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EDITORIAL

The concept of "fictitious weight" in pharmacokinetic simulations and target-controlled infusion

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Keywords Propofol · Target-controlled infusion · Marsh model · Pharmacokinetics

Abbreviations

TCI	Target-controlled infusion
PK	Pharmacokinetics
LBM	Lean body mass

Zhong and Xu recently published a paper titled "General Purpose Propofol Target-Controlled Infusion Using the Marsh Model with Adjusted Weight Input" in *Journal of Anesthesia* [1]. This study aimed to improve the performance of target-controlled infusion (TCI) in adjusting the gap between predicted propofol concentrations and actual plasma levels. This improvement is achieved by mimicking the TCI behavior of the Eleveld model [2], which is currently considered the best model, through modifying the input weight in the Marsh model. The Marsh model is adopted by the Diprifusor system [3, 4], the only TCI system available in Japan. To understand the concept of Zhong and Xu's study, it is essential to understand the foundational principles regarding how patient characteristics influence the pharmacokinetics (PK) of commonly used anesthetic drugs, and consequently, their impact on PK simulations and the predictive performance of TCI. This paper explains these concepts using propofol as the primary example, and also provides supplementary information on remifentanil and fentanyl.

PK models based on the compartmental model concept consist of a set of PK parameters, including volumes of distribution, clearance, and rate constants. With a PK model established for a specific aesthetic, one can simulate the time-dependent changes in plasma and effect-site concentrations based on the drug's dosing history. Moreover, using a dedicated algorithm and PK model to control a syringe pump, TCI is made possible.

Even for the same drug, PK (i.e., dose-concentration relationship) can vary depending on patient characteristics such as body size and metabolic capacity. For example, administering 50 mg of propofol each to a 50 kg patient and a 100 kg patient would result in different plasma concentration profiles. To account for such patient-specific factors, covariates are incorporated into the PK parameter values, allowing for adjustments. For instance, the Marsh model used by the Diprifusor system inputs the actual body weight as a covariate. However, these adjustments have limitations. This is because, in principle, the predictive performance of a PK model is most applicable for patients with backgrounds similar to those from which the model's data were derived. Generally, PK models that are widely used in clinical practice have been developed using subjects with "standard" background factors. Therefore, it is rational to use a PK model developed from data collected from "special" patients when dealing with such cases. Moreover, in recent years, PK models for typical anesthetics covering a broader range of patient backgrounds, including obesity, elderly patients, and children, have been published [2, 5, 6]. PK models, when implemented in simulations or TCI systems, can provide more accurate predictions for patients with similar characteristics to those used in model development.

Propofol

Currently, the only TCI system approved for clinical use in Japan is the Diprifusor TCI system for propofol [7], which utilizes the Marsh model. The predictive performance of this system has been thoroughly validated in standard adults [3, 8]. The Marsh model considers only body weight as a

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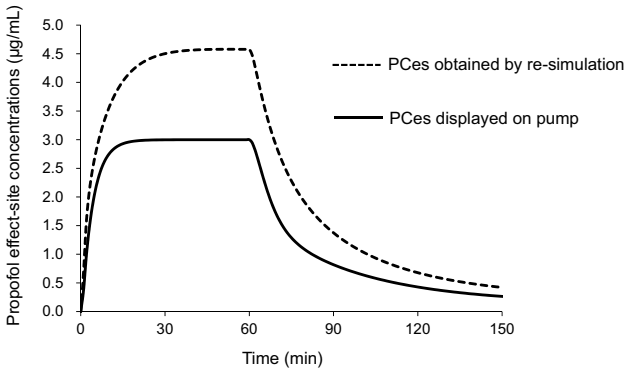

Fig. 1 Propofol effect-site concentrations displayed on the Diprifusor pump (solid line) and those obtained through re-simulation with the Eleveld model (dashed line), using the dosing history of target-controlled infusion. The patient is a 40-year-old man, 176 cm in height and 150 kg in weight. Propofol target-controlled infusion was performed with a target plasma concentration of 3 μg/mL for 60 min. It is assumed that simulations based on the Eleveld model, which accounts for severely obese individuals, are more accurate than those based on the Marsh model. PCes, propofol effect-site concentrations

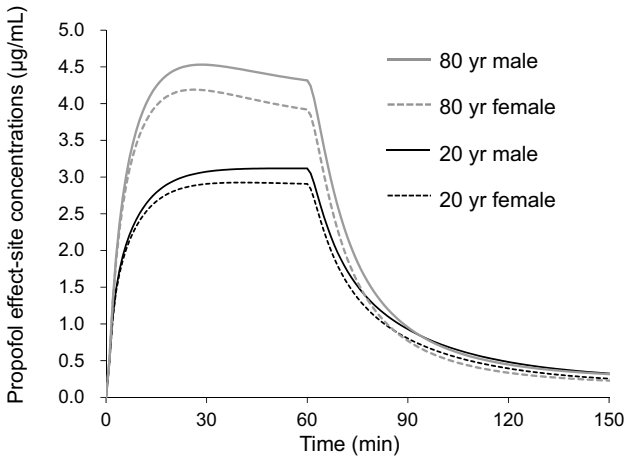

Fig. 2 Propofol effect-site concentrations obtained through re-simulation with the Eleveld model, based on the dosing history of target-controlled infusion using the Diprifusor system. The patients are four individuals, either 80 or 20 years of age, and of either gender, all with the same height and weight (170 cm, 68 kg). Propofol target-controlled infusion was performed with a target plasma concentration of 3 μg/mL for 60 min. It is assumed that simulations based on the Eleveld model, which accounts for severely obese individuals, are closer to reality than those based on the Marsh model

