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Anesthetic Pharmacology and the Morbidly Obese Patient

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Abstract

Anesthesiologists are increasingly being faced with treating obese patients. Physiologic and anthropometric associated with obesity—most notably increases in cardiac output, changes in tissue perfusion and increases in total body weight (TBW), lean body weight (LBW), and fat mass affect the pharmacokinetics (PK) of anesthetic agents. In addition, redundancy of airway tissue, obstructive and central sleep apnea and CO_2 retention affect the pharmacodynamics (PD) of anesthetics and narrow the therapeutic window of numerous anesthetic drugs. Safe and effective pharmacologic management of the obese patient requires a thorough understanding of how obesity affects the PK and PD of anesthetics.

Keywords

obesity; pharmacokinetics; pharmacodynamics; total body weight; lean body weight; volume of distribution; clearance; cardiac output; distribution; peak effect; elimination; half-life

INTRODUCTION

The prevalence of obesity among adults in the United States is increasing. According to the Centers for Disease Control and Prevention, more than one-third of US adults are obese (35.7%).[1] In addition, the incidence of obesity has increased dramatically over the last decade. By 2010, the number of states with an obesity rate of 30% or more had risen to twelve. By comparison, in the year 2000, no state had an obesity rate greater than 30%.[2] Obesity and the length of exposure to obesity have been shown to be risk factors for both number of hospital admissions and length of hospital stay.[3,4] In 1998, the National Institutes of Health recommended bariatric surgery as the primary treatment of morbid obesity.[5] Since then, the number of bariatric surgeries has increased dramatically, although this amount has plateaued since 2006.[6] Anesthesiologists are now managing obese patients —and their associated comorbidities—at an increasing rate. The increased risks of anesthesia in obese subjects have been described.[2,7,8] The physiologic and anthropometric changes associated with obesity likely affect the pharmacokinetics (PK) of anesthetic agents. [9] Obesity is associated with an increase in cardiac output and in total blood volume, which

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may alter drug distribution, peak concentration and clearance.[7,9] In addition, increases in fat- and lean-body mass and changes in tissue perfusion may affect the apparent volume of distribution of many anesthetic agents. Pathophysiology associated with obesity, including an increased prevalence of obstructive sleep apnea and $C0_2$ retention, reduced functional residual capacity, and cardiac dysfunction, alter the pharmacodynamics (PD) of anesthetics. The result is a narrowing of the therapeutic index of anesthetic agents.

The narrow therapeutic indices of anesthetics require knowledge of how obesity affects drug PK/PD to ensure safe and effective dosing. However, the studies specifically addressing the effect of obesity on anesthetic drug management have been sparse or conflicting. The following is a review of the PK and PD of anesthetic agents in obese subjects.

VOLUME OF DISTRIBUTION AND CLEARANCE

Obesity was once thought of as simply a disease of excess adiposity. Currently, it is understood that although all obese subjects share a common phenotype (adiposity), the excess adiposity of obesity is also associated with multi-organ system dysfunction. In order to understand how obesity affects the PK and PD of anesthetic agents, it is necessary to understand the specific pathophysiologic changes associated with obesity.

Obesity is associated with an increase in total body weight (TBW), lean body weight (LBW), and fat mass. LBW accounts for 20–40% of the increase in TBW in obese subjects. [10] However, with increasing obesity, fat mass increases to a greater extent than LBW, and the ratio of LBW to TBW decreases.[11] The increase in fat mass has been shown to increase the volume of distribution of lipophillic drugs.[12–14] Central volume of distribution is the major pharmacokinetic parameter governing selection of a loading dose. It makes intuitive sense then to administer larger initial loading doses of drugs to obese individuals. However, plasma protein binding, cardiac output and tissue perfusion also play major roles in drug distribution. While obesity has not been shown to alter drug binding to albumin and α-acid glycoprotein, there is an increase in cardiac output associated with obesity.[15,16] The increase in cardiac output is strongly related to the increase in LBW. [17] Cardiac output is a significant predictor of early distribution kinetics.[18] It can be debated whether a loading dose should be administered based on TBW to reflect the increase in volume of distribution or administered based on LBW to reflect the change in cardiac output.

