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CLINICAL PRACTICE

Dose adjustment of anaesthetics in the morbidly obese

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Key points

- Morbidly obese patients require special dosing regimens.
- Lean body weight is the optimal scalar for most i.v. opioids and anaesthetics.
- Knowledge of the altered pharmacological behaviour of anaesthetic drugs is essential for optimal management of the morbidly obese.

Anaesthesiologists must be prepared to deal with pharmacokinetic and pharmacodynamic (PD) differences in morbidly obese individuals. As drug administration based on total body weight can result in overdose, weight-based dosing scalars must be considered. Conversely, administration of drugs based on ideal body weight can result in a sub-therapeutic dose. Changes in cardiac output and alterations in body composition affect the distribution of numerous anaesthetic drugs. With the exception of neuromuscular antagonists, lean body weight is the optimal dosing scalar for most drugs used in anaesthesia including opioids and anaesthetic induction agents. The increased incidence of obstructive sleep apnoea and fat deposition in the pharynx and chest wall places the morbidly obese at increased risk for adverse respiratory events secondary to anaesthetic agents, thus altering the PD properties of these drugs. Awareness of the pharmacology of the commonly used anaesthetic agents including induction agents, opioids, inhalation agents and neuromuscular blockers is necessary for safe and effective care of morbidly obese patients.

Keywords: anaesthetics, i.v., pharmacokinetics; anaesthesia, inhalation, pharmacokinetics; obesity, morbid

Morbid obesity is defined as a body mass index (BMI) greater than 40, or greater than 35 with associated comorbidites such as diabetes mellitus and hypertension. Morbidly obese (MO) patients pose significant challenges to anaesthesiologists. Many studies have described the effects of obesity on metabolic, cardiovascular, and pulmonary function, and have documented the increased risk of anaesthesia in these subjects.[1–5] The physiological and anthropometric changes associated with MO alter the pharmacokinetic (PK) properties of most drugs.[6] Obese subjects have both an increased amount of fat- and lean body weight (LBW) when compared with non-obese subjects of similar age, height, and gender.[6 7] The increase in LBW can account for as much as 20–40% of the excess total body weight (TBW).[6 7] These changes markedly affect the apparent volume of distribution of some drugs in obese patients. Additionally, increases in cardiac output, total blood volume, and changes in regional blood flow can affect peak plasma concentration, clearance and elimination half-life of many anaesthetic agents.[1 6 8] MO also alters pharmacodynamic (PD) properties of some drugs. For example, derangements in cardiac and respiratory function associated with MO exaggerate side-effects of anaesthetics and narrow the therapeutic window.

Despite the growing recognition of the impact of obesity on the PK/PD properties of pharmaceutical agents, MO individuals are often excluded from clinical trials during the drug development process. As a result, dosing information in package inserts is usually based on a kilogram of TBW, which can result in incorrect doses when applied to the MO patients. Relatively few studies have assessed the relevance of dosing scalars other than TBW in MO patients.[9 10]

Systematic knowledge is lacking or derived from relatively small studies in moderately obese subjects. Therefore, although supported by references, the following is an opinion-based review of dosing scalars used in MO patients and the effects of obesity on the clinical pharmacology of commonly used anaesthetic agents.

Dosing scalars

Doses of drugs are scaled based on the individual patient characteristics including age, weight, gender and comorbid conditions. For MO patients in particular, changes in body composition and changes in cardiac output and regional blood flow must be considered. In an attempt to compensate for some of the obesity-related anthropometric and physiological changes, dosing scalars other than TBW, such as ideal body weight (IBW), body surface area (BSA), BMI, and LBW have been used.

Total body weight

Dosing recommendations are generally based on TBW. This approach is valid for normal weight subjects whose TBW, LBW, and IBW are similar. However, in MO patients, fat

mass and LBW do no not increase proportionately.[11] With increasing obesity, fat mass accounts for an increasing amount of TBW, and the LBW/TBW ratio decreases (Fig. 1). The majority of the cardiac output is still directed to the vessel rich or lean tissue groups. Therefore, administration of a drug based on a TBW metric may result in overdose in an MO individual.

