

Pharmacokinetics in obese patients

Luc EC De Baerdemaeker MD

Eric P Mortier MD DSc

Michel MRF Struys MD PhD

Key points

Obesity affects the pharmacokinetics of many i.v. anaesthetic drugs.

The pharmacokinetics of the new generation of inhalational anaesthetics are affected only slightly by obesity.

Ideal body weight is useful when assessing dosage of many (but not all) modern anaesthetic drugs.

Recent target-controlled infusion (TCI) models for propofol, remifentanyl and sufentanyl consider age, gender, weight and height as covariates, allowing improved dosage adjustments in the obese.

One of the many problems in providing anaesthesia for morbidly obese patients is the influence of obesity on pharmacokinetics and pharmacodynamics. Drug administration in obese patients is difficult because recommended doses are based on pharmacokinetic data obtained from individuals with normal weights; therefore, mistakes in the determination of the appropriate dose are often made. Because of comorbidity in these patients, the function of organs involved in drug elimination (e.g. kidney, liver) can be affected making pharmacokinetics more difficult and complex.

Practical guidelines for dosage adjustment are proposed in this article. However, in some cases (e.g. super-obesity, BMI >55) our recommendations are not appropriate. Our present knowledge of the influence of obesity on drug pharmacokinetics is still limited or confused by concomitant pathophysiological disorders. In these cases, close pharmacodynamic monitoring is essential in order to titrate anaesthetic drug administration towards the desired clinical effect.

Changes in pharmacokinetics

Pathophysiological changes in obese patients are likely to affect drug distribution and elimination. Anaesthetists have become highly skilled at titrating toxic drugs within their narrow therapeutic window towards specific therapeutic effects. It has been observed that most anaesthetists reduce doses in obese patients based on experience and intuition alone. However, a better knowledge of pharmacokinetics might improve drug titration.

Does size matter during drug titration? Before being able to answer this question, the clinician must appreciate what 'weight' should be used to calculate dosage: total body weight (TBW), lean body mass (LBM) or ideal body weight (IBW)? TBW is defined as the actual weight and IBW can be estimated from the formula:

$$\text{IBW(kg)} = \text{height(cm)} - x$$

(where $x = 100$ for adult males and 105 for adult females).

LBM can be calculated using the following formulae:

$$\text{Male LBM} = 1.1(\text{weight}) - 128(\text{weight/height})^2$$

$$\text{Female LBM} = 1.07(\text{weight}) - 148(\text{weight/height})^2$$

Mostly, dosage recommendations in the package inserts are scaled to TBW (not to LBM or IBW) and the assumption is made that pharmacokinetics are weight proportional. Therefore, different strategies of adjusting the dosage in obese patients are adopted, for example scaling to TBW, LBM, IBW or not adjusting at all. In their editorial, Bouillon and Shafer show which of these weight approaches (as a function of patient sex, height and TBW) can be used clinically when we are unsure about the true relation between size and pharmacokinetics. This weight can then be multiplied by the published doses scaled to TBW. As seen in Figures 1 and 2, weight scaling is important in persons heavier than IBW. Below IBW, TBW and LBM are similar. When TBW is greater than IBW, TBW overestimates LBM.

Classical pharmacokinetic parameters such as volume of distribution (V_d), clearance (Cl) and protein binding can change for some drugs in morbidly obese patients. Highly lipophilic substances such as barbiturates and benzodiazepines show significant increases in V_d for obese individuals. Less lipophilic compounds have little or no change in V_d with obesity. Exceptions to this rule include remifentanyl, which is a highly lipophilic but shows no significant change in distribution in obese individuals. Consequently, the absolute V_d remains relatively unchanged and the dosage should be calculated on the basis of IBW.

Drugs with weak or moderate lipophilicity can be dosed on the basis of IBW or more accurately on LBM. These values are not identical because 20–40% of an obese patient's

Luc EC De Baerdemaeker MD

Staff Anaesthesiologist
Department of Anaesthesia
Ghent University Hospital
De Pintelaan 185
B-9000 Gent
Belgium
Tel: +32 9240 3281
Fax: +32 9240 4987
E-mail: luc.debaerdemaeker@ugent.be
(for correspondence)

Eric P Mortier MD DSc

Professor and Chair of Anaesthesia
Department of Anaesthesia
Ghent University Hospital
De Pintelaan 185
B-9000 Gent
Belgium

Michel MRF Struys MD PhD

Professor in Anaesthesia and
Co-ordinator of Research
Department of Anaesthesia
Ghent University Hospital
De Pintelaan 185
B-9000 Gent
Belgium