The increase in cardiac output associated with obesity results increased hepatic and renal blood flow. In addition, there are regional differences in the perfusion of adipose tissue. Abdominal and visceral fat receive less blood flow than subcutaneous adipose tissue.[19,20] Obesity is associated with an increase in drug clearance.[18,21,22] However, recent studies are demonstrating that the effect of obesity on drug metabolism and clearance is dependent on the metabolic pathway. Obesity decreases clearance of drugs metabolized by the cytochrome P450 3A4 pathway, while drugs metabolized by 2D6, 2E1, 1A2, and 2C9 show higher clearance in obese versus non-obese individuals.[23,24]

INTRAVENOUS INDUCTION AGENTS

Thiopental

After a single bolus dose, thiopental enjoys a rapid time to peak effect (loss of consciousness within 15– 20 seconds) owing to its rapid distribution into the central nervous system.[25] Redistribution from the plasma to peripheral tissue explains the rapid offset of action. The distribution and redistribution of thiopental is largely governed by cardiac output.[25] In normal weight subjects, thiopental shows 2- or 3-compartment kinetics with a steady state

volume of distribution of 2–3 L/kg and clearance of 3–4 ml/kg/min. Volume of distribution is increased and elimination half-life is prolonged in obese subjects.[26] The increased volume of distribution in the obese is thought to be secondary an increased fat mass. Simulations of thiopental concentrations in the obese demonstrate that after a single bolus dose, there is a 60% reduction in thiopental peak plasma concentration compared to normal weight subjects.[27] Animal studies have demonstrated that distribution clearance of thiopental increases linearly with cardiac output.[28] With the increase in cardiac output associated with obesity, it is not surprising then that total clearance of thiopental is increased in obese vs. lean subjects.[26] There is no difference in thiopental clearance between obese and lean subjects when normalized to total body weight.

Propofol

Propofol is a highly lipophilic hypnotic (octanol-water partition coefficient of 4300) and is the most commonly used hypnotic in the bariatric population. Like thiopental, propofol's kinetics are highly dependent on cardiac output (perfusion limited). In normal weight subjects, propofol has a high volume of distribution and clearance. It is primarily metabolized by the liver, however, its clearance exceeds hepatic blood flow, suggesting extra-hepatic metabolism. Propofol's high lipophillicity may suggest that the volume of distribution would be considerably higher in obese subjects compared to normal weight subjects, owing to their higher fat mass. In addition, the higher cardiac output seen in obese subjects may increase clearance. In a study in which propofol was used for induction and maintenance of anesthesia in eight morbidly obese subjects, the volume of the central compartment was similar to nonobese subjects.[29] However, steady state volume of distribution and clearance were found to increase linearly with total body weight.[29] When normalized to total body weight, these differences disappeared. Similarly, Cortinez et al. found that an allometric model using total body weight was superior to other size metrics when describing volume and clearance of propofol in morbidly obese subjects.[30] Simulated propofol plasma target controlled infusions using the Cortinez model and the Marsh model (scaled to total body weight) showed similar infusion rate profiles.[30,31]

With steady state volume and clearance increasing linearly with total body weight, it has been suggested that maintenance doses of propofol be based upon a total body weight scalar as it is in lean subjects.[29,30] However, La Colla and colleagues found administration of propofol in obese subjects via a weight-adjusted or TBW scaled infusion resulted in significant performance bias for both groups.[32] There was no statistically significant difference in performance bias between the weight-adjusted and TBW models. These authors suggested therefore that propofol be titrated to effect in obese subjects.