Ideal body weight

IBW is a description of the ideal weight associated with maximum life-expectancy for a given height. Before BMI was used to define obesity, obesity was defined as TBW greater than 20% of IBW. Numerous equations exist to calculate IBW, all of which show general agreement.[12] The use of IBW has two major disadvantages: (i) it indicates that all patients of the same height receive the same dose, and (ii) it does not account for changes in body composition associated with obesity. Specifically, the calculated IBW of a MO patient is less than their actual LBW. Therefore, administration of a drug based on IBW may result in under dosing.

Body surface area

BSA is the scalar used for dosing of chemotherapeutic agents. Equations used to calculate BSA contain TBW and height. Mosteller's equation is the most commonly used.[13] Like IBW, BSA does not take into account changes in body composition in MO patients by failing to differentiate fat mass and LBW. BSA is not commonly used to determine doses of anaesthetic agents.

Lean body weight

LBW is the difference between TBW and fat mass. In MO patients, LBW increases with increasing TBW. However, this increase is not proportional, and although the absolute value of LBW increases, the ratio of LBW/TBW decreases. LBW is significantly correlated to cardiac output,[14] which is an important determinant in the early distribution kinetics of drugs.[8] In addition, drug clearance increases proportionately with LBW.[15 16] These data suggest that LBW is the ideal weight scalar for drug administration in MO patients. However, there are no data available describing the relationship between cardiac output and LBW in subjects with obesity-related cardiomyopathy, which might invalidate dose administration based upon LBW in such individuals.

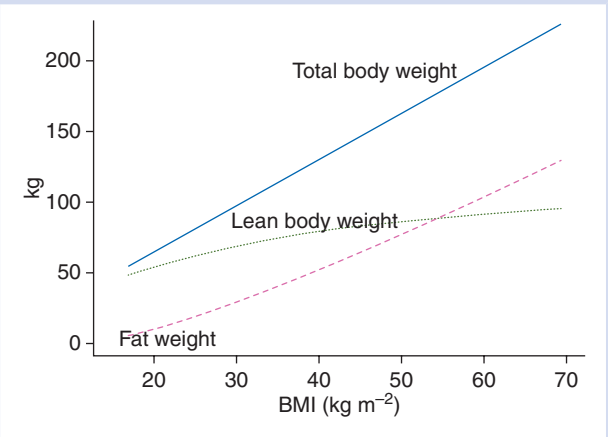

Fig 1 Relationship of TBW, fat weight, and LBW to BMI in a standard height male. LBW and fat weight were derived from the equations of Janmahasatian *et al.*[11]

Although LBW is a useful dosing metric for many anaesthetic agents, its use as a weight scalar in the MO population has been limited by the relative inability to accurately measure it under normal clinical circumstances. James' equation is commonly used to calculate LBW, yet at extremes of TBW, this equation underestimates LBW and can even yield negative values.[17–19] Janmahasatian and colleagues[11] introduced equations for estimating LBW that are more accurate in estimating LBW for MO patients. These equations are gender-specific, and incorporate TBW and BMI. La Colla and colleagues[18] found that a PK parameter set for remifentanil in MO subjects was biased when James' equations were used to calculate LBW. However, in a follow-up study, the same authors showed a better predictive performance of the same PK parameters when the Janmahasatian equations were used.[19]

Allometric scaling

Allometry is the study of changes in the characteristics of organisms according to body size. Allometric scaling has been used to extrapolate the PK principles of different animal species to man, and from adult to paediatric populations in humans.[20–22] The use of allometric scaling to determine PK parameters in MO subjects from the data obtained from normal weight subjects has been sparse. Cortinez and colleagues[23] used allometric scaling to derive a population PK model for propofol in obese individuals. They found an allometric model using TBW as the size descriptor of volume and clearance was superior to other models. The use of allometric scaling to derive PK parameters is not without limitations.[24] Further studies are needed to evaluate the utility of this approach in extrapolating PK characteristics in the MO population.

