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Research Article

Performance of a Propofol Pharmacokinetic Model for Target-Controlled infusion in Morbidly Obese Japanese Patients

Natsuki Anada[1], Takeshi Umegaki[1*], Chisato Sumi[1], Teppei Iwai[1], Munehiro Masuzawa[2], Kenichiro Nishi[1], Kiichi Hirota[3], Koh Shingu[4]

[1]Department of Anesthesiology, Kansai Medical University Hospital, Osaka, Japan

[2]Department of Anesthesiology, Kansai Medical University Medical Center, Osaka, Japan

[3]Department of Human Stress Response Science, Institute of Biomedical Science, Kansai Medical University, Osaka, Japan

[4]Department of Anesthesiology, Jusendo General Hospital, Fukushima, Japan

**Corresponding author: Dr. Takeshi Umegaki, Department of Anesthesiology, Kansai Medical University, 2-3-1 Shin-machi, Hirakata, Osaka 573-1191, Japan. Tel: +81-72-804-0101; Fax: +81-72-804-2786; Email: umegakit@hirakata.kmu.ac.jp*

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Abstract

Study Objectives: To evaluate the accuracy of target-controlled infusion (TCI) of propofol based on total body weight (TBW) in severely obese patients using the Marsh pharmacokinetic model.

Design: Prospective study.

Setting:

A large tertiary care teaching hospital.

Patients: Severely obese (body mass index ≥35) adult patients who underwent scheduled surgery between April 1, 2014 and March 31, 2015.

Interventions: None.

Measurements

Propofol was administered to patients during surgery using the 'Diprifusor' TCI system to maintain a bispectral index of 40 to 60. TBW was used to calculate blood propofol concentration (μg/ml). The median performance error (MDPE) and median absolute performance error (MDAPE) were calculated to examine the difference between the calculated and measured blood propofol concentrations. We obtained 39 sampling points from 13 patients (Six orthopedic surgery patients, five general surgery patients, and two neurosurgery patients) for analysis.

Main Results

The calculated blood propofol concentration was 2.8±0.6 μg/ml, whereas the measured concentration was higher at 4.9±1.4 μg/
ml. Both MDPE and MDAPE exceeded 60%, and a Bland-Altman analysis showed the presence of both fixed and proportional

errors. However, both MDPE and MDAPE gradually decreased as surgery progressed in each patient. A multiple regression analysis was used to identify possible variables to develop a formula to describe the relationship between the calculated and measured blood propofol concentrations. The covariates included calculated blood propofol concentration, weight, body mass index, and body surface area. However, only the calculated concentration was significantly associated with measured concentration (coefficient: 1.60; P<0.001).

Conclusions

Measured propofol concentrations were substantially higher than calculated concentrations in obese patients administered propofol through TCI using the Marsh model. Measured propofol concentration could be predicted as 1.6 times the calculated propofol concentration. Further studies are needed to explore appropriate methods for calculating blood propofol concentrations during TCI-based anesthesia in obese patients.

Keywords: Propofol; Target-Controlled Infusion; Severe Obesity

Abbreviations

ASA-PS: American Society of Anesthesiologists Physical Status;
BIS: Bispectral Index;
BMI: Body Mass Index;
HPLC: High-Performance Liquid Chromatography;
MDAPE: Median Absolute Performance Error;
MDPE: Median Performance Error;
TBW: Total Body Weight;
TCI: Target-Controlled Infusion

Introduction

The Marsh model is a popular pharmacokinetic model for the target-controlled infusion (TCI) of propofol, and incorporates the use of a 'Diprifusor' system that includes pharmacokinetic parameters[1]. This model was based on the pharmacokinetics of propofol determined by Gepts and colleagues[2]. In another study, White and Kenny analyzed 33 adult surgical patients to demonstrate the usability of a three-compartment mathematical model, and also established the appropriate ranges of blood propofol concentration for anesthesia induction and maintenance[3]. While these studies form the foundation of the Marsh model, the reported patient characteristics of the study sample in Gepts et al. indicate that few, if any, of the patients had a BMI that exceeded 35[2]. Although the Marsh model stipulates the use of body weight as a standard, there is a need to assess the validity of this model in obese patients.