Etomidate

Etomidate is associated with minimal cardiovascular suppression when administered as an intravenous bolus for induction of anesthesia. It is therefore widely considered to be the induction agent of choice in hemodynamically unstable patients. Etomidate is associated with a transient suppression of the adrenocortical axis, and this property has fueled controversy as to whether acutely ill patients are exposed to an increased risk of morbidity and mortality after its use. However, recent studies have refuted these claims.[33,34]

In lean subjects, etomidate shows 3-compartment kinetics with rapid distribution with the central compartment. It has a time to peak effect of 30–60 seconds. Its rapid offset is owed to its rapid redistribution to the peripheral tissues. Etomidate's clearance (11–25 ml/min/kg) approximates hepatic blood flow.[35] Its pharmacokinetic properties have not been established in obese subjects. However, since etomidate has similar pharmacokinetic and

physicochemical properties as propofol, its pharmacokinetic profile is likely to behave similarly to propfol in obese subjects.

Dexmedetomidine

Dexmedetomidine is a highly selective α-2 agonist with an α-2:α-1 selectivity ration of 1500:1. It is used for procedural sedation and as an adjunct to general anesthesia due to its sedative, analgesic and anxiolytic effects. Its use as an adjunct to general anesthesia for bariatric surgery has been advocated because of reductions in peri- and postoperative opioid requirements.[36] In addition, dexmedetomidine has been found to lower volatile anesthetic requirements, and attenuate hemodynamic stability when used during laparoscopic bariatric surgery.[37] However, the use of dexmedetomidine failed to improve quality of recovery or speed time to hospital discharge.[36]

There have been no studies to date analyzing the effects of obesity on the PK/PD of dexmedetomidine. An infusion rate of 0.2 μg kg hr^{-1} has been recommended to avoid bradycardia and hypotension.[36]

OPIOIDS

Obese subjects are at increased risk for opioid-induced respiratory depression and airway obstruction due to their pathophysiology.[38] With increasing obesity, there is an increased incidence for obstructive sleep apnea, hypoxia, and central sleep apnea. In addition, redundant pharyngeal tissue places these patients at risk for upper airway obstruction. Upper airway obstruction, OSA, and hypoxia are increased following the administration of opioids.[39–41] Together, these changes narrow the therapeutic window for opioids.

Fentanyl

Fentanyl is a synthetic opioid with a potency approximately 100-times that of morphine. It is the most widely used opioid in anesthetic practice. Fentanyl has a predictable time to peak effect of 3–5 minutes. Its short duration of action following a single bolus dose is attributed to rapid redistribution from the central nervous system into the plasma and peripheral tissues. Despite its short duration of action after a single bolus dose, after prolonged administration (i.e continuous infusions) saturation of the peripheral compartments occurs. Decrement in plasma concentration becomes more dependent on metabolism and elimination rather than redistribution. Numerous PK/PD models of fentanyl have been constructed, however none of these have been validated in obese individuals.[42–44]

Fentanyl has a large volume of distribution due mainly to its high lipophillicity. Theoretically, obese subjects would have a larger volume of distribution due to their larger amount of adipose tissue, effectively lowering the plasma concentration after a single bolus dose. While obese subjects do have a lower plasma concentration during the early distribution phase, this is related to their higher cardiac output, rather than an increased volume of distribution.[45] The clearance of fentanyl is significantly increased in obese subjects.[46] The relationship between clearance and total body weight is nonlinear, however, fentanyl clearance increases linearly with “pharmacokinetic mass”, which is highly correlated to lean body weight.[46]

Alfentanil

Alfentanil is a fentanyl derivative with one-tenth the potency and lower lipohilicitly. It has a faster time to peak effect (1.4 minutes), largely due to its lower pKa. The lower lipophilicty of alfentanil decreases its effective volume of distribution compared to fentanyl. Like fentanyl, the increased cardiac output in obese subjects lowers the plasma concentration of

alfentanil during the early distribution phase.[43][45] Obese individuals should have a theoretically increased volume of distribution and longer terminal elimination half-time compared to normal weight subjects. No validated PK/PD models for alfentanil exist for obese individuals.

