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Pharmacological Considerations in Morbidly Obese Patients

S. S. Nethra*, D. Shobha and Satish Kumar

Department of Anaesthesiology, Bangalore Medical College and Research Institute, Bengaluru – 560002, Karnataka, India; nethrahn@gmail.com

Abstract

With the increased prevalence of obesity globally, knowledge of the altered pharmacological behaviour of anaesthetic drugs is essential for optimal anaesthetic management of morbidly obese patients and requires special dosing regimens. Failure to account for the pharmacokinetic changes associated with obesity can lead to incorrect doses. So awareness of this is necessary for safe and effective care of morbidly obese patients. This article intends to highlight the dosing regimens in morbidly obese patients.

Keywords: Body Mass Index, Lean Body Weight, Morbidly Obese

1. Introduction

According to the World Health Organization (WHO), 1.6 billion people are overweight, out of which 400 million people are obese[1]. The prevalence of obesity in India is > 135 million which has been increasing over the past few years and has turned into a global epidemic[2]. Obesity, in particular morbid obesity, is known to influence several physiological processes such as cardiac output, gut permeability, gastric, liver and renal functions. Hence pharmacokinetic and pharmacodynamic properties of anaesthetic agents altered, narrowing the therapeutic index of the drugs. Thus, close pharmacodynamic monitoring is required to titrate anaesthetic drug administration towards the desired clinical effect.

2. Definition

The WHO defines Obesity as a condition with excess body fat to the extent that health and well-being are adversely affected and uses a class system based on the Body Mass Index (BMI).

(BMI) = Weight(kg)/Height (m^2)

Morbid Obesity is defined as a BMI of above 35kg/m^2 with co-morbid conditions or above 40kg/m^2 without co-morbid conditions.

3. Body Composition and Drug Clearance

Body composition changes with total body weight. Normal-weight patients have a body weight consisting of lean and adipose body weight in an approximate 4:1 ratio[3]. In obese patients, the excess adipose weight is accompanied by a 20-40% increase in lean body weight. This results in a lean: adipose weight ratio of approximately 3:2.

4. Dosing Scalars

4.1 Allometric Scaling

Allometry is the study of the relationship of body size to body characteristics and properties including anatomy, physiology and behaviour. Body size is usually described by TBW and in some instances, other descriptors are

*Author for correspondence

applied. This has been used to extrapolate the differences in pharmacokinetic or pharmacodynamics properties between individuals with different body sizes and is the standard in many areas of pharmacokinetic research including in that of obesity[4].

4.2 Total Body Weight (TBW)

Doses of drugs are generally based on TBW. This approach is valid for normal-weight subjects whose TBW, Lean Body Weight (LBW) and Ideal Body Weight (IBW) are similar. But, in obese patients, fat mass and LBW do not increase proportionately. Administration of drugs based on TBW may lead to overdose in obese individuals. Hence dosing scalars other than TBW, such as IBW, Body Surface Area (BSA), Body Mass Index and LBW have been used.

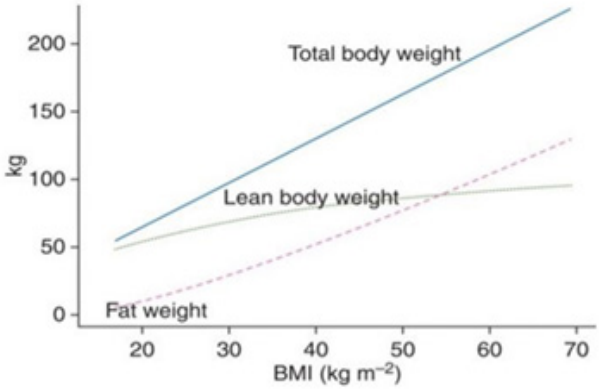

Figure 1. Relationship of TBW, fat weight AND LBW in a standard height male. LBW and fat weight were derived from the equations of Janmahasatian *et al.* [5]

4.3 Body Mass Index (BMI)

It is a measure of body fat based on height and weight that applies to adult men and women. It has been used as a standard by the WHO for recording statistics since the early 1980s.