Hypnotics

Thiopental

After a single bolus dose, thiopental is rapidly distributed from the plasma to the peripheral tissues. The decline in plasma concentration and termination of effect is because of rapid redistribution of thiopental to peripheral tissues. The high lipophilicity of thiopental increases its apparent volume of distribution and elimination of half-life in obese subjects. Total clearance is increased two-fold in the obese *vs* normal weight subjects.[25] However, when normalized to TBW, there was no difference in clearance. Obese individuals have an increased cardiac output when compared with normal weight subjects, and cardiac output is an important determinant in the early distribution kinetics of i.v. drugs.[8] Simulations of the effects of alterations in blood flows and

body composition associated with MO showed a 60% decreased peak plasma thiopental concentration after a 250 mg dose when compared with normal weight subjects.[26] Thiopental plasma concentrations were also decreased up to 2 h after administration. Thiopental induction doses adjusted to LBW resulted in the same peak plasma concentrations as dose adjusted to cardiac output. These data suggest that administering induction doses based on LBW is appropriate. However, the increased cardiac output can result in a more rapid redistribution of thiopental from the effect site into the plasma, resulting in more rapid awakening after a single bolus dose.

Propofol

Propofol is currently the most commonly used induction agent for MO subjects. Propofol is highly lipophilic, and distributes rapidly from the plasma to peripheral tissues. Redistribution from the effect site into the plasma, and subsequently into peripheral tissues, accounts for its short duration of action after a single bolus dose. Like thiopental, cardiac output is a significant determinant of peak plasma concentration.[27]

When propofol was administered by continuous infusion to obese subjects, apparent volume of distribution and clearance increased with increasing TBW.[28] Clearance and volume of distribution were similar to lean subjects when obese subjects were normalized to TBW. An allometric model for propofol using TBW as the size descriptor for volumes and clearances was found to be superior to models using other size descriptors.[23] These data suggest that propofol maintenance infusions should be based on TBW. For induction of anaesthesia, LBW is a more appropriate dosing scalar. MO subjects who were administered a rapid propofol infusion based on LBW for induction of anaesthesia required similar doses and had similar times to loss of consciousness as lean control subjects who were administered propofol based on TBW (Fig. 2).[29] In addition, induction dose requirement was related to cardiac output, which is correlated to LBW.

Dexmedetomidine

Dexmedetomidine is a selective α_2-agonist with anxiolytic, analgesic, and sedative effects. It is commonly given by continuous infusion, and has been advocated as an anaesthetic adjunct to general anaesthesia for MO subjects.[30] It reduces perioperative and postoperative opioid requirements and length of recovery room stay when given as an adjunct infusion during laparoscopic bariatric procedures.[30] However, the same study found no significant change in the quality of recovery or time to hospital discharge. The effects of MO on the PK/PD parameters of dexmedetomidine have yet to be determined.

A loading dose of dexmedetomidine (0.5 μg kg^{-1} h^{-1}, given over 10 min), followed by an infusion of 0.4 μg kg^{-1} h^{-1}, lowered volatile anaesthetic requirements and attenuated increases in blood pressure and heart rate when used as a substitute to fentanyl in laparoscopic bariatric surgery.[31] Dexmedetomidine reduces sympathetic outflow, and therefore can cause hypotension and bradycardia. Its use might not be appropriate in subjects with hypotension, heart block, or severe cardiomyopathy. During laparoscopic bariatric surgery, an infusion rate of 0.2 μg kg^{-1} h^{-1} has