Sufentanil

Sufentanil is a synthetic derivative of fentanyl that is ten times as potent. It is the most highly liphophillic opioid. The apparent volume of distribution and elimination half-life of sufentanil both increase with obesity.[47] However, sufentanil clearance is similar in obese subjects compared to normal weight subjects.[47] Slepchenko et al. validated the performance of sufentanil target controlled infusions using PK models of sufentanil derived from normal weight subjects.[48] These authors found that PK models over-predicted sufentanil plasma concentrations in obese individuals. This over-prediction was found to increase with increasing BMI.

Remifentanil

A highly potent synthetic opioid, remifentanil is characterized by a rapid time to peak effect (approximately 1 minute) and rapid offset of action. Remifentanil's chemical structure contains an ester linkage. The drug undergoes rapid metabolism via non-specific tissue and plasma esterases, resulting in organ-independent clearance. This rapid metabolism accounts for its rapid termination of effect, even after prolonged administration. Remifentanil is commonly administered as a continuous infusion for sedation or in combination with an intravenous hypnotic agent or inhalational anesthestic for general anesthesia. Simulations of remifentanil blood concentrations in obese subjects demonstrated that obese individuals administered a remifentanil infusion based upon LBW had similar plasma concentrations as normal weight subjects given the drug based upon TBW.[49] In addition, infusions based upon total body weight resulted in significantly higher plasma concentrations. Remifentanil's pharmacokinetic profile has popularized its use as an analgesic in obese subjects. However, when comparing remifentanil and sufentanil target controlled infusions in obese subjects undergoing laparoscopic gastrectomy, Bidgoli et al. demonstrated that subjects given remifentanil had quicker times to extubation but significantly higher scores on the visual analogue pain scale and required more rescue analgesia in the immediate recovery period.[50] Similarly, De Baerdemaeker and colleagues showed that remifentanil offered no significant advantages in recovery profile compared to sufentanil in obese subjects undergoing laparoscopic gastric banding.[51] In addition, the subjects given remifentanil had higher opioid consumption in the immediate postoperative period. Despite remifentanil's forgiving termination of effect, its use may be questioned as an adjunct to general anesthesia in obese subjects undergoing bariatric surgery.

INHALATIONAL AGENTS

Isoflurane

Of the major inhalational agents used today in clinical practice, isoflurane is the most lipid-soluble. Its high lipid solubility, together with the increased adipose tissue mass found in obese subjects, would theoretically increase peripheral distribution of isoflurane and result in increased time to recovery. However, obese subjects given 0.6 minimum alveolar concentration (MAC) of isoflurane for surgery lasting 2–4 hours showed similar recovery profiles as non-obese subjects.[52] In addition, the time constant for isoflurane to reach equilibrium with adipose tissue is approximately 2110 minutes, much longer than most surgical cases.[53] This property, coupled with low adipose tissue blood flow, diminish the effect of excess adiposity on isoflurane distribution and recovery. In their study comparing the pharmacokinetics of volatile agents in obese and lean individuals, Lemmens et al.

demonstrated a statistical but clinically insignificant effect of obesity on isoflurane uptake. (Figure 1) [52]

Sevoflurane

Sevoflurane has a blood-gas partition coefficient of 0.65 making it half as soluble as isoflurane, resulting in a more rapid uptake and elimination in obese subjects. The lower solubility of sevoflurane offers the theoretical advantage of a more rapid uptake and decreased peripheral tissue distribution, leading to a faster recovery. In a randomized clinical trial comparing uptake and recovery profiles of sevoflurane compared to isoflurane in obese subjects, Torri and colleagues showed a more rapid wash-in and washout of sevoflurane compared to isoflurane in obese subjects.[54] Faster recovery was seen only within the first minute of discontinuation of the drug. However, in a similar study, these same authors reported significantly faster recovery and earlier times to PACU discharge following administration of sevoflurane compared to isoflurane in obese subjects undergoing gastric banding.[55]