BMI = Weight (kg)/Height (m^2)

4.4 Lean Body Weight (LBW) (Figure 1)

It is the difference between TBW and fat mass. LBW is significantly correlated to cardiac output and drug clearance increases proportionately with LBW. This suggests that LBW is the ideal weight scalar for drug administration in obese patients. Janmahasatian formula is frequently used[5]. It is as follows:

Male: (9270x TBW)/[6680(216X BMI)]
Female: (9270X TBW)/[8780+(244 X BMI)]

4.5 Body Surface Area (BSA)

It is the scalar used for the dosing of chemotherapeutic agents. Mostellar's equation is the most commonly used which uses TBW and height[6]. BSA does not take into account changes in body composition in obese patients, hence not commonly used for anaesthetic agents.

$$BSA(m^2) = \sqrt{\frac{[\text{height } (cm) \quad x \text{ weight } (kg)}{3600}}$$

4.6 Ideal Body Weight (IBW)

It is a description of the ideal weight associated with maximum life expectancy for a given height. Before BMI was used, obesity was defined as TBW greater than 20% of IBW.

IBW = height (cm)–X (X is 100 for males and 150 for females)

4.7 Adjusted Body Weight (ABW)

It is a commonly used measure for calculating an individual's nutritional needs and is popular among dieticians.

ABW = IBW+0.4 (TBW-IBW)

4.8 Body Mass Index (BMI)

It is a measure of body fat based on height and weight that applies to adult men and women. It has been used as a standard by the WHO for recording statistics since the early 1980s.

BMI = Weight (kg)/Height (m^2)

5.0 Influence of Obesity on Pharmacokinetic and Pharmacodynamic Parameters (Figure 2)

5.1 Obesity and Drug Absorption

- After oral ingestion of a drug, the absorption from the intestine is determined by the rate of absorption (k_a) and the total amount of drug

absorbed (bioavailability or F). In obesity, gastric emptying is accelerated while CYP-mediated gut or liver metabolism might be affected. Hence obese individuals are prone to changes in F or k_a[7]. Drugs must be administered with caution via the subcutaneous and intramuscular routes. Incorrect placement of the needle in the adipose tissue can lead to unpredictable drug absorption. Otherwise, there are no significant changes in bioavailability observed between the obese and non-obese patients. Absorption depends on the lipophilicity of the drugs.

- Adipose tissue does not affect the absorption. Hence studies suggest that the effect of obesity on absorption is limited. However, there is not yet enough evidence to draw firm conclusions. In morbidly obese patients, changes in Volume of distribution (V_d) depend on drug properties, such as
  i. Lipophilicity of the drug
  ii. Ionization properties
  iii. Blood Plasma ratio
  iv. Protein binding
- Albumin and total protein concentrations seem to be unaltered between lean and obese subjects.
- Although, Alpha-1-Acid Glycoprotein (AAG), which is important in binding basic drugs, could be altered in morbid obese patients.

5.2 Obesity and Drug Distribution

5.2.1 Loading Dose

The loading dose is primarily based on V_d. If the drug is primarily distributed into lean mass, LBW or IBW will be used to calculate the loading dose. In contrast, if the drug is largely distributed into fat tissues TBW will be used[8]. If the distribution is in between, ABW may be used.

5.2.2 Maintenance Dose

Primarily depends on drug clearance. The most commonly used equation to estimate the Glomerular Filtration Rate (GFR) is the Cockcroft-Gault equation[9].

$$eGFR=\frac{(140-age)xweig\,htxcont\;ant}{seru\,m\;creatinine}$$

where, the constant is 1.23 for males and 1.04 for females.

5.2.3 Estimation of Creatinine Clearance by CG Equation

Recommended to use TBW in underweight patients. IBW in patients with normal weight. ABW for overweight, obese and morbid obese patients.

5.2.4 Hydrophilic Drugs

Drugs like aminoglycosides, lithium, acyclovir, glycopeptides, beta-lactams, and low molecular-weight heparin typically remain in extracellular fluid and their volume of distribution correlates with lean mass. These drugs have a high plasma concentration relative to the dose and a smaller volume of distribution. The distribution of hydrophilic drugs should not be significantly influenced by excess adipose tissue.