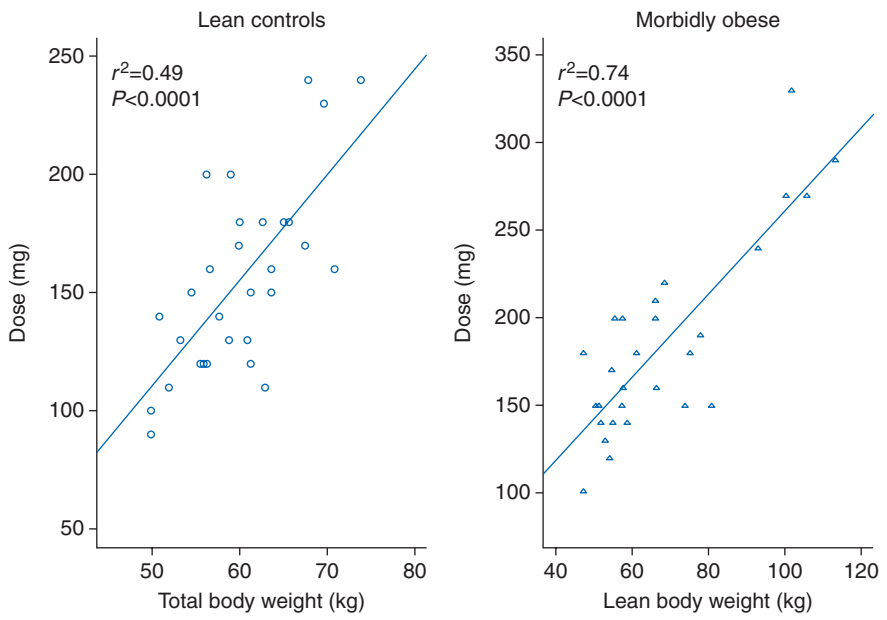

Fig 2 Relationship between propofol induction dose and body weight in lean control subjects and MO subjects. There is a significant relationship between induction dose and body weight in control subjects given propofol based on TBW and MO subjects given propofol based on LBW.[29]

been recommended to minimize the risk of adverse cardiovascular side-effects.[30]

Etomidate

Etomidate can be considered for use in haemodynamically unstable patients. However, controversy exists as to whether acutely ill patients who receive etomidate for induction of anaesthesia have an increased incidence of in-hospital mortality or end-organ dysfunction owing to its adrenal suppressant effects.[32 33] Recent evidence suggests that ketamine is an acceptable alternative to etomidate for anaesthetic induction that does not cause adrenal suppression.[34] There are no studies that have compared etomidate to ketamine in MO individuals, and the PK/PD parameters of etomidate have not been determined in MO subjects. The induction dose is 0.2 mg kg^{-1} for normal weight subjects. Given the similar PK parameters of etomidate to propofol, an induction dose based on LBW is recommended.

Opioids

According to the ASA closed claims database, 48% of adverse respiratory events secondary to opioids were in obese or MO individuals.[35] Increases in cardiac output and changes in body composition (increases in fat and lean mass) associated with MO alter the PK properties of opioids.[36 37] Administration of opioids has been associated with obstruction of the upper airway.[38 39] In addition, use of opioids has been associated with abnormal breathing patterns including central sleep apnoea, obstructive sleep apnoea (OSA), ataxic breathing and hypoxaemia.[40] In patients with OSA, remifentanil decreases the number of obstructive apnoeas but markedly increases the number of central apnoeas. Arterial haemoglobin oxygen saturation was also significantly lower in OSA patients receiving remifentanil.[41] Cardiovascular and respiratory physiological derangements make these subjects more susceptible to opioid-induced upper airway obstruction and respiratory depression.[42]

Fentanyl

Fentanyl is the most commonly used opioid in anaesthesia, and has a time to peak effect of 3–5 min. PK/PD models specific to MO subjects have yet to be constructed. Numerous PK/PD models have been described for fentanyl,[43–45] but have never been validated in MO individuals. When these models were scaled to TBW, they have been shown to overpredict fentanyl plasma concentrations.[46]

The increased cardiac output in MO individuals lowers plasma fentanyl concentrations during the early distribution phase.[47] Cardiac output governs the early distribution of many drugs,[8] and is highly correlated to LBW.[14] In addition, clearance is significantly higher in obese subjects, and increases nonlinearly with TBW.[46] Clearance increased linearly with a hypothetic 'pharmacokinetic mass', which is highly correlated to LBW. These data suggest that fentanyl administration for MO individuals be based on LBW.

