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Tae Kyun Kim

Department of Anesthesia and Pain Medicine, Pusan National University School of Medicine, Pusan, Korea

Running title: Obesity and Anesthetic Pharmacology

Contact of corresponding author:

Name: Tae Kyun Kim

Mailing address: (ZIP: 50612), Pusan National University Yangsan Hospital, 20, Geumo-ro, Mulgeum-eup, Yangsan-si, Gyeongsangnam-do, Korea

Phone: +82-55-360-2756

Fax: +82-55-360-2149

e-mail: anesktk@pusan.ac.kr

ORCID : https://orcid.org/0000-0002-4790-896X

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Obesity and Anesthetic Pharmacology: simulation of target-controlled infusion models of propofol and remifentanil

Running title: Obesity and Anesthetic Pharmacology
Abstract

The prevalence of obesity is increasing and the number of surgeries of obesity-induced diseases and obesity itself is on the rise. Besides the comorbidities of obesity, pharmacokinetic (PK) and pharmacodynamic (PD) changes in obese patients make it difficult to control the appropriate dose of anesthetic agents. Factors that affect the pharmacokinetic changes in obese individuals includes increase of adipose tissue, increase of lean body weight, increase of extracellular fluid and increase of cardiac output. These physiologic and body compositional changes affect the changes of PKPD parameters. Increased central volume of distribution and clearance affect the plasma concentration of propofol and remifentanil in obese population. Obese can affect even pharmacodynamic properties of EC50 or Ke0. Simulation of target-controlled infusion based on the PKPD models in which obese populations is included help physicians understand the effect of obese on the PKPD changes of anesthetic drugs.

Keywords: Cardiac output; Clearance; Lean Body Weight; Obesity; Volume of distribution; Simulation.
Introduction

The prevalence of obesity is increasing year by year worldwide. By the report of WHO, obesity population accounts for 13% of the world's adult population. The number is growing steadily and is about three times that of 1975 as of 2016. In particular, the morbidly obese population with a BMI of more than 40 is on the rise. As the number of surgeries to treat obesity-induced diseases and obesity itself is increasing, the increased comorbidity of obese patients has become a burden of care to the anesthesiologist. Anesthesiologist used to have troubles with the obese patients care in regard to the difficult airway management and intubation before and after surgery, mechanical ventilation, diabetes, hypertension, obstructive sleep apnea, and cardiopulmonary disease.

In addition, pharmacokinetic and pharmacodynamic changes in obese patients make it difficult to control the appropriate dose of anesthetic agents. The increase of body mass and composition changes influences the pharmacokinetic parameters such as distribution volume, clearance and elimination half-life. Comorbidity of obese patients like obstructive sleep apnea may cause narrowing of therapeutic dynamic range of anesthetic drugs.

This review would be discussions about how the increase of body mass and compositional changes affect the various anesthetic drug's pharmacokinetic and pharmacodynamic behaviors in obese patients based on reviewing published articles.

Changes of body mass composition

In obese individuals, the lean body mass including vessel-rich organs and tissues at which drugs act does not usually increase proportionally as the total body mass increase. As the body weight increase, the blood volume, fat mass, lean body mass, extracellular water volumes increase along with the increase of total body weight, however, the composition of the mass would not always increase in proportion along with the total body mass. The fat mass tends to increase along with the total body
mass, but, lean body mass does not. The ratio of lean body mass to total body weight would rather decrease as the total body weight increase (Figure 1). The proportion of lean body mass which explains increase of total body weight is about 20-40% [1].

When the amount of drug administration is determined, it is usually scaled based on the total body weight. However, dosing simply scaled by the total body weight in obese patients would result in an overdose. Obese individuals need other mass scalar which is used to calculate appropriate dose, such as lean body weight, ideal body weight, fat free mass and so on. Various mass scalars have been introduced and show their own characteristic features and equations (Table 1).

Total body weight (TBW)

Dosing based on TBW is valid for the normal weight person. In obese patients, however, the lean tissue which majority of cardiac output is delivered to do not increase in proportion to TBW. The use of TBW to determine the dose in obese patients would result in overdose and other mass scalar should be considered.

