12. Thromboprophylaxis practices and outcomes (n=212)

Regimen	**Primary Procedures (n=112)**	**Revisional Procedures (n=100)**		**P-value**
		Band adjustment/ replacement/ removal (n=24)	**Port adjustment/ replacement/ removal (n=76)**	
TED/SCD only, n (%)	0 (0.0)	5 (20.8)	50 (65.8)	***<0.001***
Enoxaparin only, n (%)	0 (0.0)	1 (4.2)	1 (1.3)	
TED/SCD and Enoxaparin, n (%)	112 (100.0)	18 (75.0)	14 (18.4)	
None, n (%)	0 (0.0)	0 (0.0)	11 (14.5)	
Peri-operative anticoagulant				***<0.001***
Enoxaparin 40mg daily, n (%)	111 (99.1)	17 (70.8)	7 (9.2)	
Enoxaparin 60mg daily, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Enoxaparin 80mg daily, n (%)	1 (0.9)	0 (0.0)	1 (1.3)	
None, n (%)	0 (0.0)	7 (29.2)	68 (89.5)	
Post-operative anticoagulant				***<0.001***
Enoxaparin 40mg daily, n (%)	110 (98.2)	16 (66.7)	11 (14.5)	

Enoxaparin 60mg daily, n (%)	1 (0.9)	0 (0.0)	0 (0.0)	
Enoxaparin 80mg daily, n (%)	1 (0.9)	0 (0.0)	0 (0.0)	
None, n (%)	0 (0.0)	8 (33.3)	65 (85.5)	
Duration of chemoprophylaxis				***<0.001***
Peri-op only, n (%)	0 (0.0)	3 (12.5)	4 (5.3)	
Peri-op until discharge, n (%)	0 (0.0)	1 (4.2)	0 (0.0)	
Post-op until discharge, n (%)	0 (0.0)	2 (8.3)	7 (9.2)	
10 days post-discharge, n (%)	110 (98.2)	13 (54.2)	4 (5.3)	
30 days post-discharge, n (%)	2 (1.8)	0 (0.0)	0 (0.0)	
None, n (%)	0 (0.0)	5 (20.8)	61 (80.3)	
Enoxaparin use*				***<0.001***
Yes, n (%)	112 (100)	19 (79.2)	15 (19.7)	
VTE within 90-days, n (%)	1 (0.9)	0 (0.0)	1 (1.0)	
Major bleed within 90-days, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	

Only statistically significant values (p<0.05) are shown under the p-value column.
*Any of the following regimen of enoxaparin: start at induction until discharge, start post-operatively until discharge, start at induction until post-discharge, or start post-operatively until post-discharge.

The majority of clinical and demographic variables in our primary procedure cohort were similar to those reported in the ACS-NSQIP and SNIIRM databases. The reported incidences of VTE in primary LAGB patients in the ACS-NSQIP (30 days) and the SNIIRM databases (90 days) were 0.1% (26/24,650) and 0.2% (31/14,947), respectively (218, 297). Our study's 30-day and 90-day VTE incidences were not significantly different compared to the ACS-NSQIP database (0.0% vs. 0.1%, p-value = 0.63, 95% CI = 0.00-3.24) and the SNIIRM database (0.9% vs 0.2%, p-value = 0.09, 95% CI = 0.02-4.89), respectively.

Table 13. Logistic regression for variables associated with enoxaparin use (n=212)

Variable	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Gender				
Female	0.49 (0.21-1.13)	0.09	2.09 (0.32-13.64)	0.44
Age	0.99 (0.96-1.02)	0.86	--------	------
Procedure				
Primary	0.00 (0.00-0.00)	0.99	0.00 (0.00-0.00)	0.99
Duration of surgery (minutes)	1.03 (1.01-1.06)	**0.001**	1.02 (0.99-1.06)	0.15
BMI	1.08 (1.04-1.12)	< **0.001**	1.03 (0.94-1.12)	0.45
Overnight stay*				
Day procedure	307.78 (86.92-1089.87)	< **0.001**	33.32 (7.99-130.00)	< **0.001**
ASA score				
1	1.91 (0.11-32.00)	0.65	------	------

Smoker *Yes*	1.15 (0.58-2.92)	0.68	------	------
VTE risk *Mild*	1.84 (0.20-16.82)	0.59	0.00 (0.00-0.00)	0.99

ASA (American Society of Anesthesiologist), BMI (Body mass index), CI (Confidence interval), OR (Odds ratio).
Variables with p-value less than 0.15 and other factors which were associated with anticoagulant use (procedure type and VTE risk) were considered in multivariate regression analysis.
VTE risk is categorised into mild and moderate/severe.
*Overnight stay is categorized into ≥ 1 day or day procedure (0 days).

4.5 Discussion

We observed low incidences of VTE and no major bleeds in both primary and revisional LAGB procedures. Surgical procedures performed laparoscopically are less likely to result in post-operative VTE compared to open procedures (298). However, guidelines such as those of ASMBS, CHEST and NICE do not recommend specific VTE prophylaxis for LAGB. These guidelines suggest the same prophylactic chemoprophylactic approach based on the individual patient risk assessment (VTE vs. bleeding risk) and clinical judgment of the surgeon for all bariatric procedures regardless of type (gastric banding, gastric bypass and sleeve gastrectomy) or technique (laparoscopic or open) (290, 291). Despite the mild risk of VTE development, all of our primary LAGB procedure patients received chemoprophylaxis (majority received standard 40 mg doses).

LAGB is considered the safest bariatric procedure in terms of VTE risk (299). According to the ACS-NSQIP database, the 30-day prevalence of VTE following LAGB was 0.1% compared to 0.6% and 0.4% in laparoscopic sleeve gastrectomy (LSG) and laparoscopic gastric reduction (RYGB) patients, respectively (218). Similarly, according to the SNIIRM database, the reported incidence of 90-day VTE with LAGB was lower (0.2%) compared to LSG (0.5%) and RYGB (0.6%) (297). A German nationwide survey reported a gradually declining trend of chemoprophylaxis in LAGB surgery from 2005 (100%) till 2010 (95%), due to shorter LOS and less complicated procedures (300).

A total of 97% of patients who had mild risk of VTE development received chemoprophylaxis. Yet, studies of laparoscopic bariatric surgery have reported that mechanical prophylaxis alone provides sufficient VTE prophylaxis if the operation time is short and the patient becomes ambulatory soon after surgery (211, 212). Our patients fulfilled both of these criteria; the mean operation time was shorter (mean=49.7 minutes) compared to sleeve gastrectomy (100 minutes) and gastric bypass (135 minutes) patients reported in the ACS-

NSQIP database (218), and the majority of our patients were ambulatory on the day of surgery, likely due to the less complex surgical procedure.

A 10-year longitudinal study reported that LAGB resulted in a higher surgical revision rate compared to gastric bypass and sleeve gastrectomy (301). This is a possible explanation for the relatively high number of revisional procedures in our study, because LAGB has been the principal bariatric procedure conducted at our study site since the late 1990s. The mean duration from primary to revisional procedures was 7.36 years in our study patients.

This study had some limitations. Firstly, the retrospective study design meant that we had to rely on the notes available in digital medical records, and verbal advice from the principal bariatric surgeon. Secondly, our sample size was relatively small, with limited statistical power when examining relatively rare outcomes. Thirdly, we did not screen all patients for VTE after their surgery, so the incidence may have been under-reported. Lastly, LAGB is now not a first-choice bariatric procedure in many countries, including USA, but this is still widely employed in other countries.

4.6 Conclusion

A low incidence of VTE was observed in the LAGB surgical cases in this study, which included a heterogenous mix of primary and revisional surgeries, with varying use, dose and duration of enoxaparin. Because of the low VTE risk associated with LAGB, chemoprophylaxis may not be required in all patients unless there are additional risk factors, such as super-super-morbid obesity (BMI >60 kg/m^2) or concomitant HRT. As there is no procedure- and technique-specific thromboprophylaxis advice for bariatric surgery, surgeons should follow current recommendations, modifying them as required to suit individual patients' risk. Further research to provide procedure- and technique-specific thromboprophylaxis evidence may improve outcomes.