5.2.5 Lipophilic Drugs

Highly lipophilic drugs (phenytoin, midazolam, voriconazole, propofol) distribute extensively into adipose tissue, resulting in a larger volume of distribution compared to less lipophilic drugs, hence lower plasma levels. The volume of distribution is more likely to correlate with total body weight. Drugs with a large volume of distribution often require loading doses followed by a constant dose rate to maintain steady-state plasma concentrations[10]. Steady-state concentrations are dependent on drug clearance.

5.2.6 Changes in Metabolism

With the increase in cardiac output, the liver blood flow is increased in obesity leading to increased drug clearance. The prevalence of liver abnormalities is extremely high in obese patients. It has been hypothesized that low-grade inflammation decreases the expression of PXR (Pregnane X Receptor) resulting in less expression of certain CYP enzymes in particular CYP3A4 enzyme[11].

Phase I metabolism is not affected. Phase II conjugation is elevated in morbid obesity especially glucuronidation. Hence, the clearance of glucuronidation-dependent drugs such as lorazepam, and oxazepam is markedly increased. Conditions such as Non-Alcoholic Steatohepatitis (NASH) might influence the functionality of transporters such as Organic Anion Transporters (OAT) and Organic Anionic Transporting Polypeptides (OATP), which play an important role in the uptake of drugs such as statins and ACE inhibitors.

6. Obesity and Drug Clearance

Predicting drug clearance in obesity for hepatically metabolized drugs is challenging. Drug clearance represents the functional capacity of the body to metabolise and excrete a drug. Clearance is correlated to lean than adipose weight as adipose tissue has little metabolic activity. When lean body weight increases there will be a corresponding increase in drug clearance and an increased dose may be required. Clearance has been correlated with lean body weights such as opioids - fentanyl, anaesthetics- propofol, ranitidine, lithium and enoxaparin.

7. Effect of Obesity on Renal Clearance

Many drugs are eliminated through the kidneys[12] via

Glomerular filtration - higher clearance in the obese group for vancomycin, daptomycin enoxaparin carboplatin and dalteparin.

Tubular secretion - significantly higher tubular secretion was reported for procainamide, ciprofloxacin and cisplatin.

Tubular reabsorption - the tubular reabsorption of lithium was significantly lower in the obese group compared to the non-obese.

8.0 Obesity and Anaesthetic Drugs

8.1 Hypnotics

8.1.1 Thiopental

After a single bolus dose, thiopental is rapidly distributed from the plasma to the peripheral tissues. The high lipophilicity increases its apparent volume of distribution and elimination half-life in obese patients. Total clearance is increased two-fold in the obese vs normal weight subjects. However, when normalized to TBW, there was no difference in clearance. Obese individuals have increased cardiac output, and it is an important determinant in the early distribution kinetics of IV drugs. Thiopental induction doses adjusted to LBW resulted in the same peak plasma level as dose adjusted to cardiac output, suggesting that induction based on LBW is appropriate[13].