Ideal body weight (IBW)

Numerous equations have been introduced for calculating the IBW [2]. The disadvantage of this mass scalar is that individuals who have same sex and height receive the same dose regardless of the obesity and the body mass compositions.

Lean body weight (LBW)

LBW is the body mass without fat or adipose tissues. The James’s equation has been frequently used to calculate the LBW for the past several decades, however, it has serious limitation to apply to the obese individuals. The equation underestimates the LBW of morbidly obese individuals and even yields a flawed negative LBW. In 2005, Janmahasatian and colleagues [3] suggested another equation to overcome the James’s formula. It is derived from the dual energy X-ray absorptiometry measured from men and women of various body weight and height. Most metabolic activities occur in the lean
body mass and increase of cardiac output is closely correlated with the increase of LBW. For that reason, early distribution kinetics of drug and clearance are influenced by the cardiac output.

**Adjusted body weight (ABW)**

It is defined as IBW plus a proportion (40%) of total body weight excess compared to the ideal body weight. ABW is calculated as $\text{IBW} + 0.4 \times (\text{TBW} - \text{IBW})$.

**Body mass index (BMI)**

It is widely used index to determine the degree of obesity which is a ratio of body weight to the squared height. There is no consideration of the body mass composition.

**Body surface area (BSA)**

Mostly, it has been used for the dosing scalar for the chemotherapeutic agent. Equations derived by Mosteller [4] are widely used. It cannot discriminate the fat and lean body mass.

**Pharmacokinetic mass**

Because of the non-linear relationship between fentanyl clearance and TBW, obese patients would be overdosed when the fentanyl was given based on the TBW. Shibutani and colleagues devised a modified weight called ‘pharmacokinetic mass’ in which mass scalar increases in proportion to the increase of clearance, is known to be highly correlated with LBW [5].

**Allometric scaling**

Allometric scaling is a method which makes a relationship between the body mass and pharmacokinetic or pharmacodynamics parameter with certain fixed exponent constant $\alpha$ like $\text{Clearance} = \beta \times (\text{TBW})^\alpha$. The alpha is usually called allometric coefficient. Allometric scaling has been designed in order to apply the results of animal experiments to human or to assume pediatric dose from the data of adult [6-8]. Sometimes, the allometric scaling is useful to determine the dosing amount for obese patients. However, the extrapolation out of the range of analyzed data such like data from non-obese to obese populations, seems to have problems inherently.
Changes of pharmacokinetic properties

Physiological and anthropometric changes in obese patients affect the pharmacokinetic parameters such as volume of distribution and clearance that determine drug concentration and dosage. Unlike normal weight patients, the characteristic changes that affect the pharmacokinetic parameters in obese patients include increased lean body mass, increased muscle mass, increased fat mass, increased circulatory blood volume, and increased total body water. In addition, changes in lipophilicity or hydrophilicity of the drug and protein binding of the drug affect the pharmacokinetic parameters of obese patients [9,10].

Increased fat mass in obese patients increases the volume of distribution of lipophilic drugs [11-13]. In the study of thiopental, which has high lipophilicity, it was found that the steady-state volume of distribution of obese patients was greatly increased and that the elimination half-life was also increased [14]. The propofol study also showed that volume of distribution increased in proportion to TBW increase [15]. The volume of distribution of the lipophilic drug increases as fat mass increases, however, it does not increase proportionally. The reason for this is related to the changes of blood flow to the adipose tissue. The blood flow to adipose tissue accounts for 5% of cardiac output in non-obese, but it is reduced to 2% in obese patients [16].

An increase in the central volume of distribution in obese leads to a rapid decrease in concentration at initial distribution phase. The loading dose is mainly determined by the size of the central volume of distribution, which determines the initial concentration changes after drug administration. In addition, the increase in cardiac output, which is commonly observed physiological changes in obese patients, is another factor explaining low plasma concentrations in a distributive period [17,18].

Increased cardiac output plays an important role in the increase of overall clearance of drugs, thus lowering the elimination half-time of drug. The increase in cardiac output in patients with obesity is
highly correlated with the increase of LBW [19,20]. Increased cardiac output and increased LBW are associated with increased renal and hepatic blood flow, which in turn increases more of the overall clearance as well as initial distributive clearance [21,22].