Van Kralingen and colleagues previously developed a three-compartment pharmacokinetic model to analyze the disposition of propofol in morbidly obese patients[4]. That study reported total body weight (TBW) to be the primary predictive covariate for clearance from the central compartment. However, there is limited research on this topic in Japanese patients.

In this study, we calculated and measured blood propofol concentrations in severely obese surgical patients in Japan, and examined the differences between the calculated and measured concentrations. In addition, we examined the development of a formula to describe the relationship between the calculated and measured blood propofol concentrations using multiple regression analysis.

Materials and Methods

Study design

We conducted a prospective single-center study of patients who had undergone scheduled surgery between April 1, 2014 and March 31, 2015 at a large tertiary care teaching hospital. Patients who had a BMI of 35 or higher and were 20 years or older at admission were included in the analysis. We excluded pregnant patients and patients with allergies to soybean oil or egg lecithin. General anesthesia was performed using total intravenous infusion of propofol and remifentanil. Target bispectral index (BIS) values were set between 40 and 60 to indicate a suitable depth of anesthesia.

Patient characteristics

We collected information on the following patient baseline characteristics: age, sex, height, weight, American Society of Anesthesiologists Physical Status (ASA-PS) classification, preoperative serum albumin levels, surgical site, operation time, anesthesia time, estimated blood loss volume, and urine output.

Blood sampling

Blood was sampled from each patient during surgery at least 15 minutes after the target blood propofol concentration level was set by the anesthetist. Each patient was administered total intravenous anesthesia using a Diprifusor TCI system (Astra Zeneca, Osaka, Japan) programmed according to the Marsh model. Propofol TCI was input by total body weight as proposed by Servin[5]. This study's subjects were administered with remifentanil at 0.25 to 0.4 μg/kg/min by ideal body weight. Ideal body weight was defined as 45.4+0.89×(height[cm]-152.4)+4.5(if male)[6]. Propofol TCI was started by 3.0–3.5 μg/ml, and then, set to get suitable depth of anesthesia by BIS values. First sampling was gained within 20 minutes after staring propofol infusion. After sampling, we changed the target blood propofol levels within acceptable range, and second and third sampling were gained after 15minutes. If there were any changes to the target blood propofol concentration levels within 15 minutes before the scheduled blood sampling,

an additional 3.0 ml blood sample was taken 15 minutes after the most recent change. This sampling method was based on a previously described technique[7]. Each patient was allocated a maximum of three changes. The blood sampling schedule is presented in Figure 1. For each measurement, the blood sample was aliquoted into two centrifuge tubes. The blood propofol concentrations were measured in each tube using high-performance liquid chromatography (HPLC), and the mean value of the two measurements was used in analysis. Preoperative serum albumin, AST, ALT were measured on one day before the day of surgery.

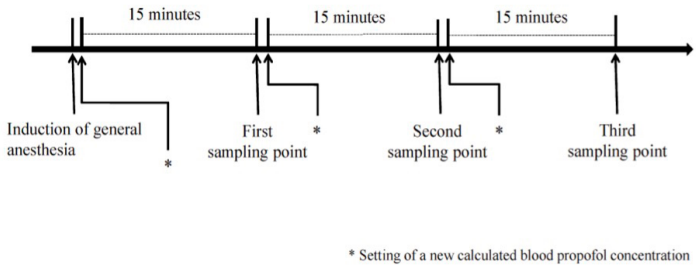

Figure 1. Time schedule for blood sampling.

Blood propofol concentration

Based on a technique described in a previous report[2], blood propofol concentration was measured using HPLC as follows: Thymol (internal standard) was added to the blood samples, which were then buffered with 1 ml potassium dihydrogen orthophosphate and extracted with 5 ml cyclohexane. Next, 0.2 M alcoholic tetramethylammonium hydroxide (50 μl) was added to an aliquot of the organic phase (4.5ml). The alkalinized cyclohexane was evaporated under a stream of nitrogen at ambient temperature. The residue was reconstituted in HPLC eluent, and an aliquot was injected into an HPLC column containing Hypersil ODS. Using fluorescence at 310 nm, propofol and thymol was detected after excitation at 276 nm. Concentrations of propofol in test samples were determined by comparing the peak height ratio of propofol to thymol in the test samples with those from a calibration series that were extracted as part of the same analytical run. The blood concentration measurements were conducted by BML, Inc. (Tokyo, Japan).