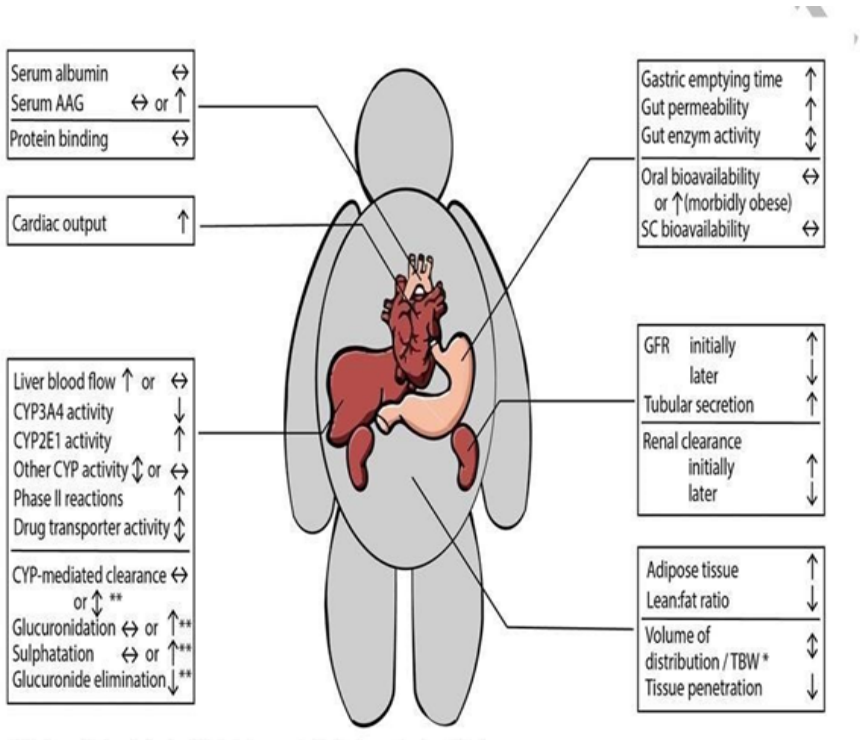

Figure 2. Summary of pharmacological changes in obesity and corresponding effects on PK parameters.

8.1.2 Propofol

Propofol is currently the most commonly used induction agent for morbidly obese patients. It is highly lipophilic and distributes rapidly from the plasma to peripheral tissues. Clearance and volume of distribution were similar to lean subjects when obese subjects were normalized to TBW, suggesting propofol maintenance infusions must be based on TBW. For induction, LBW is more appropriate for dosing scalar. Obese patients who were administered propofol based on LBW for induction required similar doses and had similar times of loss of consciousness as lean control subjects. In addition, the induction dose requirement was related to cardiac output, which is correlated to LBW.

8.1.3 Dexmedetomidine

Dexmedetomidine is a selective alpha-2 agonist with anxiolytic, analgesic and sedative effects. It is commonly advocated as an anaesthetic adjunct to general anaesthesia for morbidly obese patients. During laparoscopic bariatric surgery, an infusion of 0.2mcg/kg/h has been recommended.

8.1.4 Etomidate

It is a carboxy-imidazole intravenous anaesthetic. It acts by modulating GABA receptor function in the central nervous system. For etomidate dosing in obese patients, predicted doses based on Ideal body weight are best suited for morbidly obese and TBW for non-obese patients.

8.1.5 Ketamine

It is a cyclohexanone derivative that is rapidly acting and produces profound analgesia and anaesthesia which acts through its NMDA antagonistic action. Consistent use of an IBW or adjusted body weight is suggested for weight-based dosing in obese patients.

9.0 Inhalational Agents

9.1 Isoflurane

It is more lipophilic than sevoflurane and desflurane. Administration of 0.6 MAC for 2-4 hrs in obese and non-obese subjects had similar times of recovery. In routine practice, the effect of BMI on isoflurane uptake is clinically insignificant[14].

9.2 Sevoflurane

It is less lipophilic and has slightly more rapid uptake and elimination in obese subjects. Increasing BMI is associated with an increased incidence of acute kidney injury. Glomerular hyperfiltration with increased creatinine clearance – nephrotoxicity due to inorganic fluoride and compound A. Hence, it is advisable to use sevoflurane with caution.

9.3 Desflurane

It is the least lipophilic and least-soluble volatile anaesthetic available and theoretically has limited distribution into adipose tissue. Hence advocated for use in obese patients. Emergence and recovery are faster with desflurane in both obese and non-obese subjects. The effect of BMI on desflurane uptake is not significant.

Neuromuscular Blockers

10.1 Succinyl Choline

It is still considered to be the neuromuscular blocking agent of choice in obese subjects, as 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 is 0.5mg/kg. In obese subjects, a dose of 1mg/kg TBW resulted in optimal intubating conditions.

In obese subjects, the amount of pseudocholinesterase is increased[15]. This raises the dose requirement necessary to achieve optimal intubating conditions. Despite the rapid metabolism of the drug, the duration of effect is dose-dependent. Doses of 1mg/kg TBW were found to take 8-12 minutes for dissipation of effect.