CHAPTER FIVE: Anaesthetists' Drug Dosing Practices in class-III Obese Surgical Patients: A Bi-national Survey

Overview

This chapter presents study addresses the fourth objective of this thesis. This cross-sectional survey aimed to understand anaesthetists' dosing practices for class-III obese surgical patients, explore if they had experienced increased incidences of adverse events related to drug dosing with these patients, and assess which resources they consulted for dosing advice in this population.

This work is a reproduction of the following submitted manuscript.

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5.1 Summary

Class-III obese patients, now regularly encountered clinically, have increased perioperative risks, including potentially from suboptimal drug dosing. However, current dosing guidelines are based on low level evidence and may not be widely accepted. This study aimed to understand anaesthetists' dosing practices for class-III obese surgical patients, explore if they had experienced increased incidences of adverse events related to drug dosing with these patients, and assess which resources they consulted for dosing advice in this population. After validation, an electronic survey was emailed to 1000 randomly selected members of the Australian and New Zealand College of Anaesthetists. Data was summarised, and the Pearson's $\chi 2$ and Fisher's exact tests were used to identify associations between respondents' characteristics and dosing practices. There were 230 completed responses (response rate 23%). Anaesthetists often reported dosing class-III obese patients in keeping with current recommendations; however, substantial heterogeneity in dosing practices was found. Lean body weight was most frequently used for dosing propofol, non-depolarising muscle relaxants, sugammadex and opioids, whereas total body weight was most frequently used for suxamethonium. Importantly, increased incidences of adverse events in class-III obese patients related to drug dosing were commonly experienced by anaesthetists. Many anaesthetists did not use any published drug dosing resources. Until higher level drug dosing evidence is available for class-III obese patients, anaesthetists should consider current recommendations as well as exercising increased attention with dosing, along with associated intra- and post-operative cares, to minimise drug-related adverse events in these patients.

Key Words: anaesthetists, adverse events, class-III obese, drug dosing, dosing resources, survey

5.2 Introduction

The prevalence of obesity in developed countries has been rapidly increasing in the last two decades (11, 302). Obese patients are more likely than non-obese to undergo surgery, including for bariatric procedures and obesity-related co-morbidities (303). Obesity-related physiological changes, combined with altered pharmacokinetics and pharmacodynamics, may increase the risk of drug dosing problems perioperatively in obese patients (304).

The combined guidelines of the Association of Anaesthetists of Great Britain and Ireland (AAGBI) and the Society for Obesity and Bariatric Anaesthesia (SOBA), mainly based on small-scale pharmacokinetic studies rather than large-scale clinical studies, state that dosing based on total body weight (TBW) increases the risk of relative overdose, and suggest some dosing strategies (149, 207). Various expert reviews and commentaries suggest similar perioperative drug dosing strategies in obesity to the AAGBI/SOBA guidelines (208, 233-235, 304, 305). Pharmacokinetic studies can provide important baseline dosing knowledge; however, this knowledge may not always be the most clinically practical information (202). And, there are no drug dosing recommendations based on level 1 evidence available for class-III obese patients undergoing anaesthesia (306). There is also a lack of studies exploring anaesthetists' actual dosing practices for these patients.

This survey study aimed to understand current perioperative drug dosing practices for class-III obese patients, explore if anaesthetists have experienced more adverse events related to dosing with these patients, and identify the dosing resources they used.

5.3 Methods

Ethical approval to conduct this survey was obtained from the Tasmanian Human Research Ethics Committee (H0017165). Participation in this survey was considered implied consent as was outlined in the participant information sheet. The survey's initial draft was developed by the research team (comprised of a consultant anaesthetist and five pharmacists) based on an extensive literature review. This first draft was emailed to a small group of other consultant anaesthetists (n=10) for face and content validation. The feedback was extensively reviewed by the research team and suggested changes were incorporated. This process was similarly repeated with the second draft (n=10) to assist in producing the final survey. The final survey (Appendix D) consisted of four sections designed to capture anaesthetists': i) demographic information; ii) dosing practices for commonly used intravenous peri-operative medications in class-III obesity; iii) relative incidence, compared with non-obese individuals, of adverse

events related to drug dosing experienced with class-III obese patients; and iv) resources regularly referenced for dosing advice in class-III obese patients.

After the survey's validation process, application was made to the Australian and New Zealand College of Anaesthetists' (ANZCA) Clinical Trials Network (CTN) to seek assistance in distributing the survey to its membership. After review and approval by the CTN, a cover letter and online survey link (using Lime Survey version 2.06, Hamburg, https://www.limesurvey.org/) was emailed by ANZCA to 1000 randomly selected members (786 fellows and 214 trainees) in August 2018. Prior published ANZCA-distributed survey studies were considered to have provided broad representation of the ANCZA membership with relatively low response rates (33% in 2015, and 29% in 2019) (307, 308). The survey was blinded as investigators were not involved in the randomised recipient selection process by ANZCA. Therefore, also, information about non-respondents could not be collected. The survey was anonymous, and no internet protocol addresses were collected. The survey remained active for a period of 2 months, with email reminders sent by ANZCA to all recipients at 1 week, and then again at 6 weeks, following the initial invitation.

Categorical variables were presented as counts and percentages. Pearson's $\chi 2$ test and Fisher's exact test were used to identify the association between respondents' characteristics and drug dosing practices. P-values<0.05 were considered statistically significant. Analyses were performed using SPSS version 24 (IBM Inc., Chicago, IL).

5.4 Results

Of 1000 invitations sent to ANZCA members, 230 complete responses were received (response rate 23%). The demographics of respondents were representative of the majority of the ANZCA membership, with no significant differences between the distribution of respondents and ANZCA members for gender (p=0.24), designation (fellows/trainees; p=0.76), and the majority of geographical locations (Table 14). Respondents were mostly males (69%), fellows (85%), working full time (76%) and with more than 10 years of anaesthesia experience (49%).