Statistical analysis

Continuous variables were calculated as means and standard deviations, whereas categorical variables were calculated as percentages. The operation/anesthesia time were calculated as median and interquartile range, and those of 3 different type of surgery (orthopedic, general, and neurosurgery) were compared by Kruskal-Wallis test. The intrinsic error of HPLC was evaluated using the standard error of a paired t-test between the two samples of each measurement. Performance error was used to evaluate the performance of the pharmacokinetic model. Using a previously proposed definition[8], performance error was determined by the following equation:

$$\text{Performance Error (\%)} = [(Cm-Ccalc)/Ccalc]\times 100$$

where Cm is the measured blood concentration and Ccalc is the calculated blood concentration[7]. The accuracy of the pharmacokinetic model was assessed using the median performance error (MDPE) and the median absolute performance error (MDAPE)[8].

The fixed and proportional errors of the measured and calculated blood propofol concentrations were evaluated using a Bland-Altman analysis[9].

In order to elucidate a possible mathematical relationship between the measured and calculated blood propofol concentrations with the state becoming a steady condition, we developed a multiple linear regression model using measured propofol concentration as the dependent variable; the independent variables included calculated propofol concentration, BMI, weight, and body surface area (BSA). The coefficients of covariates that were found to be significantly associated with measured propofol concentration would be used to create a formula to explain the relationship between the measured and calculated blood propofol concentrations.

P values lower than 0.05 were regarded as statistically significant. All analyses were performed using SPSS Version 22.0 (IBM Japan, Ltd., Tokyo, Japan).

Results

Patient characteristics are presented in Table 1. All patients had an ASA-PS classification of 3 due to a BMI of 35 or higher. The most common comorbidities were diabetes mellitus (n=7) and hypertension (n=7), followed by sleep apnea syndrome (n=2). The mean BMI of the study subjects was 39.7 kg/m^2. There were six orthopedic surgery patients, five general surgery patients, and two neurosurgery patients. The mean anesthesia and operation time was 280.8 and 187.7 minutes, respectively, and mean blood loss volume was 203.2 ml. The anesthesia time of the orthopedic, general, and neurosurgery patients were 216.0 (200.5–235.3), 231.0 (154.5–426.5), and 481.0 (414.0–481.0) minutes, respectively (P=0.13). The operation time of the orthopedic, general, and neurosurgery patients were 133.0 (113.0–144.0), 149.0 (85.0–329.5), and 336.0 (293.0–336.0) minutes, respectively (P=0.15). No blood transfusions or albumin preparations were used in the study subjects.

The mean calculated and measured blood propofol concentrations are also shown in Table 1. Six samples were taken from each patient, and the measured blood propofol

Patient Characteristics	
Age (years)	55.4±9.1
Women, No. (%)	11 (84.6)
Height (cm)	154.8±7.2
Weight (kg)	95.6±16.7
Body mass index (kg/m^2)	39.7±4.5
ASA-PS classification	
Class 3, No. (%)	13 (100)
Comorbidities	
Diabetes mellitus, No. (%)	7 (53.8)
Hypertension, No. (%)	7 (53.8)
Sleep apnea syndrome, No. (%)	2 (15.4)
Preoperative serum albumin	4.0±0.4
Preoperative AST	19.4±4.4
Preoperative ALT	18.0±5.7
Intraoperative measures	
Calculated blood propofol concentration (μg/ml) (n=39)	2.8±0.6
Measured blood propofol concentration (μg/ml) (n=39)	4.9±1.4
Operation time (min)	187.7±110.4
Anesthesia time (min)	280.8±129.9
Estimated blood loss (ml)	203.2±238.2

[a]Values are presented as mean±standard deviation for continuous variables and number (percentage) for categorical variables