Desflurane

Desflurane is the least soluble volatile anesthetic in clinical use with a blood gas partition coefficient of 0.45. Because of its low solubility desflurane has limited distribution to peripheral tissue. The time constant for equilibrium with adipose tissue for desflurane is approximately 1350 minutes.[53] Recovery after desflurane is faster than isoflurane in both obese and non-obese subjects.[52,56] A meta-analysis of six studies comparing recovery profiles of desflurane versus sevoflurane demonstrated that desflurane was superior to sevoflurane with regard to time to eye opening and time to obeying command.[57] However, this study failed to show superiority of desflurane over sevoflurane in times to PACU discharge. While some studies have shown faster emergence with desflurane over sevoflurane in obese subjects,[56,58,59] others have shown no difference between the two drugs.[60,61]

NEUROMUSCULAR BLOCKERS

Succinylcholine

Succinylcholine is currently the only non-depolarizing neuromuscular blocker in clinical use. It is characterized by a rapid onset of action and an ultra-rapid duration of effect, owing to its metabolism by pseudocholinesterase. Succinylcholine is still considered to be the neuromuscular blocking agent of choice in obese subjects, as the rapid onset of action facilitates rapid tracheal intubation, and rapid duration of effect allows quick return of spontaneous ventilation. In normal weight subjects, the ED95 of succinylcholine in the absence of nitrous oxide is 0.5 mg/kg.[62] Nitrous oxide and opioids potentiate succinylcholine’s effect, and in the presence of nitrous oxide and opioids the ED95 is decreased to 0.3–0.35 mg/kg.[63] In obese subjects, the amount of pseudocolinesterase is increased.[64] This raises the dose requirement necessary to achieve optimal intubating conditions in obese individuals. In a study analyzing the optimal dosing strategy of succinylcholine in morbidly obese subjects, Lemmens and Brodsky determined that a dose of 1 mg/kg TBW resulted in optimal intubating conditions in this patient population.[65] Despite the rapid metabolism of succinylcholine by psesudocholinesterase, the duration of effect is dose dependent, and doses of 1 mg/kg TBW were found to take 8–12 minutes for dissipation of effect.[63] Dose administered was found to explain close to 60% of the variability in duration of effect.[63]

Pancuronium

Pancuronium is an aminosteroid neuromuscular blocker with a very long time of onset (5 minutes) and duration of effect (60–90 minutes). Obese subjects have an increased extracellular fluid volume and therefore, have an increased volume of distribution for pancuronium compared to lean subjects. When compared to normal weight subjects, obese subjects require an increased amount of pancuronium for maintenance of twitch depression.[66] There is no difference in dose requirements when corrected for body surface area. With the introduction and widespread use of the intermediate-duration neuromuscular blocking agents, the use of pancuronium, especially in obese subjects, has waned.

Vecuronium

Vecuronium is an aminosteroid neuromuscular relaxant with an intermediate duration of effect. After a single intubating dose of 0.1 mg/kg, vecuronium has a time of peak effect of approximately 3 minutes, and a duration of effect of 45–60 minutes. Although obese subjects have an increased extracellular fluid volume compared to normal weight subjects, there is no change in the volume of distribution of vecuronium. In a study comparing PK and PD variables of vecuronium in obese versus non-obese subjects, Schwartz et al. found no difference in PK variables between the two groups.[67] In addition, these same authors found a prolonged duration of effect in obese subjects.[67] Similarly, after a dose of 0.1 mg/kg TBW of vecuronium was given, Suzuki and colleagues demonstrated a prolonged time to spontaneous recovery of 25% twitch in obese subjects (68.4 minutes) compared to normal weight subjects (41 minutes).[68] Vecuronium is eliminated by hepatic clearnace and biliary excretion. Weinstein et al. postulated that the prolonged recovery of vecuronium in obese subjects is likely secondary to impaired hepatic clearance and an overdose effect when the drug is given based upon TBW.[69]