Sufentanil

Sufentanil is a highly lipophilic synthetic derivative of fentanyl with a potency that is about 10 times greater. Like fentanyl, the time to peak effect is 3–5 min. Obese subjects have an increased apparent volume of distribution and elimination half-life compared with normal weight subjects, although plasma clearances are similar.[48] PK models of sufentanil derived from normal weight subjects over-predicted plasma sufentanil concentrations in the MO population.[49] This overestimation was found to increase with increasing BMI.

Alfentanil

Alfentanil is a fentanyl derivative with about one-tenth its potency. It has a rapid time to peak effect of 1.4 min.[50] Alfentanil is less lipophilic than fentanyl, and has a smaller apparent volume of distribution. The increased cardiac output in MO individuals lowers alfentanil plasma concentrations during the early distribution phase.[47] Theoretically, obesity should increase apparent volume of distribution and terminal elimination half-life, however there are no data examining the effects of obesity on alfentanil PKs.

Remifentanil

Remifentanil is a fentanyl congener with a rapid time to peak effect of approximately 1 min. It is characterized by an ester structure, and is rapidly metabolized by tissue and plasma esterases resulting in organ-independent clearance. Remifentanil is commonly administered by a continuous infusion as an adjunct to general anaesthesia. Its effects terminate within 5–10 min after stopping the infusion. An infusion based on LBW results in similar plasma concentrations as normal weight subjects were given an infusion based on TBW.[51] Administration of remifentanil to obese subjects based on TBW results in supratherapeutic plasma concentrations, and might increase the risk of side-effects such as bradycardia and hypotension.

Inhalation agents

Isoflurane

Isoflurane is more lipophilic than sevoflurane and desflurane, and therefore has fallen out of favour for use in MO patients. Yet, after administration of 0.6 minimum alveolar concentration (MAC) of isoflurane for procedures lasting 2–4 h, obese and non-obese subjects had similar times to recovery.[52]

The increased lipophilicity of isoflurane coupled with the increased fat mass in MO subjects would increase peripheral tissue uptake. However, not only are the time constants (time to reach 63% of equilibrium) for equilibrium of isoflurane and desflurane with fat long (2110 and 1350 min, respectively),[53] but blood flow to adipose tissue also decreases with increasing obesity.[54] The long time constants together with decreased fat perfusion combine to minimize the effect of increased adipose tissue. When isoflurane is used in routine clinical practice, the effect of BMI on isoflurane uptake is clinically insignificant.[52]

Sevoflurane

Sevoflurane is less lipophilic and less soluble than isoflurane, which results in a slightly more rapid uptake and elimination in MO subjects when compared with isoflurane.[55] However, the observed differences were only significant 30–60 s after discontinuation of the drugs.

The use of sevoflurane in patients with renal impairment is somewhat controversial, although widespread use has not revealed a clinically significant effect. Obesity is associated with glomerular hyperfiltration, and an increased creatinine clearance.[56] However, a prospective cohort study examining more than 119 000 subjects admitted to an intensive care unit showed that increasing BMI was associated with an increased incidence of acute kidney injury.[57] In addition, in a retrospective cohort of more than 320 000 subjects followed in outpatient clinic settings, increased BMI was an independent risk factor for the development of end-stage renal disease.[58] Inorganic fluoride, a byproduct of sevoflurane metabolism, is nephrotoxic at concentrations greater than 50 mmol litre^{-1}. Carbon dioxide absorbers containing barium hydroxide or soda lime degrade sevoflurane into Compound A. In addition, high-temperature gas mixtures, or low fresh gas flow rates ($<$2 litre min^{-1}) can increase the production of Compound A. Compound A has been shown to cause nephrotoxicity in animal studies, but this has not been observed in humans. Kharasch and colleagues[59] randomized 55 subjects with normal renal function to receive sevoflurane or isoflurane for 9 MAC hours at fresh gas flow rates $<$1 litre min^{-1} and found no difference in postoperative renal function between the two groups.