It has been reported that the increased cholesterol and free fatty acids in obese patients inhibits the binding of the drug to plasma proteins such as albumin. There is also a disagreement, however, binding of the drug to plasma proteins increase because the α-acid glycoprotein is increased in obese patients [23-26].

Changes of Pharmacodynamic properties

Excess fat caused by obesity causes disturbances in the body metabolism and inflammatory reactions and increases the sensitivity to drugs [27,28]. Some studies have shown that obesity makes pain sensitive, while others have no adverse or pharmacodynamic effects [29-31]. Cortinez et al. [32] did not find any change in pharmacodynamic parameters in obese patients. Dong et al. [33], however, reported that EC50 decreased in obese patients and they were sensitive to propofol.

Considering that obesity affects not only pharmacokinetics but also pharmacodynamics, determining the doses of propofol based on the EEG processed monitor should be considered. Subramani et al. [34] said that when propofol was administered with the target of BIS 50 during anesthesia induction, there was a difference from the dose administered at 2.6 mg/kg based on LBW. In this study, compared to the amount of propofol administered based on LBW, a larger amount was administered when administered based on BIS. They also reported that in order to obtain a sufficient depth of anesthesia for those who were administered based on LBW, 60% of them required an additional dose of propofol. The Eleveld model also suggests that ke0 changes as the body weight changes with equation of $0.146 \times (\text{weight/70})^{-0.25}$. 

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Target Controlled Infusion (TCI) model for obese population

Studies on the TCI model related to obesity have been conducted on several drugs including propofol and remifentanil [35-40]. If the obese populations were not included in the process of building a TCI model and not equipped into the anesthetic delivery pump, the exact target effect concentration cannot be obtained by calculating doses simply based the total body weight of the obese patient.

However, some reports said that changing the weight scalar of known TCI model to something other than TBW improves the performance of the model in obese patients. Cortinez et al. [41] reported the improvement of performance of TCI model by just switching original weight scalar with an alternative weight scalar. They said that the performances of Shinider and Marsh model were dramatically improved as a result of substituting TBW with ABW. La Colla and colleagues proposed using a fictitious height which is adjusted height to offset the inaccurate influence of LBM of Minto model when the model is applied to the obese individual [38].

Nevertheless, those kinds of proposed shortcut would not be a definitive solution. Constructing a new pharmacokinetic model including data obtained from obese patients should be more reasonable approach. Eleveld et al. [42] and Kim et al. [40] presented an integrative model for propofol and remifentanil, respectively, by gathering data from various propofol and remifentanil pharmacokinetic studies including obese patients.

Simulation

Before administering drugs to obese patients, simulations based on pharmacokinetic or pharmacodynamic models is helpful in planning drug administration. Simulation model including obese population would help physicians discover unexpected errors and prepare for them in advance.
Therefore, Eleveld and Kim models are simulated to discover the difference of pharmacokinetics of propofol and remifentanil between obese and non-obese person.

It is clinically impractical to administer propofol and remifentanil independently at each target concentration without consideration of interaction. The interaction between propofol and remifentanil should be considered for the simulation of obese patients as well. Target concentration of propofol and remifentanil should be changed as if the target concentration is controlled in real clinical situation in which interaction of drugs works.

For the interaction model, the hierarchical model of Bouillon et al. [43] was referenced. The target concentration for induction and maintenance of anesthesia were maintained at target concentration combinations of the two drugs achieving 95% no response to intubation or hypnosis (Fig. 1). Resultant predicted concentration of each drug simulated by scenario is plotted in Fig. 2.

Eleveld and Schnider models were compared for propofol simulation, and Minto and Kim models were compared for remifentanil simulation. In the Eleveld model, various covariates determine the pharmacokinetic and pharmacodynamic parameters. Eleveld model has especial covariates, which are coadministration of opioid and status of health (patient or healthy volunteer) and so on. All the cases cannot be covered by this simulation but influences of weight and age were simulated. Simulation was done for the healthy volunteer who is administered with opioid, remifentanil and 170 cm height. Ke0 of Kim model was referenced with that of Minto model since Kim model does not represent Ke0. The purpose of simulation is to show the changes of total cumulative doses and infusion rate by varying BMI or age.

