Morbid Obesity Alters Both Pharmacokinetics and Pharmacodynamics of Propofol: Dosing Recommendation for Anesthesia Induction

Received May 16, 2016; accepted July 29, 2016

ABSTRACT

The prevalence of obesity has markedly increased worldwide. Obese patients pose significant challenges to anesthesiologists with regard to accurate dosing of anesthetics due to potentially altered pharmacokinetics (PK). Here we determined the PK and pharmacodynamics (PD) of propofol for anesthesia induction in morbidly obese (MO) subjects (body mass index > 35 kg/m²) at two dosing regimens: dosing based on total body weight and lean body weight (LBW), respectively. The propofol pharmacokinetic profile was well fitted with a two-compartment model. Both elimination clearance (223%–180% of controls; P < 0.01) and peripheral compartment volume (156%–180% of controls; P < 0.01) were significantly increased in MO subjects, resulting in an equal or decreased propofol level in plasma (total body weight–based dosing).

Furthermore, propofol PD (measured by the bispectral index) was adequately described by a PK/PD model that linked an effect compartment to the two-compartment PK model through a sigmoidal E_max model. All PD parameters except EC_{50} values (the half maximal effect concentration) were similar (P > 0.05) between MO subjects and controls. Morbid obesity led to a significant decrease (37.9%–38.6%; P < 0.01) in EC_{50} values, which suggests increased brain sensitivity to propofol in the MO population. Moreover, dose reduction (i.e., dosing based on LBW) generated identical anesthetic effects in MO subjects compared with controls. In conclusion, morbid obesity significantly altered both PK and PD of propofol. LBW was a better weight-based dosing scalar for anesthesia induction with propofol in MO subjects.

Introduction

Propofol is a commonly used drug for the induction and maintenance of general anesthesia. Basic pharmacokinetic properties of propofol in humans are well documented (Campbell et al., 1988; Morgan et al., 1990). In line with its highly lipophilic feature, propofol has a very large volume of distribution (Shafer, 1993). Although propofol undergoes extensive metabolism (mainly glucuronidation and oxidation) in the liver, it has a very long apparent elimination half-life (Campbell et al., 1988; Favetta et al., 2002). The relatively long elimination is accounted for by the multicompartment pharmacokinetics (PK) of the drug, wherein the elimination process is primarily governed by intercompartment distribution (Morgan et al., 1990). Propofol PK is generally described by a two-compartment (Peeters et al., 2008a; Bientert et al., 2010; Wiczling et al., 2012) or three-compartment (Schnider et al., 1998; van Kralingen et al., 2011) model. Selection of the best model seems to depend on the duration of blood collection, sampling frequency, and manner of administration (e.g., bolus or infusion) (Wiczling et al., 2012).

Propofol PK and pharmacodynamics (PD) are subjected to high interindividual variability. Factors contributing to this variability include age, body weight, and disease state (Peeters et al., 2008a; van Kralingen et al., 2011; Diepstraten et al., 2012). Of note, obesity is shown to significantly affect propofol PK (van Kralingen et al., 2011). Individuals with body mass index (BMI) values > 30 kg/m² are defined as obese, whereas those with BMI values > 35 kg/m² are defined as morbidly obese (MO). Ogden et al. (2014) previously reported a 34.9% prevalence of adult obesity in the United States. Therefore, it remains a major task to determine the dosing regimen for propofol use in obese patients. Mistakes are often made in drug administration using the same recommended dose as that for individuals with normal body weight (de Baerdemaeker and Margarson, 2016).

It has been reported that morbid obesity significantly influences propofol PK, possibly resulting in altered drug responses (Ingrande et al., 2011; van Kralingen et al., 2011). However, there is still no consensus on the correct dosing regimen of propofol for MO patients (Friesen, 2016). This study aimed to evaluate the PK/PD of propofol dosed based on total body weight (TBW) and lean body weight (LBW), respectively, in MO subjects and to explore the correct dosing regimen of propofol in this population. A clinical trial was performed to determine and compare propofol PK/PD in MO subjects versus controls. Concentrations of propofol in plasma were quantified by high-performance liquid chromatography (HPLC) analyses. Bispectral index (BIS) values were collected to define the PD effects, and population PK/PD modeling was performed.