covariate, and the dataset used for its development did not account for extreme obesity [9]. Additionally, gender and age are not incorporated into the model parameters. Consequently, there may be discrepancies between the plasma/effect-site concentrations displayed on the pump and the actual values (Figs. 1, 2).

When performing total intravenous anesthesia with a focus on plasma or effect-site concentration under the aforementioned limited conditions for special patients, such as those who are morbidly obese or elderly, the following options can be considered:

(1) Abandon TCI and adjust the dosage manually while referring to PK simulations: Regarding the choice of PK model, the Schnider model [10], which is implemented in many PK simulators, allows for the input of gender, age, height, and weight. Furthermore, the Eleveld model [2], which enables simulations across a broader range of patient populations (from newborns to adults aged 88 years, with body weight up to 160 kg and BMI up to 50), is considered one of the most reliable PK models as of 2024.

(2) Recognize the qualitative discrepancies that occur with Diprifusor TCI and have the anesthesiologist interpret the predicted effect-site concentration accordingly: Fig. 1 suggests that, in severely obese patients, the effect-site concentration displayed on the pump is likely underestimated and may be higher in reality. Additionally, Fig. 2 indicates that differences in gender and age can result in variations in effect-site concentration. When the target value for TCI is the same, the effect-site concentration is higher in elderly patients compared to younger ones. For the same age, the effect-site concentration is slightly lower in females than in males. Therefore, if the clinical effects observed during TCI, such as clinical signs or electroencephalogram indicators, do not correspond with the effect-site concentration displayed on the pump, it should be understood that there may be discrepancies in the predictions.

(3) Improve predictive performance by adjusting the covariates input into the TCI system: Cortinez et al. demonstrated that, in obese patients, entering adjusted body weight (note: different from the 'adjusted body weight' mentioned in Zhong and Xu's Excel sheet explained later) into the Diprifusor TCI system can maintain clinically acceptable predictive performance [11]. Zhong and Xu [1] explored in silico how entering a fictitious weight as a covariate in the Marsh PK model, along with adjusting the PK parameters for plasma TCI and combining it with a corrective bolus dose, could mimic the behavior of the Eleveld model's effect-site TCI, thereby achieving clinically acceptable predictive performance across a broad patient population. They used a combination of age, height, actual body weight, and gender to generate numerous pairs of fictitious weights and corrective bolus doses, using an optimization algorithm to match the simulation results with those of the Eleveld model. The Excel sheet they provided calculates the fictitious weight and corrective bolus doses using complex regression equations (Fig. 3). For clinical use, an approval process may be required depending on the facility's policy.