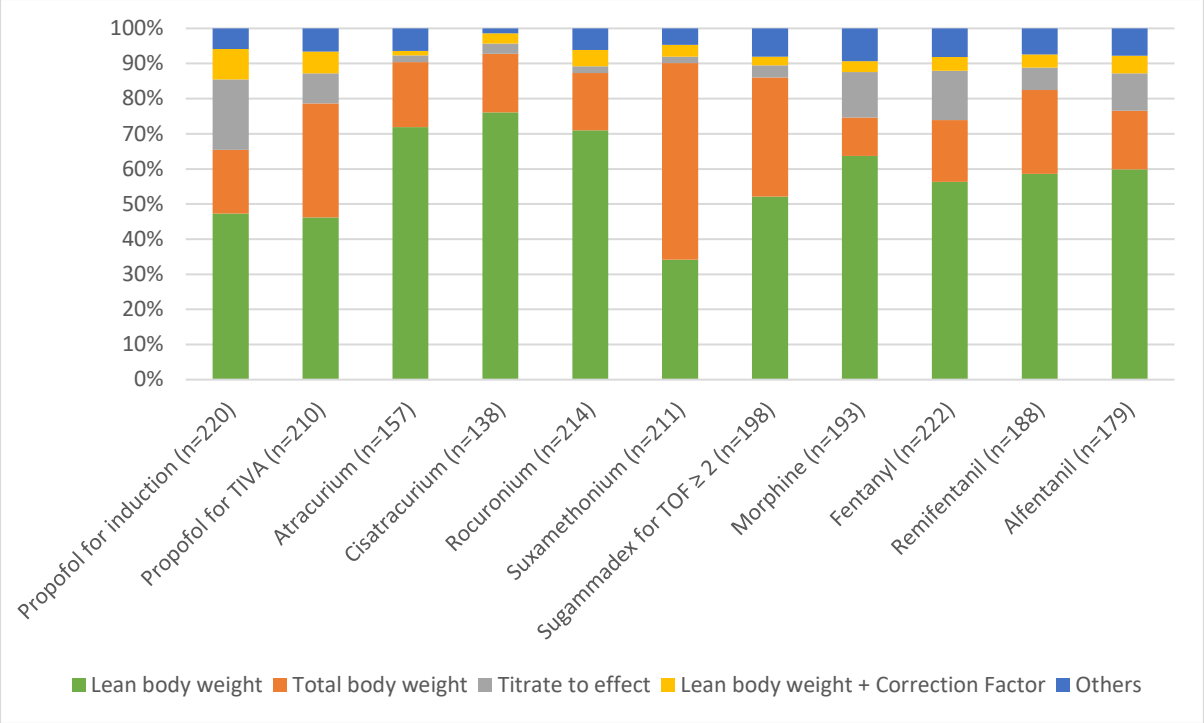
Table 14. Details of survey respondents

Variables	Study participants (N=230) n (%)	ANZCA members (N=7,071) n (%)	P-value
Sex			
Male	159 (69.1)	4,624 (65.4)	0.240
Female	71 (30.9)	2,447 (34.6)	
State/Territory/Country			
Australian Capital Territory	5 (2.2)	115 (1.6)	0.520
New South Wales	49 (21.3)	1,868 (26.4)	0.083
Northern Territory	5 (2.2)	41 (0.6)	**0.002**
Queensland	40 (17.4)	1,327 (18.7)	0.599
South Australia	17 (7.4)	461 (6.5)	0.599
Tasmania	7 (3.0)	145 (2.1)	0.299
Victoria	45 (19.6)	1,477 (20.9)	0.747
Western Australia	15 (6.5)	642 (9.1)	0.182
New Zealand	47 (20.4)	995 (14.1)	**0.006**
Designation			
Fellows	196 (85.2)	6,076 (85.9)	0.760
Trainee	34 (14.8)	995 (14.1)	
Years of experience			
Fellows			
< 5 years		39 (16.9)	
5 – 10 years		45 (19.5)	
11 – 20 years		56 (24.3)	
> 20 years		56 (24.3)	
Trainees			
1- 2 years		11 (4.8)	
3 – 4 years		20 (8.7)	
≥ 5 years		3 (0.4)	
Primary workplace			
Public		148 (64.4)	
Private		52 (22.6)	
Equal in both settings		30 (13.0)	
Work schedule			
Full-time		175 (76.1)	
Part-time		55 (23.9)	
Proportion of patients seen in last 4 weeks that were class-III obese			
Up to one-third		204 (88.7)	
More than one-third		26 (11.3)	

Resources used by anaesthetists	
Journal reading	107 (46.5)
Colleagues	102 (44.3)
Drug dosing phone apps/Online dosing calculators	46 (20.0)
Australian Medicines Handbook/Australian Therapeutic Guidelines	30 (13.0)
Internal hospital/Departmental guidelines	23 (10.0)
Lectures/Meetings/Conferences/Societies' websites	15 (6.5)
"Clinical Experience"	11 (4.8)
Pharmacy	1 (0.4)
None	70 (30.4)

Pearson's χ2 test/Fisher's exact test
Bold indicates significant P-values (<0.05)

Figure 8 shows that, with the exception of TBW for dosing suxamethonium, lean body weight (LBW) was the most frequently selected scalar for dosing all of the other drugs asked about in the survey. Still, for all drugs, a heterogeneous pattern of dosing practices was observed. Table 15 shows that some significant differences were observed in dosing patterns when looking at anaesthetists' genders, career stages, and whether they worked predominantly in public or private practice. These differences appeared to influence dosing practices for many of the drugs asked about in the survey.



TIVA (total intravenous anaesthesia), TOF (train of four)
Don't use/ not specified survey responses for propofol (IV) = 10 (4.3%), propofol (TIVA) = 20 (8.7%), atracurium = 73 (31.8%), cisatracurium = 92 (40.0%), rocuronium = 16 (6.9%), suxamethonium = 19 (8.3%), sugammadex = 32 (13.9%), morphine = 37 (16.0%), fentanyl = 8 (3.5%), remifentanil = 42 (18.2%) and alfentanil = 51 (22.2%)

Figure 8. Dosing practices of anaesthetists in class-III obese patient

Regarding adverse events related to drug dosing for class-III obese patients seen in anaesthetic practice, respondents commonly reported increased incidences for all types listed. Specifically, increased incidences were reported for inadequate paralysis for intubation (n=39, 17%), hypoxic events in recovery due to inadequate reversal (n=44, 19%), hypoxic events in recovery due to narcosis (n=101, 44%) and post-operative hypoxic problems on wards (n=130, 56%).

Many anaesthetists (30%) responded that they do not use any published drug dosing resources to assist their practice (Table 14). Of those who did, journal reading (46%) and consultation with colleagues (44%) were the most common. Understandably, trainees were significantly more likely than fellows to consult colleagues for dosing advice (68% trainees vs. 40% fellows, P=0.005).

Table 15. Relationship between respondents' characteristics and dosing practices

Variable	LBW	TBW	Titrate to effect	LBW + Correction factor	Other approach
Gender	NS	NS	Propofol (induction)* *28.8% females vs. 16.2% males (P=0.01)*	NS	NS
Anaesthetist Fellow or Trainee	Morphine *78.1% trainees vs. 60.9% fellows (P<0.001)*	Propofol (induction) *39.4% trainees vs. 14.4% fellows (P<0.001)*	NS	NS	NS
	Fentanyl *67.6% trainees vs. 54.3% fellows (P=0.01)*	Suxamethonium *79.4% trainees vs. 51.4% fellows (P=0.013)*			
Experience*	NS	Propofol (induction) *23.8% with ≤ 10 years of experience vs. 7.5% with > 10 years of experience (P=0.03)*	NS	NS	NS
		Propofol (TIVA) *44.3% with ≤ 10 years of experience vs. 20.4% with > 10 years of experience (P=0.02)*			
		Atracurium *30.0% with ≤ 10 years of experience vs. 6.9% with > 10 years of experience (P=0.006)*			
		Cistracurium *28.8% with ≤ 10 years of experience vs. 1.8% with > 10 years of experience (P=0.001)*			
		Rocuronium *21.0% with ≤ 10 years of experience vs. 8.1% with > 10 years of experience (P=0.009)*			
		Sugammadex *41.6% with ≤ 10 years of experience vs. 18.4% with > 10 years of experience (P=0.001)*			

Setting for majority of clinical time	NS	Suxamethonium *64.1% who mainly practice in public compared to 30.0% and 50.0% who mainly practice in private, and equally in both settings, respectively (P=0.02)*	NS	NS	NS

Pearson's χ2 test/Fisher's exact test. Only findings which had significant p=values (P<0.05) are listed in Table. NS (Not significant), LBW (Lean body weight), TBW (Total body weight).
** Fellows only (Trainees were excluded from the experience variables due to the possibility of confounding with the "designation" variable).*

5.5 Discussion

This is the first study to provide insights into anaesthetists' dosing practices for commonly used intravenous peri-operative drugs in class-III obese patients. It provides a thorough picture of dosing practices across two countries. It demonstrates that anaesthetists often employ dosing practices (for propofol, common muscle relaxants, sugammadex, and common opioids) in keeping with current advice. However, for all of these drugs, substantial heterogeneity in dosing practices was observed, influenced by anaesthetists' gender, career stage and work setting (public or private). Probably the most important finding to come from this survey, is that anaesthetists commonly reported an increase in the incidences of adverse events related to drug dosing in class-III obese patients, possibly implying that these patients can be more difficult to safely dose anaesthesia and post-operative analgesia for. A large proportion of anaesthetists reported using no published references for dosing advice in this patient group.

Propofol is the most widely used intravenous induction agent due to its fast onset, predictable pharmacokinetics and short duration of action (208). AAGBI/SOBA guidelines recommended LBW and adjusted body weight (ABW) as a suitable dosing scalar for propofol induction and total intravenous anaesthesia (TIVA), respectively (149, 207). Survey results showed that LBW was the most commonly used scalar for both induction and TIVA, yet still over half of the respondents used a variety of other dosing methods. Titration to effect was used by female anaesthetists more than males, which is plausible, and might indicate a difference in the degree of caution applied at inductions. TBW was generally used less frequently as anaesthetists progressed through their career.