For the results of the simulation, comparing the cumulative dose of Schnider and Eleveld models, the cumulative dose of the Eleveld model is larger than that of the Schnider model early in the time of TCI. This is because the Schnider model has a small and fixed central compartment volume, however, the Eleveld model has relatively larger central compartment volume which requires a
relatively larger amount of propofol at the beginning of TCI to maintain the same target concentrations (Fig. 3).

Later time of TCI infusion, however, the cumulative dose of the Schnider model increases more than that of Eleved model. As the BMI increases, the clearance of the Schnider model increases much more than that of the Eleved model (Fig. 3). It is because a relatively high clearance requires a higher dose of drug to maintain the same target concentration. This trend shows significantly prominent in obese person than in non-obese person (Fig. 4). Therefore, when TCI is performed with the same target concentration, the initial infusion rate of the Eleved model is faster, but the infusion rate gradually decreases over time as the clearance is lower than Schnider model (Fig. 4).

When the two models of remifentanil were compared in normal BMI person, the central compartment volume and clearance of Minto model and Kim model does not look like different. As the BMI increase, however, central compartment volume and clearance of Minto model does not increase in proportion to the BMI increase because the LBM of James equation is installed in every parameter of Minto model. In James equation, LBM decreases with increasing body weight in morbidly obese person (Fig. 3). On the contrary, central compartment volume and clearance of Kim model increase according to the increase of BMI. Kim model does not use James’s equation but rather uses the FFM of Janmahasatian equation which is applied for calculation of the fast-peripheral compartment volume. The central compartment and clearance of Kim model are generally predicted larger than those of Minto model. As the BMI increase, the difference of central compartment volume and clearance between two models would be larger (Fig. 3). Therefore, when TCI is performed with the Kim model, it can be predicted that the cumulative dose will be larger over time than that of the Minto model. The cumulative dose differences of two models would be larger in obese patients (Fig. 4). The infusion rate shows higher in Kim model but both models represent similar trend throughout the simulation (Fig. 4).
An additional simulation for the influence of age shows that the difference of cumulative dose of propofol between the models gets larger with age. In the case of remifentanil, the difference of cumulative dose between the two models maintained a constant interval in all age groups (Fig. 5).

**Discussion**

No matter how appropriate mass scalar is applied for induction and maintenance of anesthesia, the targeted concentration cannot be guaranteed by manual administration with simple calculation of dose. In other words, a holistic TCI method equipped with an appropriate pharmacokinetic and pharmacodynamic model is needed to control the concentration of anesthetic drugs. Drugs infusion through TCI system is theoretically the most accurate and fastest way to reach the target concentration, but it requires an accurate model to support it. However, many pharmacokinetic and pharmacodynamic models are created from data which do not include obese patients’ information, which is the reason why such model cannot predict blood concentration accurately in obese patients. Recently, a few models that can be applied to obese patients as well as general patients have been introduced.

The Eleveld model can be well constructed model that can administer more accurate concentrations to individual patients by including various covariates that can be encountered in actual clinical situations. From a point of view that Eleveld model includes covariate defining whether opioids are used or not, it can be said that this model is a more practical model. When propofol is administered in clinical practice, opioid such as remifentanil is almost always administered together and the two drugs may affect each other pharmacokinetically or pharmacodynamically [44]. The simulation of this review also included covariates for opioid use to reduce the bias from the coadministration of remifentanil.
Based on the Eleveld model, the central compartment volume does not increase significantly (16.2%) compared to the increase of BMI. The clearance of obese patient, however, increases as the BMI or weight increase (54.9%). Clinically, this means that if propofol is administered to obese patient during anesthesia induction as a bolus dose based on the total body weight, an overdose may occur. In the case of continuous infusion, however, total body weight could be adopted as a dosing scalar even in the obese patient anesthesia [15,32]. These observations are coincided with other reports in which the increase of clearance is prominent but the increase of volume of distribution is relatively small [16,21,22].

Even though the best model which can predict concentrations accurately, it cannot cover all the clinical situations. Pharmacokinetic change of propofol can be influenced by various causes, such as very lean or underweight body type, laparoscopic surgery, and prone patient posture [45-48]. Even propofol itself could cause pharmacokinetic changes. Cardiac depression caused by propofol itself affects its distribution and clearance. Therefore, rather than trying to find out all the cases which affects the pharmacokinetics and put it into a new model, it is important to check a monitor such as BIS and confirm whether the purpose of the drug is finally achieved.