Desflurane

Desflurane has been advocated for use in MO patients because it is the least lipophilic and least-soluble volatile anaesthetic available, and theoretically has limited distribution into adipose tissue. However, the effect of BMI on desflurane uptake is not significant.[52] Emergence and recovery is faster with desflurane than isoflurane in both obese and non-obese subjects.[52 60] Studies comparing desflurane to sevoflurane have yielded conflicting results. Some authors have demonstrated that MO subjects have faster emergence from desflurane when compared with sevoflurane,[61–63] while others have shown no difference in times-to-awakening between the two drugs.[64 65]

Neuromuscular blockers

Succinylcholine

Succinylcholine is a depolarizing neuromuscular blocker with a rapid onset and short duration of action. As MO subjects have a reduced safe apnoea time, its rapid-onset allows rapid tracheal intubation. In addition, its short duration of action allows earlier resumption of spontaneous ventilation should difficulty in securing the airway be encountered. These properties make it the neuromuscular blocking agents of choice in MO patients.

In MO subjects, the amount of pseudocholinesterase is increased.[66] In addition, the amount of extracellular fluid is increased. As both of these factors determine the duration of action of succinylcholine, administration should be based on TBW.[67] When compared with administration based on 1 mg kg^{-1} IBW or LBW, 1 mg kg^{-1} TBW administration results in a more profound block and better tracheal intubating conditions, with clinically insignificant postoperative myalgia.[67]

Pancuronium

Pancuronium is an aminosteroid non-depolarizing neuromuscular blocker with an onset time of 5 min and duration of effect of 60–90 min after an intubating dose of 0.1 mg kg^{-1}. The kidneys excrete the majority of this compound and its metabolites. Respiratory acidosis enhances its action and this must be considered as many MO subjects present with some element of CO_2 retention. Obese subjects require significantly more pancuronium than lean subjects to maintain constant twitch depression.[68] However, when corrected for BSA there was no significant difference in dose requirement. The increased pancuronium requirement is likely owing to an increased extracellular fluid volume, which is known to increase in proportion to BSA. In order to avoid prolonged neuromuscular block, a pancuronium dosing regimen based on IBW is recommended. The use of shorter acting neuromuscular blockers such as rocuronium, vecuronium, or cisatracurium is preferred for the MO population.

Vecuronium

Vecuronium is an aminosteroid molecule with an average duration of effect of 45–60 min after a single intubating dose of 0.1 mg kg^{-1}. Its elimination depends primarily on hepatic and biliary excretion. Doses based on TBW result in a prolonged duration of action in obese *vs* non-obese subjects.[69 70] There are no differences in the PK variables in the obese.[70] With smaller doses, recovery from drug effect is secondary to distribution rather than metabolism. Doses based on IBW are recommended to avoid drug overdose in the obese.[70]

Rocuronium

Rocuronium is a weakly lipophilic aminosteroid molecule with an average duration of effect of 30–45 min after a single intubating dose of 0.6 mg kg^{-1}. Its quaternary ammonium group makes rocuronium highly ionized, limiting its distribution outside the extracellular fluid. Although MO subjects have increased extracellular fluid volume compared with normal weight subjects, it is not entirely understood how this affects rocuronium dosing. The duration of action of rocuronium was doubled when the drug was given based on TBW *vs* IBW.[71] In contrast, another study demonstrated a similar time to recovery in both obese and non-obese subjects after a dose of 0.6 mg kg^{-1} based on TBW with no differences in the PK parameters between the

Table 1 Weight-based dosing scalar recommendation for commonly used i.v. anaesthetics. CO, cardiac output; IBW, ideal body weight; LBW, lean body weight; TBW, total body weight