For non-depolarising muscle relaxants (atracurium, cisatracurium, and rocuronium), the majority of respondents reported using the LBW scalar, which is in concordance with the AAGBI/SOBA recommendations (149, 207). When TBW was reported to be used, this was by new fellows more frequently than those more experienced. The AAGBI/SOBA guidelines,

however, do not provide recommendations for dosing suxamethonium or sugammadex. For suxamethonium, survey results showed that most anaesthetists use TBW, which is in keeping with the advice of other current literature (208, 234). TBW was used for suxamethonium by trainees more than fellows, and those fellows who work publicly more than privately. This may reflect a desire for safe intubating conditions in more complex cases in the public system, or how practice changes with maturity and environment. For sugammadex, most anaesthetists used LBW. There is controversy in the literature regarding the appropriate dosing scalar for sugammadex in class-III obese patients, with studies suggesting either IBW, ABW or TBW (253-255, 309, 310). TBW was used for sugammadex by new fellows more than those with over 10 years' experience. Anaesthetists reported that they did experience increased incidences of adverse events likely related to the under-dosing of relaxants, and possibly sugammadex in class-III obese patients.

According to the AAGBI/SOBA guidelines, LBW is the preferred dosing scalar for most opioids, except alfentanil (149, 207). Survey results found that most anaesthetists followed this scalar. Still, nearly 40% reported using a variety of other dosing strategies. Importantly, more anaesthetists reported increased incidences of adverse effects in class-III obese patients (versus non-obese patients) with opioids than with any other drugs included in the survey. This finding may be multifactorial (including due to inappropriate drug dosing, drug selection and post-operative ward monitoring), combined with pre-existing obesity-related pathophysiology. There may be no dosing scalar that is always the safest for dosing these drugs in class-III obese patients, when considering age differences, comorbidities such as obstructive sleep apnoea and renal impairment, as well as opioid tolerance, dependence and addiction (311). Further, opioids are generally higher risk in class-III obese patients because of the risk of obesity hypoventilation syndrome (312, 313). Therefore, opioid-sparing techniques are ideal, but when opioids are required then appropriate drug selection and dosing, as well as postoperative use of continuous positive airway pressure (CPAP; via a CPAP machine or high flow-nasal prongs) and care in an appropriately monitored environment (such as a high dependency unit), can all improve safety (312, 313).

The observed heterogeneity in drug dosing practices may be in part related to a lack of broad acceptance of the current AAGBI/SOBA dosing guidelines, perhaps because they were developed from lower level evidence (149). Also, the AAGBI/SOBA guidelines recommend different dosing scalars for different drugs that can require relatively complex calculations (149, 207). A recent systematic review reported that no dosing strategy for perioperative drugs in

obesity has high level evidence and, further, that there is a paucity of clinical outcomes data for peri-operative drug dosing in this patient group (306). Anaesthetists may therefore be choosing to make educated dosing estimations (314).

This study has some limitations. Firstly, the response rate of 23% was relatively low, possibly relating to survey fatigue, or a degree of disinterest in the survey's subject, as might be the case with anaesthetists not encountering a high volume of obese patients in their practice. Also, ANZCA have advised that a small proportion of survey recipients may not have been practicing anaesthetists (i.e. purely pain medicine practitioners), but the exact number of these recipients was unable to be provided. Nevertheless, a broad representation of the ANZCA's anaesthetic membership was still achieved (307, 308). Second, not all drugs used in anaesthetic practice were included in the survey (such as volatile anaesthetics, remifentanil, and sympathomimetics), which may have biased some factors surveyed (for example, residual muscle weakness could be exacerbated by volatile anaesthesia).

5.6 Conclusion

This study has shown that anaesthetists often follow current advice based on AAGBI/ SOBA guidelines for drug dosing in class-III obese patients; however, substantial heterogenicity in dosing practices exists. Dosing scalars for certain drugs recommended in the current AAGBI/ SOBA guidelines may be safer than other scalars for those drugs, but the evidence for any given scalar is not high level. Most importantly, anaesthetists reported higher incidences of adverse events related to drug dosing in class-III obese compared to non-obese patients. Establishing higher level evidence over time may improve peri-operative drug-dosing safety in class-III obese patients. Until then, to minimise adverse events, anaesthetists should consider current dosing recommendations as well as exercising increased attention with drug dosing and associated intra- and post-operative cares such as bispectral index monitoring, loss of consciousness monitoring, train of four monitoring and visual analogue score monitoring for class-III obese patients.

CHAPTER SIX: Concluding Discussion

Obese individuals are no longer a minority group in our healthcare system. According to the Australian Home of Custom Market Research 2016 report, the rate of hospitalisation of morbidly obese individuals (BMI $\geq 40 kg/m^2$) is twice that of normal weight individuals (315). Also, according to the Australian Institute of Health and Welfare, there was more than a two-fold increase in the number of morbidly obese patients admitted nationally only for elective weight loss surgical procedures between 2005 (n=9,300) and 2015 (n=22,700) (302). The increasing proportion of obese individuals in hospitals poses a specific set of challenges, such as special equipment to move and manage these patients, intensive monitoring required by professional healthcare staff, and pharmaceutical provisions or interventions (316, 317). With reference to pharmaceuticals, obese patients require modified drug dosing due to obesity-related physiological changes which can affect drug pharmacokinetics (99). Despite the increasing proportion of obese patients presenting to the healthcare system and known alterations in many physiological and pharmacokinetic parameters, obese patients are often excluded from during drug development phases (208). Therefore, in general, no dosing information is specifically available for obese patients as a result of the drug development phases and the dosing information on product labels may not be appropriate for this group of patients.

Dose adjustment is a special concern in the case of drugs which have narrow therapeutic indices, e.g. anaesthetic drugs (233). Although a few local and national guidelines are available for drug dosing in obese surgical patients, these are not universally accepted. The major limitation most likely to be hindering their acceptability and applicability is that these guidelines are mainly based on small-scale pharmacokinetic studies. Pharmacokinetic studies have a certain degree of uncertainty because these studies provide true but unknown pharmacokinetic parameter values because there is always certain degree of uncertainty exists while fitting the model to the data results (318). Therefore, pharmacokinetic studies may not always drive clinical practice.

Due to the lack of strong clinical evidence-based dosing guidelines, a systematic review of clinical outcome studies (with control non-obese and/or dose comparator groups) was conducted to quantify the evidence and to access the quality of evidence of drug dosing in obese surgical patients (Chapter 2). The systematic review revealed that clinical studies had often reported varied dosing strategies for the same drug. One such example is for propofol

induction dose studies: one study reported CBW (241) and the other study reported LBW (240) as the appropriate dosing scalar for propofol induction dose. The possible reasons for these different findings are: i) difference in the mean weight of obese individuals, i.e. mean weights were 110kg approximately (241) and 130kg approximately (240), and ii) difference in the outcome measurements to quantify the clinical response, i.e. automated bispectral index (241) and subjective assessment of loss of consciousness (240). Also, no clinical studies were identified for some important peri-operative drugs, such as fentanyl, alfentanil and remifentanil, with a control/comparator group. Given the discrepancies in the results of observational studies and the limited number of randomised control trials, no drug dosing recommendation achieved an "Excellent" quality of evidence. Based on this limitation in the published literature, the current drug dosing practices of commonly used drugs, such as prophylactic antibiotics, prophylactic anticoagulants and anaesthetics, in obese surgical patients and potential dose-related outcomes, such as SSI, VTE, inadequate paralysis and hypoxic events, were investigated.