Rocuronium

Rocuronium is an aminosteroid neuromuscular blocking agent. Its chemical structure is characterized by a quarternary ammonium group, limiting its distribution to peripheral tissue. Despite the higher extracellular fluid volume in obese subjects, the PK of rocuronium are not altered. In a study comparing PK/PD of rocuronium in obese and normal weight subjects, Puhringer et al. found no differences in volume of distribution, clearance, mean residence time, and distribution and elimination half-times between obese and control subjects.[70] In addition, recovery profiles were similar between the two groups.[70] In a similar study examining only the PD of rocuronium in obese subjects, these same authors showed no difference in spontaneous recovery or induced recovery between obese and normal weight subjects.[71] Time to 25% recovery was slightly prolonged in obese subjects.[71]

Neuromuscular Blocking Reversal Agents

Obese subjects show a prolonged spontaneous recovery following administration of non-depolarizing neuromuscular blocking drugs.[67–69,72] Moreover, obesity increases the risk of post-operative respiratory complications.[73,74] In addition, diaphragmatic tone and end-expiratory lung volumes are decreased at the onset of sleep in obese versus normal weight subjecs.[75] Therefore, pharmacologic reversal with a neuromuscular blocking antagonist is recommended to avoid post-operative residual curarization and adverse respiratory events.

Neostigmine, an acetylcholine receptor antagonist, has long been used to facilitate recovery of neuromuscular function. In obese subjects recovery of neuromuscular function--even after full reversal with neostigmine--is incomplete compared to normal weight subjects. Obese and normal weight subjects given neostigmine for reversal of vecuronium-induced

neuromuscular blockade had similar times to achieve a train-of-four ratio of 0.7.[68] However, obese subjects showed a four-fold increase in time to achieve a train-of-four ratio of 0.9 (25.9 versus 6.9 minutes).[68] A recent study showed that obese subjects given neostigmine following rocuronium had residual curarization in the recovery unit.[76]

Recently, sugammadex has been introduced as an alternative to neostigmine for reversal of neuromuscular blockade. Sugammadex is a dextrin molecule with a lipohillic core and hydrophilic exterior that specifically binds free rocuronium molecules. It also has modest affinity for vecuronium and even less affinity for pancuronium. Sugammadex allows rapid, full reversal of neuromuscular blockade, without the autonomic side effects associated with neostigmine. A direct comparison of sugammadex with neostigmine for reversal of rocuronium-induced neuromuscular blockade in morbidly obese subjects showed that subjects given sugammadex had a faster time to recovery of a train-of-four ratio of 0.9 (2.7 vs. 9.6 minutes).[76] In addition, train-of-four ratios in the post-operative recovery unit were 109.8% and 85.5% for subjects given sugammadex and neostigmine, respectively.[76] There have been no studies examining the PK/PD of sugammadex specific to the obese population. However, a recent study showed a limited but clinically insignificant effect of bodyweight on the PK of sugammadex.[77] Whether TBW or ideal body weight (IBW) should be used as a dosing scalar for sugammadex in obese subjects has been debated. Van Lancker and colleagues concluded that IBW be used for dosing sugammadex in obese individuals.[78] However, recurarization after sugammadex administration has been reported.[79] This has led others to suggest that sugammadex be administered on the basis of TBW to ensure adequate reversal of neuromuscular blockade.[80,81]

CONCLUSION

The incidence and prevalence of obesity continues to increase globally. Anesthesiologists are being faced with these patients at an increasing rate. The pathophysiology associated with obesity, most notably anthropometric changes and derangements in cardio-pulmonary physiology, narrow the therapeutic indices of many anesthetic agents. These changes place these patients at risk for anesthetic-related complications. Knowledge of how obesity affects the PK and PD of anesthetics is necessary to derive safe and effective dosing strategies for these patients.