Materials and Methods

Materials. Propofol (reference standard) was obtained from Sigma-Aldrich (St. Louis, MO).

This research was supported by the Fundamental Research Funds for the Central Universities [Grant 21615463] and the Natural Science Foundation of Guangdong Province PhD Start-Up Fund [Grant 2015A030310339]. D.D. and X.P. contributed equally to this work dx.doi.org/10.1124/dmd.116.071605.

This article has supplemental material available at dmd.aspetjournals.org.
Study Design. The Ethics Committee of the First Affiliated Hospital of Jinan University approved this clinical trial of propofol and the study was conducted at the First Affiliated Hospital of Jinan University (Guangzhou, China). A total of 29 patients were enrolled in this clinical trial (see Supplemental Fig. 1 for the approval form). All 29 patients were American Society of Anesthesiologists physical status I or II and were scheduled for a gastrointestinal operation under general anesthesia (Supplemental Table 1). Of these subjects, 23 were MO and 6 were LBW. Six patients in the control group (BMI = 25 kg/m²) received a bolus injection of propofol (2 mg/kg) for anesthesia induction based on either TBW (n = 12) or LBW (n = 11). All MO subjects underwent laparoscopic gastric bypass surgery. Six patients in the control group (BMI = 25 kg/m²) received a bolus injection of propofol (2 mg/kg) based on TBW. All controls underwent laparoscopically assisted gastrectomy due to stomach cancer or gastric bleeding.

Anesthesia. A catheter was introduced into the cephalic vein for drug administration. All patients breathed oxygen for 3 minutes via a facemask (to maintain SpO₂ of >95%) prior to anesthesia administration. Anesthesia was induced via intravenous administration of 0.5 mg/kg midazolam, 2 μg/kg fentanyl, 0.6 mg/kg rocuronium, and 2 mg/kg propofol (Diprivan; Corden Pharma, Caponago, Italy). All patients received midazolam, fentanyl, and rocuronium at the doses based on LBW (Jannahsaa et al., 2005). MO patients were randomized to receive propofol based on TBW (n = 12) or LBW (n = 11), whereas all control patients received propofol based on TBW (n = 6). Anesthesia was maintained by continuous infusion of propofol (4 mg/kg per hour), tracrium (8 μg/kg per minute), and remifentanil (0.2 μg/kg per minute) on LBW.

BIS Monitoring. The depth of anesthesia was determined with a BIS Vista monitor (Aspect Medical Systems, Newton, MA). BIS, an electroencephalographic measure of anesthetic depth, was selected as the PD endpoint quantifying the effects of propofol on the central nervous system (CNS). BIS values were obtained before anesthesia (time 0) and at 1, 2, 4, 6, 8, 10, 15, and 20 minutes after anesthesia (propofol administration).

Blood Sampling. Approximately 3 ml of blood samples were collected via radial artery catheterization before (time 0) and at 1, 2, 4, 6, 8, 10, 15, and 20 minutes after propofol administration. The samples were subsequently transferred to heparin-pretreated Eppendorf tubes. This was followed by centrifugation at 9000g at 4°C for 3 minutes. The supernatant was collected and the samples were stored at −80°C until analysis.

Quantification of Plasma Propofol by HPLC. Plasma propofol was quantified using a Dionex U3000 HPLC system (Dionex, Sunnyvale, CA) equipped with an Acclaim 120 C18 column (4.6 × 250 mm, 5 μm; Thermo Fisher Scientific, Waltham, MA). A gradient elution was performed using water (A) and acetonitrile (B). The gradient program consisted of 30% to 80% B at 0–6 minutes, 80% B at 6–9 minutes, and 80% B at 9–12 minutes. The detection wavelength was 220 nm and the flow rate was set at 1 ml/min. The quantitation method was validated with regard to the linearity (0.12–8.0 μg/ml), intraday/interday precision (relative standard deviation <15%), and recovery (within 90%–110%) (Supplemental Fig. 2).