SSI is a major cause of morbidity and mortality, occurring in 10% of surgical patients, and obesity a major risk factors for SSI (319, 320). Administration of the correct dose of the appropriate antibiotic is the standard in SSI prevention (321). Cefazolin is the most commonly used drug for SSI prophylaxis; however, the appropriate dose for obese patients is still debatable. It was reported that volume of distribution (Vd) of cefazolin is positively correlated with total body weight and lean body weight, possibly due to higher blood flow and clearance in obese individuals (185). In obesity, a higher body weight is also accompanied by 20-40% higher lean mass, which means that the lean to adipose weight ratio is approximately 3:2 (215). Furthermore, the purpose of prophylactic cefazolin is to prevent bacteria from seeding an infection, not to treat infection. Therefore, in obese individuals, the use of TBW based doses or fixed standard doses may lead to over-dosing (with increased risk of *Clostridium difficile*) or under-dosing (increased risk of SSI), respectively (322). Based on the low lipophilic nature of cefazolin and higher absolute lean mass and increased blood volume in obese individuals, various guidelines suggest a 50% increment in dose (to 3g) for those who weigh more than 120kg, compared to a 2g dose for normal weight individuals (203, 323). This dosing recommendation appears logical; however, previous clinical studies of cefazolin prophylaxis dosing suggested that a 2-g dose is enough in obese individuals to provide adequate antibacterial coverage (173, 202).

In the current study (Chapter 3), all the patients who weighed ≥120kg received a standard 2-g dose and the incidence of SSI was almost double in these patients compared to those who weighed < 120kg and also who received a 2-g dose (9.8% vs 5%; p=0.17). The most logical explanation of this difference is the lesser extent of obesity in previous studies (mean BMI=35kg/m^2 (173) and mean BMI=36kg/m^2 (202)) compared to the current study (mean BMI=47kg/m^2). The findings of the current study seem to support the guideline's recommendations; however, this needs to be supported by a large-scale prospective clinical study of obese and morbidly obese individuals.

VTE is not a highly prevalent condition (about 0.2% in surgical patients), but it can be fatal and accounts for almost 10% of hospital deaths in both American and Australian hospitals (324). Morbid obesity is considered as an important risk factor of VTE development (218). Other significant risk factors are: major surgery, immobility, smoking, malignancy and family history of VTE (325). The three imperative measures to prevent post-surgical VTE include: early mobilisation, use of mechanical prophylaxis, and administration of chemoprophylaxis (325). It is widely accepted that LMWH are the preferred chemoprophylactic agents in bariatric procedures (292). However, the optimal dose and duration of prophylactic LMWH in obese patients is still controversial. The majority of guidelines do not specify an appropriate dose and duration of prophylactic LMWH in obese surgical patients (205, 291, 326). Various clinical studies have also reported inconsistent findings regarding the dose and duration of prophylactic anticoagulants, especially of enoxaparin. Enoxaparin is a hydrophilic drug with generally less distribution into adipose tissue and higher clearance possibly due to higher GFR and higher blood flow (327). Therefore, TBW-based dosing may result in over-dose (increased risk of bleeding) and a fixed dose approach may lead to a suboptimal dose (increased risk of VTE) in obese patients (327). Other important factors, such as complexity of surgery and immobility, should also be considered besides the degree of obesity with enoxaparin dose decision making for VTE prophylaxis.

At the current study sites, LAGB was a principal bariatric procedure (Chapter 4). LAGB is a minimally invasive procedure, and thereby is not considered major surgery (299). The majority of LAGB patients mobilise on the day of surgery, and therefore are not considered as high-risk VTE patients. In the current study, 69% of primary and revisional LAGB patients received a conventional prophylactic enoxaparin dose (mainly 40 mg once daily). The specific pattern in the use of prophylactic enoxaparin was noted: 100% patients of primary LAGB (a relatively complex procedure compared to band and port procedures), 79% of band procedures

(less complex than primary and more complex than port procedure), and 20% of port procedures patients (considered as the least complex procedure) received enoxaparin. Only two VTE events were noted: one in the primary procedure cohort (received 40 mg daily enoxaparin for 10 days post-surgery) and the other in the port procedure cohort (did not receive enoxaparin). It is difficult to establish the superiority of prophylactic enoxaparin use in LAGB patients owing to the less complex nature of this procedure and very low incidence of VTE. Also, the American Society for Metabolic and Bariatric Surgery reported that use of prophylactic anticoagulant can minimise the VTE incidence but it cannot be eliminated completely (326). Therefore, there is a need for a large-scale clinical dosing study across different bariatric procedures to identify the usefulness and optimal dosing of prophylactic enoxaparin.

Morbidly obese patients undergoing surgery are at higher risk of possessing hypertension, ischaemic heart disease, respiratory and reflux disorders (328). As a result, obesity presents a specific set of challenges during anaesthesia. The situation is further complicated because obesity can potentially alter the pharmacokinetics of many drugs (328). Despite this, there is a lack of in-depth understanding of pharmacokinetic changes of anaesthetic drugs, mainly because of the limited number of studies (with small sample sizes) and inconsistent findings of these studies. A few guidelines also suggest potentially appropriate dosing strategies for morbidly obese patients, but these recommendations are mainly based on a limited number of small sample studies (149, 207). The majority of anaesthetic drugs are lipophilic in nature, except for the muscle relaxants (e.g. rocuronium, cisatracurium) (329); thereby, having a larger volume of distribution in obese compared to non-obese individuals. TBW seems to be a more appropriate dosing scalar for lipophilic drugs, but this may lead to overdosing of anaesthetic agents because of their narrow therapeutic indices. However, it is challenging to estimate the dosing of particular anaesthetic drugs in routine clinical practice because multiple drugs are given during anaesthesia and one drug can mimic the effect of another drug. For instance, inhaled anaesthesia can potentiate the effect of muscle relaxants, and benzodiazepines can synergise the effect of opioids (330, 331).

Owing to these limitations to measuring the appropriate drug dosing and clinical outcomes from patients' medical records, a survey methodology was adopted in the current study (Chapter 5). Heterogeneity in the dosing practices was reported in the survey. Nearly 50% anaesthetists selected LBW scalar for dosing the majority of drugs asked about in the survey and the remainder selected varied dosing strategies, such as TBW and CBW. This heterogeneity raises concerns regarding the available drug dosing evidence in morbidly obese

patients. Nevertheless, a possible explanation for routinely using LBW is the narrow therapeutic window of anaesthetic agents, and anaesthetists consequently using caution in dosing these agents. Anaesthetists also reported an increased frequency of adverse events, such as hypoxic events in recovery due to narcosis and post-operative hypoxic problems on wards, in morbidly obese patients. However, it is difficult to ascertain if the reported higher incidence of adverse events was because of inappropriate selection of dosing scalar or due to the obesity-related pathophysiological changes. Therefore, there is a need for large-scale randomised control trials to generate high-level evidence for optimal dosing of anaesthetics in morbidly obese patients.

In summary, drug dosing evidence in obese surgical patients is based mainly on pharmacokinetic studies and there is scarcity of clinical outcome studies. This may possibly explain why some physicians are seemingly reluctant to adhere to the clinical guidelines. It is noted that the majority of surgeons and anaesthetists use their own clinical experience and judgment for dosing obese patients. It is also evident that dosing based on physicians' clinical judgment may not always achieve better patient outcomes. The studies outlined in this thesis may serve as an important source of information for surgeons and anaesthetists, which can aid them in their dose decision making. The findings of this thesis may also guide future research towards stronger evidence-based dosing guidelines, to optimise peri-operative drug dosing for obese surgical patients.

Based on the findings, the author recommends that obese patients should be routinely included in the drug development phases of newly-developed drugs. For already marketed drugs, there is a need for large-scale clinical outcome studies and randomised control trials to generate strong evidence-based dosing guidelines for this patient population. Also, there is a need to establish a nationwide obese patient surgical registry with drug dosing and clinical outcome information because multiple drugs are administered to these patients and having a large database would aid to statistically isolate the effects of individual agents. Lastly, obese patients are no longer a minority population in our healthcare system; therefore, clinicians should consider them as an important special population in terms of dose adjustment.