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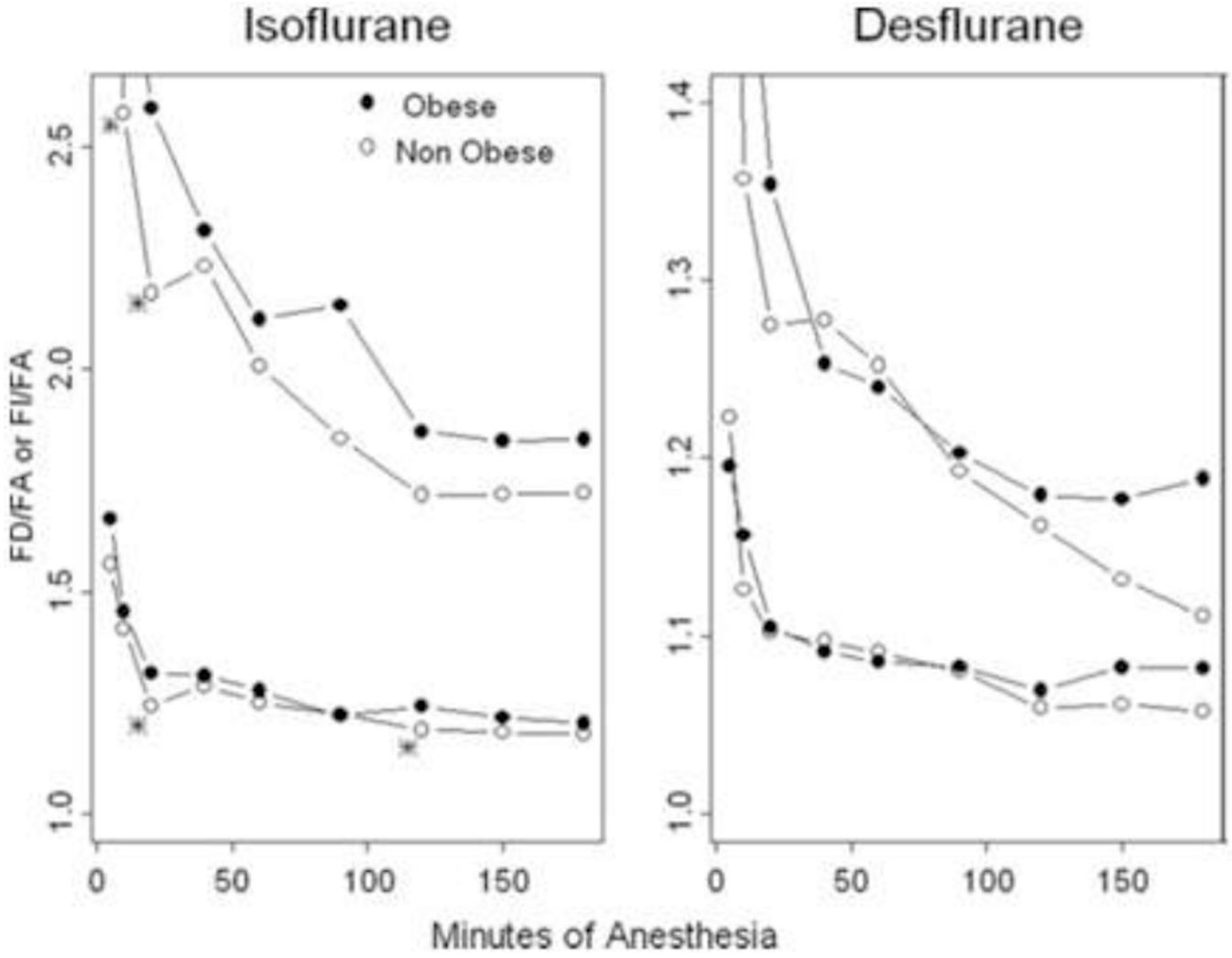

Figure 1.
Effect of obesity on FD/FA and FI/FA ratios for isoflurane and desflurane. FD/FA will always be higher than FI/FA. Obesity modestly affects FD/FA and FI/FA for isoflurane but not desflurane. From Lemmens HJ, et al., "Obesity Modestly Affects Inhaled Anesthetic Kinetics in Humans," *Anesthesia & Analgesia*, 2008; 107: 1864–70, with permission from Wolters Kluwer Health.