10.2 Rocuronium

Despite the higher extracellular fluid volume in obese subjects, the PK of rocuronium is not altered. In the study comparing PK/PD, there were no differences in the volume of distribution, clearance, distribution and elimination half-times between obese and control groups. IBW is suggested for weight-based dosing in obese.

10.3 Vecuronium

After an intubating dose of 0.1mg/kg, vecuronium has a peak effect of 3 min and a duration of effect 45-60 min.

Although these subjects have an increased extracellular fluid volume compared to normal-weight subjects, there is no change in the volume of distribution of vecuronium in obese.

It is eliminated by hepatic clearance and biliary excretion. It is postulated that the prolonged recovery in obese subjects is likely secondary to impaired hepatic clearance and an overdose effect when the drug is given based on TBW.

10.4 Atracurium

In morbid obesity, atracurium 0.5mg/kg ideal body weight results in a predictable profile of muscle relaxation allowing for adequate muscle relaxation and recovery of muscle strength. A dose-dependent prolongation of action is shown when Total body weight is used.

11. Neuromuscular Blocking Reversal Agents

11.1 Neostigmine

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 had similar times to achieve a train of four ratios of 0.7. However, obese subjects showed a 4-fold increase in time to achieve a train of four ratio of 0.9.

11.2 Sugammadex

A direct comparison of sugammadex with neostigmine for reversal of rocuronium blockade in obese subjects showed that it had a faster time to recovery of a train of four of 0.9 [16]. Whether TBW or IBW should be used as a dosing scalar for sugammadex has been debated. Studies suggest that administration based on TBW ensures adequate reversal of neuromuscular blockade.

11.3 Opioids

Obese subjects are at increased risk for opioid-induced respiratory depression and airway obstruction due to their pathophysiology. With increasing obesity, there is an increased incidence of obstructive sleep apnoea, hypoxia and central sleep apnoea with the administration of opioids. Together, these changes narrow the therapeutic window for opioids.

11.4 Fentanyl

It is a synthetic opioid with a potency of approximately 100 times that of morphine and is the most widely used opioid in anaesthetic practice. It 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 CNS into the plasma and peripheral tissues.

It has a large volume of distribution due to its high lipophilicity. Theoretically, obese subjects would have a larger V_d due to their larger amount of adipose tissue, effectively lowering the plasma concentration after a single bolus dose.

The clearance of fentanyl is significantly increased in obese subjects, which is linearly associated with "pharmacokinetic mass". This in turn is highly correlated to lean body weight[17].

11.5 Sufentanil

It is a synthetic derivative of fentanyl that is 10 times as potent. It is the most highly lipophilic opioid. The apparent volume of distribution and elimination half-life of sufentanil both increase with obesity. However, clearance is similar in obese subjects compared to normal-weight subjects. LBW for the initial dose followed by TBW for maintenance.

11.6 Remifentanil

A highly potent synthetic opioid, remifentanil is characterized by a rapid time-to-peak effect (1 minute) and rapid offset of action. It undergoes rapid metabolism via non-specific tissue and plasma esterases, resulting in organ-independent clearance, due to the presence of ester linkages. It is commonly administered as a continuous infusion for sedation or in combination with an intravenous agent for general anaesthesia.

Remifentanil infusion based upon LBW had similar plasma concentrations as normal weight subjects given the drug based upon TBW. In addition, infusions based on TBW resulted in significantly higher plasma concentrations. Hence, the remifentanil pharmacokinetic profile has popularized its use as an analgesic in obese subjects.

11.7 Morphine

The dosing depends on lean body weight. It causes respiratory depression due to its Obstuctive Sleep Apnoea (OSA) and accumulation of morphine and its metabolite. Hence cautious titration and monitoring are necessary.

12.0 Local Anaesthetics

Increased alpha 1 acid glycoprotein in obesity, increases dose requirement due to decreased free fraction[18]. The effects of the central neuraxial block are unpredictable due to the physical effects of obesity on epidural space. Hence it is recommended to calculate dose based on LBW.