Abbreviations: ASA-PS, American Society of Anesthesiologists Physical Status; AST, aspartate transaminase; ALT, alanine transaminase

Table 1. Patient characteristicsa (n=13)

concentrations were found to be consistently higher than the calculated concentrations, with the exception of one measurement. The HPLC measurements of blood propofol concentrations from duplicate samples at all 39 sampling points are presented in the Appendix. The standard error between the two samples of each measurement was 0.05 (95% confidence interval: -0.09-0.11, *P*=0.82). Figure 2 shows a scatterplot of the measured and calculated blood propofol concentrations. The MDPE was 61.9% (interquartile range: 43.1%–75.4%) and the MDAPE was 61.9% (43.7%–75.4%).

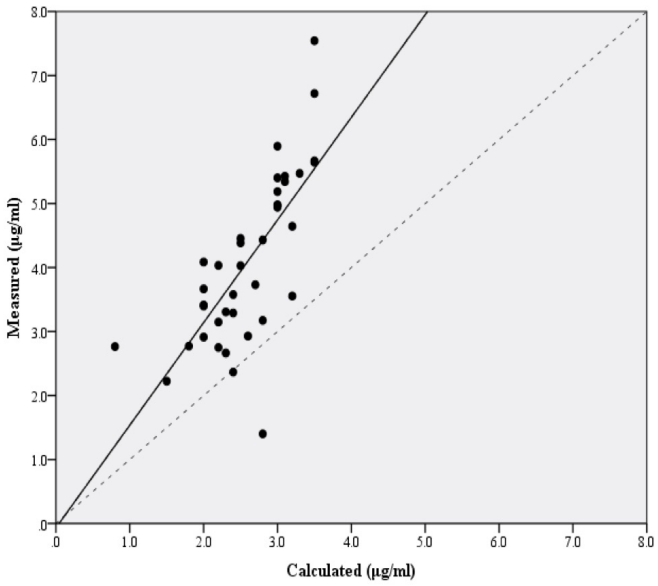

Figure 2. Scatterplot of the calculated and measured blood propofol concentrations (Solid line: primary mean values; Dashed line: y=x).

Sampling point	MDPE	MDAPE
All	61.9 (43.1-75.4)	61.9 (43.7-75.4)
Sampling point 1	70.7 (65.3-87.7)	70.7 (65.3-87.7)
Sampling point 2	61.1 (31.6-76.2)	61.1 (40.6-76.2)
Sampling point 3	48.3 (26.4-66.6)	48.3 (26.4-66.6)

[a]Values are presented as median (interquartile range)

Abbreviations: MDPE, median performance error; MDAPE, median absolute performance error.

Table 2. MDPE and MDAPE in each sampling pointa (n=13 for each measurement)

Figure 3 shows a scatterplot of TBW and the MDAPE, which indicated that increases to TBW were accompanied by small increases in the MDAPE. Table 2 summarizes the median MDPE and MDAPE values for each blood sampling point. The MDPE and MDAPE exceeded 48% even in the third sampling point. Except extremely high body weight (145 kg) patient in this study, the MDPE and MDAPE were 54.8% (39.4%–74.5%) and 57.7% (43.3%–74.5%), respectively.

In the assessment of fixed error, the result of the mean difference between the measured and calculated blood propofol concentrations was 1.50 (95% confidence intervals: 1.19–1.82; P < 0.001). In the assessment of proportional error, the results of the regression equation showed a statistically significant (*P* < 0.001) coefficient.

The Bland-Altman plot is presented in Figure 4. The mean value was estimated to be 0.42, with an upper and lower limit of agreement of 0.95 and -0.10, respectively. This indicates a difference of at least 40% between the measured and calculated blood propofol concentrations, with the former demonstrating consistently higher values.