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APPENDICES

Appendix A. Electronic search strategy for systematic review (Chapter 2)

Database	Initial Search Dated	Search Terms	No. of Results	Additional Comments
PubMed (1963-2016)	10/05/2017	(("Therapeutic Uses"[MeSH]) AND "Obesity"[MeSH]) AND "Surgical Procedures, Operative"[MeSH].	(n=1,351)	Search by using MeSH terms(restricted search to human studies)
PubMed (1958-2016)	10/05/2017	(((((Medication Use) OR Drug Dosing) OR Dose)) AND (((Obesity) OR Obese) OR Overweight)) AND ((((Surgery) OR Surgical Procedure) OR Medical Procedure) OR Surgical Patient).	(n=3,602)	Search made by using Free text (restricted search to human studies)
EMBASE (1953-2016)	10/05/2017	'Drug Therapy'/exp/mj AND 'Obesity'/exp/mj AND 'Medical Procedures'/exp/mj.	(n=1,395)	Search made by using Emtree terms (restricted search to human studies)
EMBASE (1977-2016)	10/05/2017	'Drug Dose OR Medication OR Dosing AND Obese OR Obesity OR Overweight AND Surgical Procedure OR Surgery OR Surgical Procedure OR Surgical Patient OR Medical Procedures	(n=4,424)	Search made by using free text (restricted search to human studies)
Cochrane (1978-2016)	10/05/2017	MeSH descriptor: [Therapeutic Uses] explode all trees AND MeSH descriptor: [Obesity] explode all trees AND MeSH descriptor: [Surgical Procedures, Operative] explode all trees.	(n=119)	Search made by using Mesh terms
Cochrane (1977-2016)	10/05/2017	Medication Use OR Drug Dosing OR Dose AND Obesity OR Obese OR Overweight AND Surgery OR Surgical Procedure OR Medical Procedure OR Surgical Patients	(n=1,167)	Search made by using free text
CINAHL (1969-2016)	10/05/2017	Medication Use OR Drug Dosing OR Dose AND Obesity OR Obese Patients OR Obese AND Surgery OR Surgical procedures OR Operating procedures.	(n=155)	Search made by using full text search

Appendix B. PRISMA Checklist for systematic review (Chapter 2)

Section/topic	#	Checklist item	Reported in section
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title Page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction/Method
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NO
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Study selection
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Study Identification
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Study selection
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Data extraction and analysis
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Data extraction and analysis
Risk of bias in individual	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Appendix C

studies			
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Data extraction and analysis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Data extraction and analysis
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Data extraction and analysis
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Data extraction and analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Description of included studies
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix C
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix C
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Conclusion/Table 7
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit: **www.prisma-statement.org**.

Appendix C. Quality and risk of bias assessment used in the systematic review (Chapter 2)

Appendix C1. An adapted appraisal checklist according to Joanna Briggs Institute (JBI) meta-analysis of statistics assessment and review instrument

Experimental Studies (e.g. randomised/quasi-randomised, pre-post studies)		
1. Is the assignment of intervention groups truly random?	☐ Yes ☐ No ☐ Unclear ☐ Not applicable	
2. Are participants blinded to allocation of intervention?	☐ Yes ☐ No ☐ Unclear ☐ Not applicable	
3. Is allocation of treatment groups concealed from the investigator?	☐ Yes ☐ No ☐ Unclear ☐ Not applicable	
4. Are outcomes of people who withdrew described and included in the analysis?	☐ Yes ☐ No ☐ Unclear ☐ Not applicable	
5. Are those assessing the outcomes blind to the allocation of intervention?	☐ Yes ☐ No ☐ Unclear ☐	Not applicable
6. Are the control and intervention groups comparable at entry?	☐ Yes ☐ No ☐ Unclear ☐ Not applicable	
7. Are groups treated identically other than for the named intervention?	☐ Yes ☐ No ☐ Unclear ☐ Not applicable	
8. Are outcome measured in the same way for all groups?	☐ Yes ☐ No ☐ Unclear ☐ Not applicable	

9. Are outcomes measured in a reliable way?	☐	Yes
	☐	No
	☐	Unclear
	☐	Not applicable
10. Is appropriate statistical analysis used?	☐	Yes
	☐	No
	☐	Not clear
	☐	Not applicable
Cohort (with control)/Case-controlled studies		
1. Is the sample representative of patients in the population as a whole? Note: Answer ‘’Yes’’ if wider age range patients from both genders are included.	☐	Yes
	☐	No
	☐	Unclear
	☐	Not applicable
2. Are the patients at a similar point in the course of their condition/illness?	☐	Yes
	☐	No
	☐	Unclear
	☐	Not applicable
3. Has bias been minimised in relation to selection of cases and controls?	☐	Yes
	☐	No
	☐	Unclear
	☐	Not applicable
4. Are confounding factors identified and strategies to deal with them stated?	☐	Yes
	☐	No
	☐	Unclear
	☐	Not applicable
5. Are outcome assessed using objective criteria?	☐	Yes
	☐	No
	☐	Unclear
	☐	Not applicable
6. Is follow-up carried out over a sufficient time period?	☐	Yes
	☐	No
	☐	Unclear
	☐	Not applicable
7. Are the outcomes of people who withdrew described and included in the analysis?	☐	Yes
	☐	No
	☐	Unclear
	☐	Not applicable
8. Are outcomes measured in a reliable way?	☐	Yes

	☐ No ☐ Unclear ☐ Not applicable
9. Is appropriate statistical analysis used?	☐ Yes ☐ No ☐ Unclear ☐ Not applicable
Descriptive/Case series studies	
1. Is the study representative of patients with RI prescribed with medications affected by the renal system?	☐ Yes ☐ No ☐ Unclear ☐ Not applicable
2. Were the criteria for inclusion in the sample clearly defined?	☐ Yes ☐ No ☐ Unclear ☐ Not applicable
3. Were the confounding factors identified and strategies to rule them out stated?	☐ Yes ☐ No ☐ Unclear ☐ Not applicable
4. Were outcomes assessed using objective criteria	☐ Yes ☐ No ☐ Unclear ☐ Not applicable
5. If comparisons are being made, were there sufficient descriptions of the groups	☐ Yes ☐ No ☐ Unclear ☐ Not applicable
6. Was follow-up carried out over a sufficient time period?	☐ Yes ☐ No ☐ Unclear ☐ Not applicable
7. Were the outcomes of people who withdrew described and included in the analysis?	☐ Yes ☐ No ☐ Unclear ☐ Not applicable
8. Were outcomes measured in a reliable way?	☐ Yes

	☐ No ☐ Unclear ☐ Not applicable
9. Was appropriate statistical analysis used?	☐ Yes ☐ No ☐ Unclear ☐ Not applicable

Appendix C2. Quality assessment of the studies included in the systematic review based on the adapted version of Joanna Briggs Institute