How many models can be available for TCI? Most commercial infusion pump are not equipped with the new models which was built for the obese patients. For a method of applying a new TCI model suitable for obese patients, connecting an infusion pump to a computer and run a PKPD model suitable for obese patients through TCI software on the computer. Another method is to apply an appropriately modified scalar instead of the actual patient's height or weight into the model which is already installed in commercial TCI pump. Using an ABW instead of the TBW for the traditional Schnider and Marsh models or putting in the fictitious height to the Minto model replacing actual patient height. Substitution of modified scalar, however, is not a perfect solution.
Conclusion

Simply administering a drug based on body weight to obese patients would be at high risk of overdosing. The comorbidity associated with obese patients can make the risk of overdosing more serious one. In order to determine the appropriate dose for obese patients, it is important to understand how pharmacokinetics and pharmacodynamics change as the body weight increases. Factors that affect the pharmacokinetic changes in obese individuals includes increase of adipose tissue, increase of LBW, increase of extracellular fluid and increase of cardiac output.

Several mass scalars including IBW and LBW has been introduced to determine the appropriate dose calculation for obese patients, but there is no absolute mass scalar which can be applicable to all drugs and individuals. Important point should be emphasized on the monitoring the effects and side effects of the administered drugs carefully.
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bispectral index, and electroencephalographic approximate entropy. Anesthesiology 2004; 100: 1353-72.


Table 1. Common dosing scalars

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<th>Dosing scalar</th>
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| Ideal body weight        | Male: 50 kg + 2.3 kg for each 2.54 cm (1 in) over 152 cm (5 ft)  
                           | Female: 45.5 kg + 2.3 kg for each 2.54 cm (1 in) over 152 cm (5 ft)                                                                   |
| Lean body mass           | Male: 1.1 × TBW − 128 × (TBW / Ht)^2  
                           | Female: 1.07 × TBW − 148 × (TBW / Ht)^2                                                                                             |
                           | Female: (9.27 × 10^3 × TBW) / (8.78 × 10^3 + 244 × BMI)                                                                             |
| Body surface area (Mosteller’s adaptation)[4] | [(height (cm)-TBW)/3600]^{1/2}                                                                                                        |
| Pharmacokinetic mass [5,49] | 52 / [1 + (196.4 × e^{-0.025 TBW} − 53.66)/ 100] (fentanyl only)                                                                           |
| Corrected body Weight [15,32] | IBW + 0.4 × (IBW − FFM)                                                                                                               |
| Allometric scaling       | With allometric coefficient alpha, Clearance = beta × (TBW)^alpha                                                                      |

*BMI*, Body mass index; *FFM*, fat-free mass; *Ht*, height in centimeters; *IBW*, ideal body weight; *LBM*, lean body mass; *TBW*, total body weight in kg.
Figure 1. Planning of simulation based on the predictions of loss of responsiveness.  A. Isoboles are presented on top-down view. Isoboles of 95%, 50% non-response to laryngoscope and hypnosis are presented. The inward bow of the isoboles indicates that the interaction is synergistic.  B. Simulated target concentrations are plotted on the interaction surface.
Figure 2. Resultant effect-site concentrations of propofol and remifentanil. Target concentration of propofol and remifentanil are predicted according to simulated scenario.
Figure 3. Comparison of volume of distribution and clearance. Central volume of distribution and clearance are compared between pharmacokinetic models with changing the BMI. A: central volume of distribution changes of propofol models, B: clearance changes of propofol models, C: central volume of distribution changes of remifentanil models, D: clearance changes of remifentanil models.
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Figure 4. Comparison of cumulative dose and infusion rate. The cumulative doses and infusion rate are presented with varying the BMI and fixed age 50 years. A: cumulative doses of propofol models, B: infusion rate of propofol models, C: cumulative doses of remifentanil models, D: infusion rate of remifentanil models.
Figure 5. Comparison of cumulative dose. The cumulative doses are presented with varying the age and fixed BMI 45 kg/m². A: cumulative doses of propofol models, B: cumulative doses of remifentanil models.