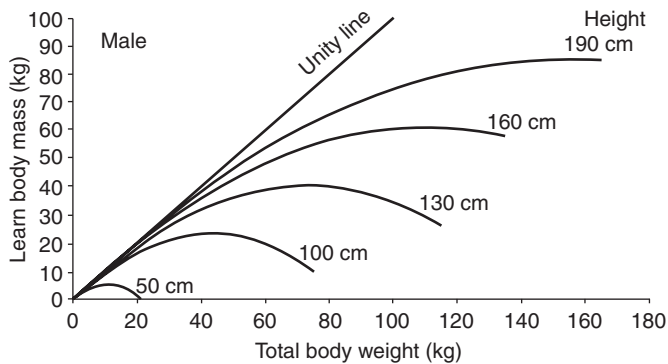


Fig. 1 Nomogram for male patients relating total body weight (kg), height (cm), and gender with lean body mass (LBM) using the formula $LBM = 1.1(\text{weight}) - 128(\text{weight}/\text{height})^2$.

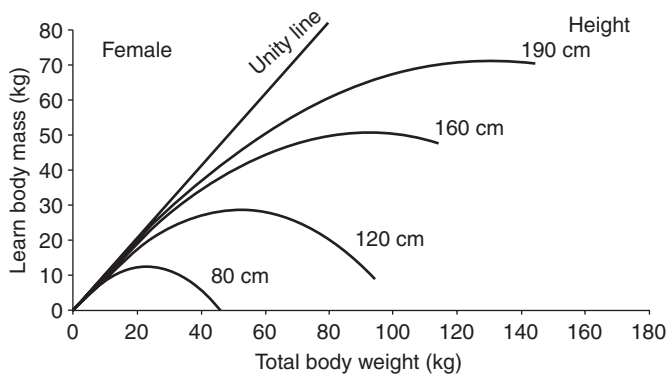


Fig. 2 Nomogram for female patients relating total body weight (kg), height (cm), and gender with lean body mass (LBM) using the formula $LBM = 1.07(\text{weight}) - 148(\text{weight}/\text{height})^2$.

increase in TBW can be attributed to an increase in LBM. Adding 20% to the estimated IBW dose of hydrophilic medication is sufficient to include the extra lean mass. Non-depolarizing neuromuscular blocking agents can be dosed in this manner. Succinylcholine is an exception, dosage should be calculated using TBW.

The majority of anaesthetic drugs are strongly lipophilic. Increased V_d is expected for lipophilic substances but this is not consistently demonstrated in pharmacological studies because of factors such as end-organ clearance or protein binding. It has been observed that the V_d of water-soluble agents is less affected by obesity than lipophilic compounds.

Application of pharmacokinetics in the obese patient

Pharmacokinetics in obese patients are different from those of lean patients in many situations but much of our knowledge is incomplete. How can the data be used in our daily anaesthetic practice?

Volatile agents

Halothane is known to have considerable deposition in adipose tissue and an increased risk of reductive hepatic metabolism in the obese, thereby increasing the risk of halothane hepatitis. Enflurane has a blood gas partition coefficient that falls with increasing obesity, possibly reducing its MAC. Morbidly obese patients metabolize halothane and enflurane more than normal patients. Inorganic fluoride concentrations rise twice as fast in obese individuals, increasing the risk of fluoride nephrotoxicity after prolonged administration of enflurane.

The pharmacokinetics of more modern volatile agents seem not to be influenced by obesity and they have been used safely and without major problems. Because of their lower blood gas solubility, sevoflurane and desflurane display rapid onset and offset of clinical effect in the obese. Some investigators have observed significantly higher concentrations of inorganic fluoride in obese patients anesthetized with sevoflurane, whereas others have found no differences.

The major metabolites of desflurane are inorganic fluoride and trifluoroacetyl chloride, which may bind to tissue proteins or appear as trifluoroacetic acid in the urine. Only a single case of desflurane hepatotoxicity has been reported. It has been suggested that desflurane is the inhaled anaesthetic of choice compared with isoflurane or propofol in this patient population because of its more rapid and consistent recovery profile and the fact that desflurane has the lowest solubility in fat tissue. In contrast, Oberg and colleagues considered isoflurane the drug of choice in obese patients because of reduced propensity to produce fluoride ions and less organ toxicity, especially when compared with halothane and enflurane.

I.V. drugs

Morbid obesity has an influence on the use of most of the i.v. administered drugs used in anaesthesia. The use of ideal or total body weight during drug administration is one of the major issues. Table 1 shows some guidelines for the most frequently applied i.v. drugs.