Randomized and quasi-randomized trials											
	True randomization	Blinding	Allocation concealment	Withdrawal report	Double blinding	Entry Comparability	Groups treated identically	Same outcome measurement	Outcomes reliability	Appropriate statistical analysis	**Quality**
Van Karlingen et al.(2010)/Netherlands	UC	YES	UC	NO	YES	UC	YES	YES	NO	YES	**Moderate**
Ingrande et al.(2011)/USA	UC	YES	YES	NA	YES	YES	YES	YES	NO	NO	**Moderate**
Lam et al.(2013)/Taiwan	UC	YES	UC	NO	YES	YES	YES	YES	YES	NO	**Moderate**
Lee et at. (2009)/Canada	NO	YES	UC	NA	NO	YES	YES	YES	YES	YES	**Moderate**
Kim et al.(2012)/South Korea	YES	YES	YES	NA	YES	YES	YES	YES	YES	YES	**Strong**
Van Kralingen et al.(2011)/ Netherlands	UC	YES	YES	NO	UC	YES	YES	YES	UC	YES	**Moderate**
Leykin et al. (2004)/Italy	UC	YES	UC	NA	YES	YES	YES	YES	YES	YES	**Strong**
Meyhoff et al. (2009) /Denmark	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	**Strong**
Sakızcı-Uyar et al. (2016)/Turkey	YES	YES	YES	NA	YES	YES	YES	YES	YES	YES	**Strong**
Lemmens et al.(2006) /USA	UC	YES	UC	NA	YES	YES	YES	YES	YES	YES	**Strong**
Van Lancker et al.(2011)/Belgium	UC	YES	UC	YES	YES	YES	YES	YES	YES	YES	**Strong**
Stitely et al.(2013)/USA	YES	NO	YES	NO	NO	YES	YES	YES	NO	YES	**Moderate**
Kalfarentzos et al.(2001)/Greece	UC	UC	UC	NA	UC	YES	YES	YES	YES	YES	**Moderate**
Imberti et al.(2009)/Italy	YES	UC	YES	NO	YES	YES	YES	YES	YES	NO	**Strong**
Steib et al. (2016)/France	UC	UC	UC	NO	UC	YES	YES	YES	YES	YES	**Moderate**
Cohort (with control)/case-controlled studies											
	Sample generalizability	Patients similarity	Minimised selection bias	Confounders	Objective outcome assessment	Sufficient follow-up period	Accurate withdrawal reporting		Outcomes reliability	Appropriate statistical analysis	**Quality**
Servin et al. (1993)/France	YES	YES	YES	YES	YES	YES	YES		UC	YES	**Strong**
Tsueda et al. (1978)/USA	UC	YES	YES	NO	UC	YES	NO		UC	UC	**Weak**
Weinstein et al.(1988)/ USA	UC	YES	YES	YES	YES	YES	NA		UC	YES	**Moderate**
Suzuki et al.(2006)/Japan	NO	YES	YES	NO	YES	YES	NA		UC	YES	**Moderate**
Varin et al. (1990)/Canada	YES	YES	YES	YES	YES	YES	NA		UC	YES	**Strong**
Pühringer et al.(1999)/ Austria	NO	YES	YES	NO	YES	YES	NA		UC	UC	**Moderate**
Sanfilippo et al.(2013)/Italy	NO	YES	YES	YES	YES	YES	NA		UC	YES	**Moderate**
Badaoui et al.(2016)/France	UC	YES	YES	NO	YES	YES	NO		UC	YES	**Moderate**
Graves et al. (1983)/USA	YES	UC	YES	YES	NO	YES	NA		YES	UC	**Moderate**
Grodofsky et al.(2012)/USA	YES	YES	YES	YES	YES	NO	NA		UC	YES	**Moderate**

Toma et al.(2011)/USA	YES	NO	NO	YES	NO	UC	NO		UC	YES	**Weak**
Unger et al.(2014)/USA	YES	YES	YES	NO	YES	YES	NA		UC	YES	**Moderate**
Ahmadzia et al.(2015)/USA	NO	YES	YES	YES	YES	YES	NA		YES	YES	**Strong**
Peppard et al.(2017)/USA	YES	NO	YES	YES	YES	YES	NO		YES	YES	**Strong**
Scholten et al.(2002)/USA	YES	NO	YES	YES	YES	YES	NA		YES	YES	**Strong**
Borkgren-Okonek et al.(2008)/USA	YES	YES	YES	YES	YES	YES	YES		UC	UC	**Strong**
Singh et al.(2012)/USA	YES	YES	YES	NO	YES	YES	NA		UC	NO	**Moderate**
Javanainen et al.(2016)/Finland	YES	YES	YES	YES	YES	YES	NA		YES	YES	**Strong**

Appendix D. Participant information sheet and survey questions (Chapter 5)

Invitation

You have been invited to participate in this study because anaesthetists are the key clinicians dosing perioperative drugs.

My name is Mr Zahid Hussain, and this study is being conducted as part of my PhD research into drug dosing in class III obese surgical patients (College of Health and Medicine, University of Tasmania) in conjunction with my supervisors Dr Tabish Razi Zaidi, Dr Colin Curtain, Dr Corinne Mirkazemi, Prof Gregory Peterson, and our clinical advisor Dr Karl Gadd (FANZCA).

What is the purpose of this research?

The purpose of this study is to explore anaesthetist's peri-operative drug dosing practices for class-III obese surgical patients. Also, the research will determine if there is a perceived need for establishing practice guidelines to assist drug dosing in class-III obese surgical patients.

What will I be asked to do?

You will be asked to complete an online survey, which will take approximately 5 minutes to complete. The survey will involve answering questions about your current peri-operative drug dosing practices for class-III obese surgical patients, any increased frequency of clinical difficulties (adverse outcomes) you may have experienced related to drug dosing for these patients, any resource/s you may use (if any) to aid drug dosing for these patients, and whether you perceive there is a need for obesity-specific peri-operative drug dosing guidelines. Your responses will be completely anonymous, and only the research team members will have access to the study data.

Do I have to take part in this study?

Your involvement in this study is entirely voluntary.

Are there any benefits associated with being in this study?

You will be contributing valuable information to give insights into clinical practice of peri-operative drug dosing in obese surgical patients. Hence, knowledge gained from this study may prompt clinical recommendations for the dosing of perioperative drugs in obese patients, and possibly lead to further research toward this.

Are they any risks or cost associated with being in this study?

There are no risks associated with being involved in this study, as your responses will be non-identifiable (and no IP addresses will be collected), and only the combined results will be published.

What will happen to the information collected when the study is completed?

Once the survey period has ended, the collated data will be analysed to describe dosing practice trends in obese surgical patients. The study data is non-identifiable and will be stored on the College of Health and Medicine server at the University of Tasmania according to protocols outlined by the university research ethics committee. The data will only be accessible by the researchers named above and will be retained for a minimum period of five years.

How will the results of the study be published?

We aim to present results at a future ANZCA ASM. We also aim to publish the results of this study in a respected, peer-reviewed anaesthesia journal. Additionally, results will be published as a component of my PhD thesis.

What if I have a complaint or any concerns about the study?

If you have any questions or concerns about any aspect of this study please do not hesitate to contact either myself through email (Zahid.Hussain@utas.edu.au) or Dr Tabish Zaidi through email (Tabish.RaziZaidi@utas.edu.au). If you have concerns or complaints about the conduct of this study (reference number: H0017165), please contact the Executive Officer of the HREC (Tasmania) Network on +61 3 6226 6254 or email human.ethics@utas.edu.au.

Thank you for taking the time to consider this survey. If you wish to assist with this study, you can access the survey online, by clicking the next button below

Demographic Information

State/Territory:

ACT / NSW / NT / New Zealand / QLD / SA / TAS / VIC / WA

What is your Professional Designation?

Specialist / Trainee

How many years have you been practising anaesthesia?

_____ (Numerical Value)

Where do you spend the majority of your clinical time?

Private / Public / Equal in both settings

What is your work routine?

Full Time / Part-time

Please estimate what proportion of your patients in the last 4 weeks have had a BMI ≥ 40kg/m^2?

Up to one third / More than one third

Dosing Practices

When anaesthetising patients with a BMI ≥ 40kg/m^2 (and no other significant comorbidities), what dosing strategy would you normally use for the following drugs?

Propofol (For IV induction)	Total body weight	Lean body weight	My own practice(specify) _____	NA (Don't use in practice)
Propofol (For TIVA)	Total body weight	Lean body weight	My own practice(specify) _____	NA (Don't use in practice)
Atracurium	Total body weight	Lean body weight	My own practice(specify) _____	NA (Don't use in practice)
Cisatracurium	Total body weight	Lean body weight	My own practice(specify) _____	NA (Don't use in practice)
Rocuronium (Not for RSI)	Total body weight	Lean body weight	My own practice(specify) _____	NA (Don't use in practice)
Suxamethonium	Total body weight	Lean body weight	My own practice(specify) _____	NA (Don't use in practice)
Sugammadex (For rocuronium reversal when TOF count ≥ 2)	Total body weight	Lean body weight	My own practice(specify) _____	NA (Don't use in practice)
Morphine	Total body weight	Lean body weight	My own practice(specify) _____	NA (Don't use in practice)
Fentanyl	Total body weight	Lean body weight	My own practice(specify) _____	NA (Don't use in practice)
Remifentanil	Total body weight	Lean body weight	My own practice(specify) _____	NA (Don't use in practice)
Alfentanil	Total body weight	Lean body weight	My own practice(specify) _____	NA (Don't use in practice)

If you selected "my own practice", please provide details in the comment box for the specific drug.