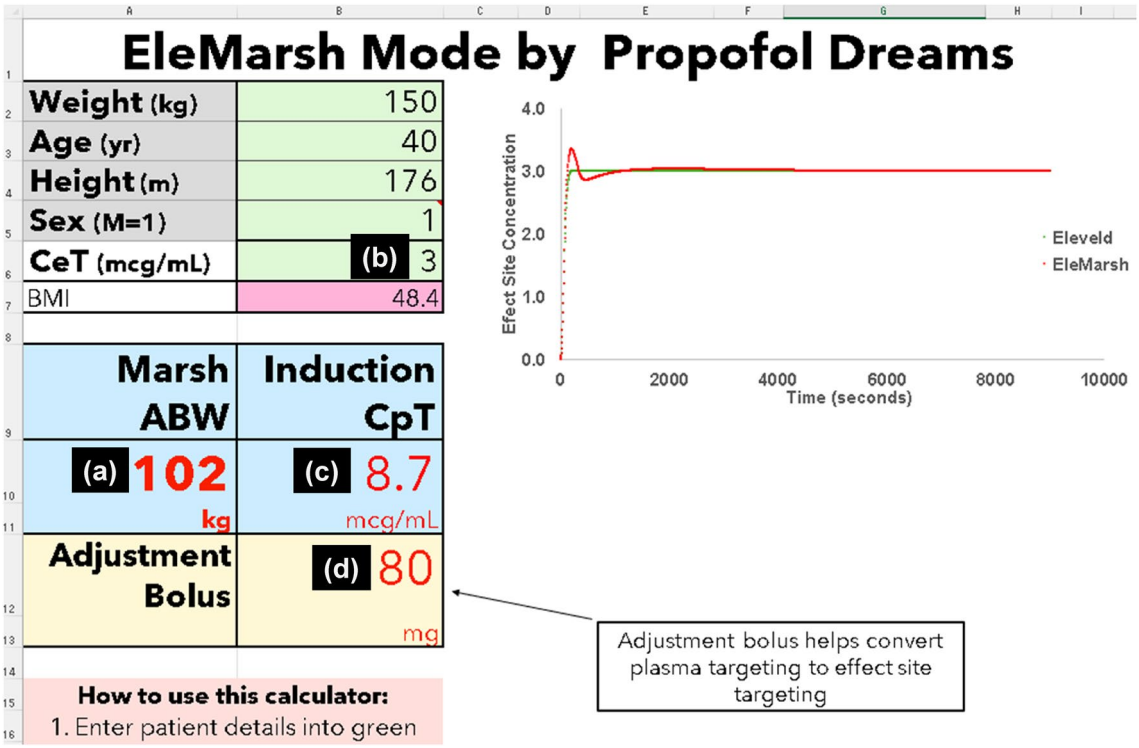

Fig. 3 Screenshot of the Excel Spreadsheet Provided by Zhong and Xu [1]. An example of a 40-year-old male, 150 kg in weight, 176 cm in height. To perform an effect-site target-controlled infusion (TCI) mimicking the Eleveld model with a target effect-site concentration of 3 µg/mL, input Marsh ABW that is calculated by the Excel sheet (102 kg) into the Diprifusor (**a**). Enter 3 for CeT (µg/mL) (**b**). For the target plasma concentration on the Diprifusor, input the value of 8.7 for Induction CpT (**c**). Once the infusion starts and the predicted plasma concentration on the Diprifusor reaches the same value, reset the target plasma concentration to 3. This adjustment brings the effect-site concentration closer to 3, as estimated by the Eleveld model. If the target effect-site concentration needs to be increased by 1 µg/mL (e.g., from 3 to 4 µg/mL), increase the target blood concentration in the TCI, and once 80 mg of propofol as specified in the Adjustment Bolus (**d**) has been infused, set the target plasma concentration to 4 µg/mL

(4) Output the propofol administration history from the Diprifusor TCI pump in real time and re-simulate using a more accurate PK model: In Japan, the Dräger Smart-Pilot® View (Drager Medical, Lubeck, Germany) allows for this process using the Schnider model. As an alternative, it may be technically feasible to obtain comparable information by exporting dosing data from the Diprifusor TCI pump and re-simulating with a different PK model using a standard PK simulator, although not in real time.

Remifentanil

Remifentanil is one of the anesthetics for which dose adjustment based on body weight is routinely practiced in clinical settings. For adult patients, the standard induction dose is 0.5–1 µg/kg/min, with a maintenance dose of 0.25 µg/kg/min. However, the Japanese prescribing information suggests that, for obese patients with a BMI over 25, dosing should be determined based on ideal body weight rather than actual body weight. This recommendation is likely derived from a study on remifentanil PK in obesity by Egan et al. [12], which states that "Because remifentanil PK parameters appear to be more closely related to lean body mass (LBM) than to total (= actual) body weight, remifentanil dosing should be based on LBM (or ideal body weight) rather than total body weight." Ideal body weight and LBM are theoretical values calculated using formulas, and tend to be smaller than actual body weight in obese patients [13]. These values are used to adjust the dosage, as the drug requirement does not increase proportionally with body weight in obese patients. It is important to note that Egan's study included patients with a BMI of up to 43, and thus, this adjustment method may not be appropriate for patients with more severe obesity.

In fact, the de facto standard Minto model [14] for remifentanil includes LBM as a covariate, which can lead to inaccurate predictions in patients with severe obesity [5], because LBM was formulated during a period when severe obesity was rare, even in Western countries. This has rendered the LBM formula to be outdated. To address this issue, a method was once devised by

inputting a "fictitious height" to adjust the Minto model's PK predictions for severely obese patients [15]. This issue has since been resolved with the introduction of the Kim–Obara–Egan [5] model, which covers obesity with BMI thresholds up to 73.7. This model is implemented into several TCI pumps that are available internationally.

Fentanyl

The PK model by Shafer et al. [16] is considered the gold standard for predicting the plasma concentrations of fentanyl. This model includes actual body weight as the sole covariate for parameter adjustments. However, there are concerns regarding prediction accuracy in obese patients. Shibutani et al. [17, 18] proposed a method to improve the prediction accuracy of Shafer's model by incorporating PK mass ($52/[1+(196.4*e^{-0.025\,TBW}-53.66)/100]$) into the model, and this method has been validated in obese patients weighing up to 181 kg.

Conclusion

As shown in this paper, efforts have been made to improve the prediction accuracy of available PK models to match the actual data (i.e., the predictions by more accurate PK models) by including values such as fictitious weight or height that are different from the actual patient data as covariates, particularly for patients whose characteristics fall outside the range covered by the existing models. In particular, the study by Zhong and Xu represents a continuation of this line of research. Rigorous validation by various facilities will be necessary to confirm the usefulness of the upcoming model.

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