13. Opioid-Free Anaesthesia (OFA) in morbidly obese patients

Opioid-free anaesthesia is a technique in which no perioperative opioids are administered through systemic neuraxial or intercavitary routes considering the patient's comfort, analgesia and haemodynamic stability.

The non-opioid analgesics include a variety of medications such as clonidine, dexmedetomidine, ketamine, lignocaine, ketorolac and magnesium.

14. Indications

- It is indicated mainly to avoid postoperative respiratory depression which is anticipated in the obese population.
- To avoid the risk of obstructed breathing, increased sedation, muscle weakness, negative ionotropism, tolerance and addiction.
- It is proven to improve wound healing and oncological outcomes and avoid immunosuppressive action of opioids and opioid-induced hyperalgesia.

15. Contraindications

It is avoided in patients with nodal rhythm, autonomic dysfunction, ischemic heart disease, beta-blocker therapy, hypovolemia, and polytrauma.

16. Disadvantages

- Potential risk of hypotension that may require vasopressor support. Especially with the use of alpha-2 agonists.
- Risk of awareness remains possible, especially in the absence of monitoring of the depth of anaesthesia.

Suggested anaesthetic drug dosing scalar for obese patients

Lean body weight	Ideal body weight	Total body weight
Propofol	Rocuronium	Propofol
Thiopentone	Atracurium	Succinylcholine
Fentanyl	Cisatracurium	Sugammadex
Remifentanil	Neostigmine	
Bupivacaine		
Morphine		
Lignocaine		

17. Techniques of Opioid Free Anaesthesia

OFA was first described in Europe by Mulier, multiple clinical studies reported its use and its benefit in morbidly obese patients[19].

(i) Sympatholytic, anaesthetic, and analgesic agents to reduce the anaesthetic requirements (clonidine or dexmedetomidine). Loading dose of dexmedetomidine: 0.5-1 μg/kg IBW followed by an infusion of 0.5-1 μg/kg IBW/h.

(ii) Non-opioid analgesic (low dose ketamine at a loading dose of 0.125 to 0.25 mg/kg followed by infusion of 0.125 to 0.25 mg/kg IBW/h).

(iii) Co-anesthetic and sympatholytic agent (intravenous lidocaine 1.5 mg/kg IBW followed by infusion of 1.5-3 mg/kg IBW/h I.V).

(iv) Intravenous infusion of magnesium as supplementary analgesic.

(v) Deep neuromuscular block throughout the whole operative period that was adequately reversed.

(vi) Titrated minimum alveolar concentration of inhalational anaesthetic (Desflurane 0.7-1.0 MAC) to maintain an adequate reading of bispectral index reading.

18. Anaesthetic Technique of Mulier

- The pre-prepared Mulimix should be started before the induction of anaesthesia.
- It should be adjusted at a rate of 20ml/ hr.
- Induction of anaesthesia is then carried out through propofol 2 mg/kg IBW along with an intubating dose of rocuronium (1mg/kg IBW).
- Anaesthesia is then maintained by a titrated concentration of inhalational anaesthetics (0.7-1.0 MAC of desflurane) and continuous infusion of rocuronium (0.5 mg/ kg IBW/hr) till the end of the surgery.
- The Mulimix infusion is continued at the loading rate throughout tracheal intubation, patient position, abdominal insufflation, and placement of laparoscopic ports.
- Then, its rate is decreased gradually to 5-10 ml/hr and stopped at the end of the surgery.
- The neuromuscular block should be adequately reversed at the end of the surgery by either neostigmine (0.05 mg/kg IBW) and atropine (0.01 mg/kg IBW) or better by sugammadex 4 mg/kg IBW.
- Ondansetron is administrated routinely as an anti-emetic agent. Also, a high dose of dexamethasone is administrated as both an anti-emetic and analgesic adjuvant.
- Paracetamol 1-2 gm intravenous infusion, parecoxib 40 mg, and local anaesthetic infiltration and intraperitoneal instillation are used. Magnesium is not used routinely.
- During the postoperative care in the Postanesthesia Care Unit (PACU), Mulimix infusion may be restored at a low infusion rate (5ml/hr) in case of inadequate control of pain.