PK Modeling. A nonlinear mixed-effect modeling approach was used to analyze the pharmacokinetic data of propofol. A population analysis was performed using MONOLIX software (version 2016R1; LIXOFT, Paris, France). The stochastic approximation expectation-maximization algorithm coupled with the Markov chain Monte Carlo procedure for likelihood maximization was used to estimate the population parameters (Chan et al., 2011). Interindividual variability in mixed-effect model parameters was described using the following exponential model:

$$P_{\text{ind}} = P_{\text{pop}} \exp(\eta) \sim N(0, \omega)$$

where $P_{\text{ind}}$ represents the individual parameter, $P_{\text{pop}}$ is the fixed effect (population mean), and $\eta$ denotes the random effect (normally distributed) accounting for the individual deviations from the population mean.

Conventional two-compartment and three-compartment models (mass balance equations are provided in the Supplemental Material) were used to fit the pharmacokinetic data (Fig. 1A). The goodness of fit was evaluated by the Akaike information criterion, Bayesian information criterion, and diagnostic plots such as visual predictive checks.

PK/PD Modeling. A PK/PD model was built by linking an effect (biophase) compartment to the two-compartment pharmacokinetic model (Fig. 1B). The rate constant $k_{e0}$ describes the drug distribution to the effect compartment from the central compartment, accounting for the delay in the PD (anesthetic) effect. The anesthetic effect (BIS) was linked to the drug concentrations in the effect compartment through a sigmoidal $E_{\text{max}}$ model as follows:

$$\text{BIS}(t) = \text{BIS}_0 \left(1 - \frac{E_{\text{max}} C_t}{EC_{50} + C_t}\right)$$

where $\text{BIS}_0$ is the baseline BIS score, $E_{\text{max}}$ is the maximal effect (fixed at 1), and $EC_{50}$ is the drug concentration associated with 50% of the maximal effect (or half maximal effect concentration). The slope factor ($\gamma$) is a PD parameter relating to the steepness of the response curve. $C_t$ denotes the effect compartment concentration. The change in $C_t$ was defined by the following equation:

$$\frac{dC_t}{dt} = k_{e0} C_e - k_{g} C_t$$

A nonlinear mixed-effect modeling approach was used to analyze the PK/PD data. The population analysis was performed using MONOLIX software (version 2016R1). Interindividual variability for the PK/PD parameters was modeled assuming log-normal distribution as follows:

$$P_{\text{ind}} = P_{\text{pop}} \exp(\eta) \sim N(0, \omega)$$

where $P_{\text{ind}}$ represents the individual parameter, $P_{\text{pop}}$ is the fixed effect (population mean), and $\eta$ denotes the random effect (normally distributed) accounting for the individual deviations from the population mean.

A sequential approach was applied in PK/PD modeling (Zhang et al., 2003). In the sequential approach, a PK model was first developed and the parameter estimates were derived. In the second step, the individual estimates of PK parameters derived from the PK analysis were used to drive the PD modeling.

Statistical Analysis. Data are presented as means ± S.D. Statistically significant differences were analyzed by one-way analysis of variance or t tests (significance levels were set at P < 0.05, P < 0.01, and P < 0.001).

Results and Discussion

Altered Propofol PK in MO Patients. The plasma levels of propofol at later time points (≥6 minutes) were significantly lower (P < 0.05) in MO-TBW subjects than in controls (Fig. 1C). This suggested that the PK of propofol was significantly altered in MO subjects. We also compared plasma levels versus time profiles for controls and MO-LBW subjects (Fig. 1C). It was not surprising that plasma levels of propofol (≥2 minutes) were markedly lower (P < 0.001) in MO-LBW subjects than in controls (Fig. 1C).