Based on the results of the multiple linear regression analysis, we found that measured propofol concentration = 1.60 × calculated propofol concentration – 0.07; the other candidate

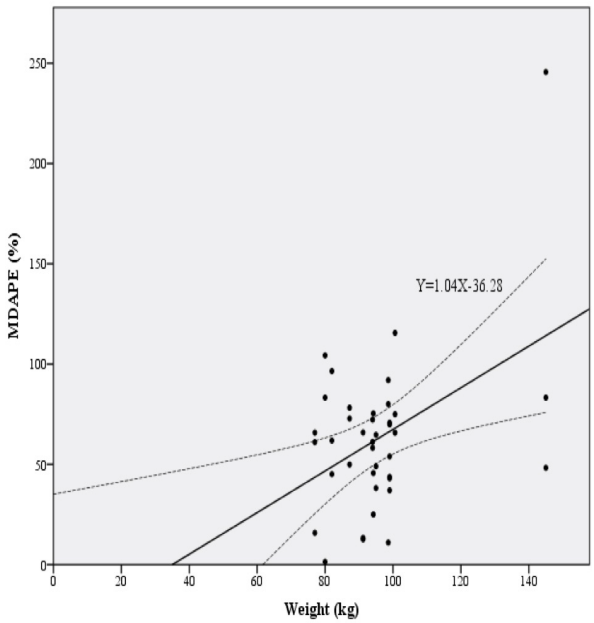

Figure 3. Bland-Altman plot with a percentage difference plot.

Variable	Coefficient	Standardized coefficient	*P* value
Calculated propofol concentration	1.60	0.73	<0.001
Weight	0.22	-	0.09
Body mass index	0.08	-	0.56
Body surface area	0.23	-	0.06
Constant	-0.07		

Table 3. Results of multiple regression analysis of measured propofol concentration (n=39).

variables (i.e., weight, BMI, and BSA) were not significantly associated with measured propofol concentration (Table 3).

None of the patients experienced any postoperative complications or adverse events.

Discussion

Our results showed that the measured blood propofol concentrations were substantially higher than the calculated blood propofol concentrations using TCI in severely obese Japanese patients. However, the error decreased as anesthesia time increased. In addition, we confirmed an extremely low level of error in the HPLC method for propofol measurements. As previous studies have not addressed the intrinsic errors in HPLC measurements of blood propofol, this aspect of our analysis provides insight into this method's accuracy.

Servin and colleagues have suggested that pharmacokinetic data of obese patients differ from those of non-obese patients in elective surgery[5]. Another previous study employed the Diprifusor system using the Marsh model, and reported that the measured blood propofol concentrations were higher than the calculated concentrations in adults (MDPE: 18.8%; MDAPE: 24.8%)[10]. Also, it has been reported that the inclusion of adjusted weight and lean body mass in the Diprifusor system resulted in measured blood concentrations that were lower than the calculated concentrations, which supports the advantage of using TBW in the TCI system[11].

The clinically acceptable ranges of MDPE and MDAPE have been reported to be <10–20% and 20–40%, respectively[12,13]. The Diprifusor system used by Swinhoe and colleagues had an MDAPE of approximately 24% and an MDPE of approximately 16%[14]. However, an examination of their reported patient characteristics indicated that few of their subjects had a BMI of 35 or higher. In the report by Cortinez and colleagues, the Marsh model had an MDPE of 36.6% and an MDAPE of 39.9%[15]. Our study focused only on patients with BMIs of 35 or higher who had undergone both bariatric and other types of surgery in a Japanese setting, and found that the MDPE and MDAPE values exceeded clinically acceptable levels. In contrast, Igarashi and colleagues reported a relatively low MDAPE of 10.7% for obese subjects[11]. The discrepancy between that study and our findings may have been influenced by differences in blood sampling protocols, as sampling in our study was conducted 15 minutes earlier than the study by Igarashi and colleagues[11].

Yufune and colleagues demonstrated that remifentanil administration at 1.0 μg/kg/min significantly increased plasma propofol concentration when compared to remifentanil administration at 0 or 0.5 μg/kg/min, but this study's subjects were administered with remifentanil at 0.25 to 0.4 μg/kg/min[16].

We attempted to develop a modified formula for linking measured and calculated propofol concentrations that incorporated patient weight, BMI, and/or BSA. However, only the calculated propofol concentration based on the Marsh model was a significant predictor of measured propofol concentration. Measured propofol concentration with the state becoming a steady condition was approximately 1.6 times the value of calculated propofol concentration.