19. Target-Controlled Infusion in the Obese

- At the end of the 1990s, the Schneider model and Minto model for Remifentanil were widely used for target-controlled infusion. But both the models did not include obese patients hence this could not be used in the TCI.
- James model included TBW and height for the calculations, if the weight increases without a change in the height, the calculated lean body mass reaches a maximum and then decreases and may even reach negative values, and was different for males and females. A few years ago, a new formula to calculate LBM in morbidly obese patients was found known as the Janmahasatian formula. However, more research is needed on this prospect[20].

20. Propofol TCI in the Obese Patient

- In the current situation, the required approach is different depending on the drug.
- Propofol TCI may be used in morbidly obese patients provided the Marsh PK model is chosen and the real TBW is used to calculate the doses.
- There have been some discussions about the appropriate dose for propofol induction of anaesthesia in morbidly obese patients.

- While the use of IBW leads to insufficient induction doses, the use of TBW may carry a risk of excessive doses with hemodynamic consequences.
- Hence while using the Marsh model, it might be practical to use a lower target concentration during induction and thereafter titrate the target upward according to the clinical response of the patient[21].

21. Remifentanyl TCI

- Remifentanil has a small volume of distribution that is nearly independent of body mass index and does not accumulate in obese patients as it undergoes extensive and rapid tissue metabolism.
- Dose using TBW can produce CVS depression, hence its dosage should not be based on TBW but on LBW.
- In the Minto model, LBM is a covariate for both the volumes of distribution and the elimination clearance. Although the Minto model underdoses the morbidly obese patient, which is not ideal, but is safer than overdosing; as it allows upward titration without hemodynamic consequences.

22. Conclusion

- Anaesthesiologists encounter obese patients at an increasing rate due to the higher prevalence rate globally

Different regimens of combination of drugs used in OFA

- ***Dexmedetomidine*** (0.6 µg/kg bolus and 0.3 µg/kg/h infusion) - ***Lidocaine*** (1.5 mg/kg bolus and 2 mg/kg/h infusion)
- ***Dexmedetomidine*** (0. 2-0.6 µg/kg/h) - ***Ketamine*** (100 mg/hr)
- ***Dexmedetomidine*** (1 µg/kg bolus and 0.7 µg/kg/ h infusion) - ***Ketamine*** (1 mg/kg bolus)
-***Dexmedetomidine*** (0. 5 µg/kg bolus and 0.1-0.3 µg/kg/h infusion) - ***Ketamine*** (0.5 mg/kg bolus)
- ***Clonidine*** (0.75-1.5 µg/kg bolus and 0.75-1.5 µg/kg/h infusion) - ***Ketamine*** (0.125-0.25 mg/kg bolus and 0.125-0.25 mg/kg/h infusion) - ***lidocaine*** (1.5 mg/kg bolus and 1.5-3 mg/kg/h infusion) - ***Magnesium*** (40 mg/kg bolus and 40 mg/kg/h infusion)
- ***Dexmedetomidine*** (bolus 0.5-1 µg/kg and 0.5-1 µg/kg/h infusion) - ***Ketamine*** (0.125-0.25 mg/kg bolus and 0.125-0.25 mg/kg/h infusion) - ***Lidocaine*** (1.5 mg/kg bolus and 1.5-3 mg/kg/h infusion) - ***Magnesium*** (40 mg/kg bolus and 40 mg/kg/h infusion)
- ***Clonidine*** (150 µg/kg bolus) - ***Ketamine*** (25 mg bolus) - ***Lidocaine*** (1 mg/kg bolus) - ***Esmolol*** (40 mg/kg bolus and 40 mg/kg for the first h infusion)

- The pathophysiological changes associated with obesity narrow the therapeutic index of many anaesthetic agents placing them at risk for anaesthetic-related complications
- Hence knowledge of pharmacokinetic and pharmacodynamic profiles of anaesthetics in obese patients is necessary to drive safe and effective dosing strategies for these patients.

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