Clinical Difficulties

In patients with BMI ≥ 40kg/m^2, have you observed any increased frequency of the following complications compared to non-obese patients (BMI < 30kg/m^2)?

Inadequate paralysis for intubation under general anaesthesia (requiring extra muscle relaxant dosing)?	Yes	No
Hypoxic events in recovery due to inadequate reversal?	Yes	No
Hypoxic events in recovery due to narcosis?	Yes	No
Post-operative hypoxic problems on wards (such as due to obesity hypoventilation syndrome)	Yes	No

Resources

Do you use any information resources to assist you in dosing patients with BMI ≥ 40kg/m^2?

(select one or more):

1. Internal hospital/departmental guidelines
2. Drug dosing phone apps
3. Australian Medicines Handbook
4. Therapeutic guidelines (eTG)
5. Journal reading
6. Colleagues
7. Nil
8. Other (Specify) _____

Appendix E. Ethics Approvals

Appendix E1. Ethics approval for retrospective studies

Office of Research Services
University of Tasmania
Private Bag 1
Hobart Tasmania 7001
Telephone + 61 3 6226 7479
Facsimile + 61 3 6226 7148
Email Human.Ethics@utas.edu.au
www.research.utas.edu.au/human_ethics/

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

05 September 2016

Dr Tabish Razi Zaidi
C/- School of Pharmacy

Sent via email

Dear Dr Razi Zaidi

REF NO: H0015795
TITLE: An Audit of Medication Use in Obese Patients Admitted to Royal Hobart Hospital for Elective Surgical Procedures

Document	***Version***	***Date***
Data Collection Form		
Low Risk Application Form		
Privacy Form		

The Tasmanian Health and Medical Human Research Ethics Committee considered and approved the above documentation on **31 August 2016** to be conducted at the following site(s):

Royal Hobart Hospital

Please ensure that all investigators involved with this project have cited the approved versions of the documents listed within this letter and use only these versions in conducting this research project.

This approval constitutes ethical clearance by the Health and Medical HREC. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approvals of other bodies or authorities are required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct in Human Research* (NHMRC 2007 updated 2014).

Therefore, the Chief Investigator's responsibility is to ensure that:

(1) The individual researcher's protocol complies with the HREC approved protocol.

(2) Modifications to the protocol do not proceed until **approval** is obtained in writing from the HREC. Please note that all requests for changes to approved documents must include a version number and date when submitted for review by the HREC.

(3) Section 5.5.3 of the National Statement states:

Researchers have a significant responsibility in monitoring approved research as they are in the best position to observe any adverse events or unexpected outcomes. They should report such events or outcomes promptly to the relevant institution/s and ethical review body/ies and take prompt steps to deal with any unexpected risks.

The appropriate forms for reporting such events in relation to clinical and non-clinical trials and innovations can be located at the website below. All adverse events must be reported regardless of whether or not the event, in your opinion, is a direct effect of the therapeutic goods being tested. http://www.utas.edu.au/research-admin/research-integrity-and-ethics-unit-rieu/human-ethics/human-research-ethics-review-process/health-and-medical-hrec/managing-your-approved-project

(4) All research participants must be provided with the current Patient Information Sheet and Consent Form, unless otherwise approved by the Committee.

(5) The Committee is notified if any investigators are added to, or cease involvement with, the project.

(6) This study has approval for four years contingent upon annual review. A *Progress Report* is to be provided on the anniversary date of your approval. Your first report is due **31 August 2017.** You will be sent a courtesy reminder closer to this due date.

(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 2764.

Yours sincerely

Digitally signed by Lauren Black
DN: cn=Lauren Black, o=Research Integrity and Ethics Unit, Office of Research Services, University of Tasmania, ou=Executive Officer, Health and Medical Human Research Ethics Committee, email=lauren.black@utas.edu.au, c=AU
Date: 2016.09.05 16:57:31 +10'00'

Lauren Black
Acting Research Integrity Coordinator & Executive Officer, Health and Medical Human Research Ethics Committee
Research Integrity and Ethics Unit
Office of Research Services
University of Tasmania
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Hobart Tas 7001
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Appendix E2. Ethics approval for validation of survey

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Email Human.Ethics@utas.edu.au
www.research.utas.edu.au/human_ethics/

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

19 April 2018

Dr Tabish Razi Zaidi
C/- University of Tasmania

Sent via email

Dear Dr Razi Zaidi

REF NO: H0017165
TITLE: Peri-operative medication dosing in obese surgical patients-a survey of Anaesthetists

Document	***Version***	***Date***
Low Risk Application form		
Participant information Sheet Pilot		
Participant information Sheet Survey Validation		
Information sheet and survey		
Consent for Qualitative Study (Revised)		
Optional Qualitative study consent		
Feedback Form		
Finance and admin form		

The Tasmanian Health and Medical Human Research Ethics Committee considered and approved the above documentation on **12 April 2018** to be conducted at the following site(s):

Royal Hobart Hospital
Launceston General Hospital
North West Regional Hospital

Please ensure that all investigators involved with this project have cited the approved versions of the documents listed within this letter and use only these versions in conducting this research project.

This approval constitutes ethical clearance by the Health and Medical HREC. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approvals of other bodies or authorities are required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct in Human Research* (NHMRC 2007 updated 2014).

Therefore, the Chief Investigator's responsibility is to ensure that:

(1) The individual researcher's protocol complies with the HREC approved protocol.

(2) Modifications to the protocol do not proceed until **approval** is obtained in writing from the HREC. Please note that all requests for changes to approved documents must include a version number and date when submitted for review by the HREC.

(3) Section 5.5.3 of the National Statement states:

Researchers have a significant responsibility in monitoring approved research as they are in the best position to observe any adverse events or unexpected outcomes. They should report such events or outcomes promptly to the relevant institution/s and ethical review body/ies and take prompt steps to deal with any unexpected risks.

The appropriate forms for reporting such events in relation to clinical and non-clinical trials and innovations can be located at the website below. All adverse events must be reported regardless of whether or not the event, in your opinion, is a direct effect of the therapeutic goods being tested. http://www.utas.edu.au/research-admin/research-integrity-and-ethics-unit-rieu/human-ethics/human-research-ethics-review-process/health-and-medical-hrec/managing-your-approved-project

(4) All research participants must be provided with the current Patient Information Sheet and Consent Form, unless otherwise approved by the Committee.

(5) The Committee is notified if any investigators are added to, or cease involvement with, the project.

(6) This study has approval for four years contingent upon annual review. A *Progress Report* is to be provided on the anniversary date of your approval. Your first report is due 12 April 2019**.** You will be sent a courtesy reminder closer to this due date.

(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 6254.

Yours sincerely

Jude Vienna-Hallam
Acting Executive Officer

Appendix E3. Ethics approval for survey

Office of Research Services
University of Tasmania
Private Bag 1
Hobart Tasmania 7001
Telephone + 61 3 6226 7479
Facsimile + 61 3 6226 7148
Email Human.Ethics@utas.edu.au
www.research.utas.edu.au/human_ethics/

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

30 April 2018

Dr ST Razi Zaidi
Pharmacy

Sent via email

Dear Dr Razi Zaidi

REF NO: **H0017165**
TITLE: **Peri-operative medication dosing in obese surgical patients-a survey of Anaesthetists**

Document	***Version***	***Date***
Online survey among anaesthetists working in all Australian and New Zealand Hospitals via Australian and New Zealand College of Anaesthetists (ANZCA) Clinical Trail Network (CTN)		

The Tasmanian Health and Medical Human Research Ethics Committee considered and approved the above amendment documentation on 30 April 2018.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on Ethical Conduct in Human Research* (NHMRC 2007).

Should you have any queries please do not hesitate to contact me on (03) 6226 6254.

Yours sincerely

Jude Vienna-Hallam
Acting Executive Officer