Thiopental

In obese patients, thiopental has an increased V_d and a longer elimination half life ($t_{1/2}$), but Cl values are unchanged. It was stated in as long ago as 1969 that thiopental dosage should be based on LBM. However, Buckley and colleagues suggested a higher dose (7.5 mg kg^{-1}) for induction based on IBW. The requirement for this larger dose is explained by an elevated cardiac output frequently found in morbidly obese patients, resulting in a lower plasma peak concentration of thiopental.

Propofol

In morbidly obese patients, the induction dose of propofol can be calculated on IBW. Although propofol is highly lipophilic, propofol does not accumulate in morbidly obese patients. Therefore, the dosage of propofol for maintenance of anaesthesia in obese

Table 1 Utilization of total body weight (TBW) or ideal body weight (IBW) to calculate dosing schemes in morbidly obese patients

Drug	Recommended dosing
Propofol	Induction: IBW Maintenance: TBW or IBW + (0.4 × excess weight)
Fentanyl	TBW Corrected weight = IBW + (0.4 × excess weight)
Thiopental	7.5 mg kg ⁻¹ IBW TBW
Midazolam	TBW for initial dose IBW for continuous dose
Vecuronium	IBW
Atracurium	TBW Initial dose 0.15 mg/kg–2.3 mg/10 kg >70 kg. Supplemental dose 0.15 mg/kg–0.7 mg/10 kg >70 kg
Cisatracurium	TBW
Rocuronium	IBW
Succinylcholine	TBW >140 kg. Maximum 120–140 mg
Mivacurium	TBW. Divided dosing 0.15 mg/kg + after 30 s 0.15 mg/kg
Neostigmine	TBW
Alfentanil	IBW or corrected weight TBW
Sufentanil	TBW corrected weight BMI > 40
Remifentanil	IBW
Morphine	IBW
Paracetamol	IBW

subjects can be established on the same basis as in lean subjects, taking into account their actual body weight with no specific risk of accumulation. However, this requires administration of large doses of propofol. The haemodynamic effects of larger doses of propofol remain to be assessed in obese patients. Plasma propofol concentration at the end of surgery after a fixed rate infusion of propofol are dependent on TBW. This may imply that when obese patients are anaesthetized with propofol based on TBW, deep anaesthesia and deleterious cardiovascular effects may result. Based on the pharmacokinetic properties of propofol, drug administration schemes have been developed that allow a defined concentration to be rapidly achieved and held constant. (e.g. 21 mg kg⁻¹ h⁻¹ for 5 min, 12 mg kg⁻¹ h⁻¹ for 10 min, 6 mg kg⁻¹ h⁻¹ maintenance). The weight used for calculation uses an empirical formula:

$$\text{Corrected weight} = \text{Ideal weight} + (0.4 \times \text{Excess weight}).$$

Various three-compartment pharmacokinetic models have been developed to describe the pharmacokinetic behaviour of propofol. These models were applied in TCI devices to administer propofol. Originally, all models were derived from lean patients. In a clinical setting, the 'Diprifusor' system (AstraZeneca, London) was the first commercially available TCI device, using the Marsh pharmacokinetic set. More recently, other devices have become available commercially for propofol TCI. These pumps include other models e.g. Schnider model.

When using TCI of propofol, the TCI device requires an input of the patient's individual characteristics. Which weight input is appropriate when anaesthetizing a morbidly obese patient? The kinetic set published by Marsh and colleagues is weight

proportional. Most anaesthetists feel that obese patients may be at risk of overdose when weight-normalized infusion schemes are used. Therefore, a LBM correction has been proposed. Gepts and colleagues have recommended the corrected body weight of the IBW + 0.4 × excess weight. More recently, it has been proposed that the propofol pharmacokinetic set of Schnider and colleagues should use of LBM instead of weight. It was concluded that inclusion into the model of weight, height and lean body mass improved the fit significantly compared with inclusion of any combination of just two of these three variables.

However, this is in contrast with the work published by Schüttler and colleagues. They made an estimation of the pharmacokinetics of propofol with respect to the variables of age, body weight and gender and at the same time made an evaluation of the inter- and intraindividual pharmacokinetic variability. The influence of body weight on all clearances and compartmental volumes could best be modelled by a power function with an exponent <1. For those patients whose heights were known, the individual pharmacokinetic parameters did not correlate better with LBM than with body weight.

Midazolam

It has been demonstrated that the V_d and $t_{1/2}$ increase in parallel with body weight but that there is no change in total metabolic Cl. Thus, midazolam should be administered in larger absolute doses, but in the same doses per unit body weight. Prolonged sedation can occur from the larger initial dose needed to achieve adequate serum concentrations. The rate of continuous infusion, however, should be adjusted to the ideal rather than the total weight.