Drug	Dosing scalar	Comments
Thiopental	Induction: LBW Maintenance: TBW	Simulations showed a 60% decrease in peak plasma concentration in MO subjects compared with lean subjects after a 250 mg dose.[26] Induction dose adjusted to LBW results in same peak plasma concentration as dose adjusted to CO.[26] Volumes and clearances increase proportionally with TBW.[25]
Propofol	Induction: LBW Maintenance: TBW	MO subjects given an induction dose based on LBW required similar amounts of propofol and similar times to loss of consciousness compared with lean subjects given propofol based on TBW.[29] Volume of distribution and clearance at steady state increases with increasing TBW.[28]
Fentanyl	LBW	Clearance increases linearly with 'PK mass', an arbitrary scalar highly correlated to LBW.[46]
Remifentanil	LBW	An infusion based on LBW results in similar plasma concentrations as normal weight subjects were given an infusion based on TBW.[51]
Succinylcholine	TBW	Administration of 1 mg kg^{-1} based on TBW resulted in a more profound block and better intubating conditions compared with doses based on IBW or LBW.[67]
Vecuronium	IBW	Doses based on TBW result in a prolonged duration of action in obese *vs* non-obese subjects.[69 70]
Rocuronium	IBW	There is an increased duration of action when the drug is given based on TBW *vs* IBW.[71]
Atracurium, Cisatracurium	IBW	The duration of action is prolonged in obese subjects when given on the basis of TBW *vs* IBW.[73 74]

groups.[72] Despite these conflicting results, administration based on IBW is prudent to avoid prolonged recovery.

Cisatracurium and atracurium

Cisatracurium and atracurium are benzylisoquinolones with an average duration of effect of 30–40 min after a single intubating dose of 0.15 mg kg^{-1} for cisatracurium and 0.4 mg kg^{-1} for atracurium. Both cisatracurium and atracurium are eliminated by organ-independent Hoffman degradation. Their use has been advocated in patients with compromised renal function. The duration of cisatracurium and atracurium are prolonged in obese subjects when given on the basis of TBW *vs* IBW (Table 1).[73 74]

Target-controlled infusions

The use of target-controlled infusion (TCI) delivery systems has improved the accuracy of anaesthetic drug delivery during induction and maintenance of anaesthesia. However, owing to the lack of PK/PD parameters specific to the MO population, many of the PK models used by TCI devices are derived from normal weight subjects. The use of these models for targeted controlled delivery can result in inappropriate dosing in MO subjects. To prevent overdosing, TBW is capped at 150 kg in the Diprifusor system and LBW is capped for the Base Primea (Fresenius, France) system. Performance of the Marsh model[75] for TCI of propofol in MO subjects was found unacceptable with or without weight adjustment.[76] The Schnider propofol model[77] uses the James equation to calculate LBW. When used for propofol TCI, this model can result in higher infusion rates during maintenance of anaesthesia.[78] The Cortinez allometric model for propofol obviates the need for calculation of LBW.[23] TCI simulations using the Cortinez model found that infusion rates were similar to those predicted by the Marsh model.[23]

La Colla and colleagues found Minto's model of remifentanil[79] to be biased in MO subjects unless a corrected formula for LBW was used.[18 19] Conversely, TCI of sufentanil using the Gepts model[78] showed acceptable performance in obese subjects, although there was increasing over-prediction of sufentanil plasma concentrations with increasing BMI.[49]

Conclusions

Anaesthetizing MO individuals requires careful considerations regarding changes in the PK and PD properties of numerous drugs used in anaesthesia. Physiological and anthropometric changes, such as increases in cardiac output, changes in regional blood flow, and increases in fat mass and lean mass affect PK properties. In addition, respiratory pathophysiology such as the increased incidence of OSA, and fat deposition in the oropharynx and chest wall alter PD properties of anaesthetics.

Dosing scalars other than TBW must be considered when administering drugs to MO individuals. Administering drugs based on TBW can result in an overdose, while administration based on IBW can result in a subtherapeutic dose. With the exception of the non-depolarizing neuromuscular-blocking agents (where IBW might be appropriate), LBW is the most appropriate dosing scalar for the majority of anaesthetic agents including opioids and anaesthetic-induction agents, especially as cardiac output is significantly correlated to LBW, except in individuals with obesity cardiomyopathy.

The incidence of MO continues to increase, and anaesthesiologists are increasingly exposed to MO subjects presenting for various procedures. Knowledge of changes in PK and PD properties that occur in MO subjects and careful consideration of the optimal dosing scalar is necessary for safe and effective administration of anaesthesia in this patient population.

Conflict of interest

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