The limitations of this study are as follows: First, the validity of collecting blood samples 15 minutes after setting the tar-

get blood propofol concentration level has yet to be verified. It may be necessary to monitor changes to blood concentration by taking more frequent samples after the initial target or changes have been set. However, this study collected blood samples after confirming the simulation provided by the TCI system when the calculated blood concentration was reached. Next, the majority of patients in this prospective study were female. However, this is unlikely to affect our findings as a previous study demonstrated that the pharmacokinetics of propofol is not associated with sex[17]. Finally, the target blood propofol concentration had a narrow range that did not exceed 3.5 μg/ml. Our study was therefore unable to obtain data of higher calculated concentrations. Despite this limitation, there were no cases of intraoperative awareness in our study sample.

Conclusions

This study demonstrated that measured blood propofol concentrations using the Marsh pharmacokinetic model were unexpectedly higher than calculated concentrations in severely obese patients who had been administered total intravenous anesthesia. In addition, we found that there was a gradual increase in the gap between measured and calculated concentrations as TBW increased, but this gap decreased with increasing anesthesia time. In morbidly obese patients, measured propofol concentration may be estimated by multiplying the calculated propofol concentration by 1.6. Further studies are needed to explore appropriate methods for calculating blood propofol concentrations during TCI-based anesthesia in obese patients.

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Ethics approval

The study was approved by the institutional ethics committee of Kansai Medical University Hospital (Approval number: H130284).

Competing interests

The authors declare that they have no competing interests.

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Appendix

Patient Number	Sample 1	Sample 2
Pt. 1 (Sampling point 1)	5.441	4.931
Pt. 1 (Sampling point 2)	1.389	1.413
Pt. 1 (Sampling point 3)	4.87	4.039
Pt. 2 (Sampling point 1)	3.712	3.083
Pt. 2 (Sampling point 2)	3.137	3.159
Pt. 2 (Sampling point 3)	3.328	3.25
Pt. 3 (Sampling point 1)	3.38	3.448
Pt. 3 (Sampling point 2)	3.274	3.338
Pt. 3 (Sampling point 3)	2.771	2.773
Pt. 4 (Sampling point 1)	5.614	5.674
Pt. 4 (Sampling point 2)	5.381	5.302
Pt. 4 (Sampling point 3)	4.429	4.432
Pt. 5 (Sampling point 1)	7.427	7.661
Pt. 5 (Sampling point 2)	5.393	5.548
Pt. 5 (Sampling point 3)	5.038	5.814
Pt. 6 (Sampling point 1)	4.876	5.074
Pt. 6 (Sampling point 2)	4.009	4.046
Pt. 6 (Sampling point 3)	2.617	2.71
Pt. 7 (Sampling point 1)	5.002	4.879
Pt. 7 (Sampling point 2)	3.732	3.73
Pt. 7 (Sampling point 3)	3.6	3.555
Pt. 8 (Sampling point 1)	4.975	4.978
Pt. 8 (Sampling point 2)	3.045	3.303
Pt. 8 (Sampling point 3)	2.714	3.144
Pt. 9 (Sampling point 1)	6.737	6.702
Pt. 9 (Sampling point 2)	5.394	5.408
Pt. 9 (Sampling point 3)	3.654	3.453
Pt. 10 (Sampling point 1)	4.718	4.049
Pt. 10 (Sampling point 2)	2.776	2.723
Pt. 10 (Sampling point 3)	2.764	3.062
Pt. 11 (Sampling point 1)	3.692	3.639
Pt. 11 (Sampling point 2)	2.707	2.822
Pt. 11 (Sampling point 3)	2.183	2.265
Pt. 12 (Sampling point 1)	2.386	2.346
Pt. 12 (Sampling point 2)	4.112	3.954
Pt. 12 (Sampling point 3)	3.834	4.337
Pt. 13 (Sampling point 1)	5.823	5.969
Pt. 13 (Sampling point 2)	5.96	5.372
Pt. 13 (Sampling point 3)	4.614	4.674

Table A1. Propofol concentration (μg/ml) measured using high-performance liquid chromatography for each patient.