Opioids

Theoretically, obesity significantly affects the pharmacokinetic profiles of lipophilic drugs, including alfentanil, fentanyl and sufentanil. This is because the peripheral compartment is characterized by a high amount of adipose tissue, which could result in a prolonged β - $t_{1/2}$. The pharmacokinetics of fentanyl have been found not to be affected by obesity and it has been suggested that fentanyl should be administered using IBW. Obesity decreases Cl and prolongs the β - $t_{1/2}$ of alfentanil but does not affect the maximum plasma concentration or V_d . Therefore, it has been suggested that the loading and maintenance dose of alfentanil should be calculated on LBM. However, others have found that obesity had no effect on alfentanil Cl but a direct relationship with the central compartmental volume. In this model, loading dose and maintenance dose could be calculated according to TBW.

In a study in morbidly obese patients comparing the effects of remifentanil, alfentanil and fentanyl on the cardiovascular responses to tracheal intubation, a corrected weight (IBW + (0.4 × excess weight)) was used for all opioids. After induction of anaesthesia, arterial pressures were decreased in all groups but within acceptable limits. It has been shown that the pharmacokinetics of sufentanil are altered in the obese patient; V_d is

increased and β - $t_{1/2}$ prolonged. One might speculate that a greater fat mass may result in a larger V_d at steady state and a longer $t_{1/2}$. In contrast, V_d/kg (whereby $kg = TBW$) was similar in the obese and non-obese group suggesting that the drug was distributed at least as extensively in the excess body mass as in LBM. In their studies of pharmacokinetics and model estimation of sufentanil, various authors have found that neither weight nor LBM was a significant covariate in their models. These studies excluded morbidly obese patients, so it has been suggested that none of these models should be assumed to be applicable to these patients. However, it has been found that the pharmacokinetic parameter set of Gepts and colleagues, derived from a normal weight population, accurately predicted plasma sufentanil concentrations in morbidly obese patients. For $BMI > 40$, the model over-estimated the plasma sufentanil concentrations. When using Sufentanil TCI with the pharmacokinetic set of Gepts and colleagues, no weight correction has to be made.

It has been shown that age and LBM are significant factors that must be considered when determining a dosage regimen for remifentanil. However, it has also been found that the pharmacokinetics of remifentanil are not appreciably different in obese vs lean subjects. Therefore, remifentanil pharmacokinetics are more closely related to LBM than to TBW. Clinically this means that remifentanil dosing regimens should be based on IBW or LBM and not on TBW. TBW dosing in obese patients can result in excessively high remifentanil concentrations, causing side-effects such as apnoea, chest rigidity, bradycardia and hypotension.

Paracetamol

Paracetamol V_d is increased in obesity and in males relative to females. Clearance increases with body weight and therefore is much greater in obese patients and males. The area under the curve for oral administration in obese patients when normalized to IBW was more consistent with that in normal subjects than when normalized to TBW. Administration of a normal dose of Paracetamol to an obese patient should yield plasma concentrations in the same range as the non-obese. Dosing according to TBW rather than IBW could lead to toxic effects.

Neuromuscular blocking agents

When using succinylcholine in obese adults or adolescents, dosage should be calculated on TBW. It has been reported that a smaller total dose of succinylcholine (120–140 mg) provided satisfactory intubating conditions in patients >140 kg. It could be assumed that mivacurium dose should be calculated on TBW also but there are no data available as yet.

It has been suggested that rocuronium should be administered on the basis of IBW. However, data concerning the duration of

action of atracurium in obese patients are conflicting. Some studies have shown that duration of action of atracurium is independent of body weight and therefore it may be recommended that the dose should be calculated on TBW. However, other studies question this. For example, clearance scaled to TBW (absolute clearance/TBW) is significantly smaller in obese than in normal patients, absolute V_d in patients weighing 45–98 kg does not increase with increasing TBW and the dose necessary to maintain 95% twitch depression has been shown to correlate with LBM.

Data on the use of cisatracurium in the obese are sparse. There are differences in pharmacokinetics of cisatracurium besilate in various populations (e.g. type of anaesthesia, age, gender, creatinine clearance and presence of obesity). These differences, however, are not associated with clinically significant differences in the recovery profile of cisatracurium but may be associated with differences in block onset time.

Residual neuromuscular block can be lethal in obese patients and antagonism of neuromuscular blocking agents is often indicated. The antagonism time of neostigmine has been shown to be independent of TBW and BMI. Therefore, TBW can be used to calculate the dose.

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See multiple choice questions 112–114.