The conventional two-compartment model was more appropriate for describing the PK data on the basis of the Akaike information criterion and Bayesian information criterion values (Supplemental Table 2). The predicted concentrations based on individual parameters were close to the observed concentrations (Supplemental Fig. 3), which suggests adequate model fitting. Clearance was significantly higher (9.15 versus 4.11 liters/min; P < 0.01) in MO-TBW subjects than in controls (Fig. 1D; Table 1). Furthermore, morbid obesity led to a significant increase (73.2–84.2 liters versus 46.9 liters; P < 0.01) in the volume of the peripheral compartment (V₂). It was interesting to note that TBW-normalized clearance and V₂ values were not changed (P > 0.05) in MO subjects (Fig. 1E). Consistently, clearance and V₂ were positively correlated with body weight according to the covariate models generated using data on both obese and nonobese subjects (Fig. 1D; Supplemental Table 3). Taken together, the results suggested that morbid obesity altered propofol PK by increasing systemic clearance and peripheral compartment volume, resulting in an equal or decreased propofol level in plasma.

Our finding that morbid obesity increased the elimination clearance of propofol and the peripheral volume of distribution was consistent with previous studies in which the authors showed that total body clearance and the volume of distribution at steady state were positively correlated to body weight (Servin et al., 1993; Cortínez et al., 2010). An increase in the volume of distribution most likely results from the increased fat and lean masses of obese individuals (Casati and Putzu, 2005). Propofol
clearance is blood flow dependent (Peeters et al., 2008b). Obesity is usually associated with a higher cardiac output owing to increased stroke volume and heart rate (Alexander, 1993; Adams and Murphy, 2000). An increase in cardiac output can result in enhanced drug elimination, which helps to explain why MO subjects in our study had increased body clearance of propofol.

**Altered Propofol PD in MO Patients.** BIS values were significantly lower ($P < 0.05$) at and after 2 minutes in MO-TBW subjects than in controls (Fig. 2A). This indicated that the anesthetic effects were greatly enhanced in MO subjects when propofol was dosed using the weight scalar of TBW (i.e., the regular dosing regimen). Interestingly, dose reduction (i.e., dosing based on LBW) generated identical anesthetic effects in MO subjects compared with controls (Fig. 2A).

TBW-based dosing of propofol produced an aggravated anesthetic effect (i.e., an overdose effect) in MO subjects (Fig. 2A). In particular, BIS values at 2–6 minutes were below 40 (Fig. 2A). BIS values ranging from 40 to 60 indicate a proper level for general anesthesia (Kissin, 2000), whereas a BIS value below a threshold of 40 is an indicator of burst suppression and of deep anesthesia that may be harmful to the patient (i.e., deleterious hemodynamic and cardiovascular effects may result) (Drexler and Grasshoff, 2012). Chidambaran et al. (2013) previously suggested that propofol may be overdosed in clinical practices in which TBW is usually used as the dosing scalar. Therefore, dose reduction seemed to be necessary for anesthesia induction in MO subjects. It was noteworthy that propofol maintenance infusion can be based on TBW in obese patients, as it was necessary for anesthesia induction in MO subjects. It was noteworthy that propofol maintenance infusion can be based on TBW in obese patients, as it was necessary for anesthesia induction in MO subjects.
value was inversely related to TBW (Fig. 2C). The results suggested that MO subjects showed enhanced brain sensitivity to propofol. MO subjects dosed based on LBW had a similar pharmacodynamic profile (i.e., BIS versus time curve) compared with controls (TBW-based dosing) (Fig. 2A). This clearly indicated that LBW was the best scalar for anesthesia induction with propofol in MO subjects. Therefore, our study and a study by Ingrande et al. (2011) consistently indicated that propofol should be given to MO subjects using LBW as the scalar for anesthesia induction. More important, our study for the first time provides explanations as to why LBW-based dosing of propofol (i.e., a dose reduction strategy) is more appropriate for MO subjects (see the following discussion).

Our finding that morbid obesity significantly decreased the EC50 value is novel (Fig. 2C) and indicates that MO subjects in our study had greater CNS sensitivity to propofol. A decreased EC50 value for propofol was also previously noted in patients undergoing abdominal aortic surgery (Wiczling et al., 2012). However, the exact reasons why MO subjects were more sensitive to the anesthetic effects remain unknown. Nevertheless, it was speculated that the increased sensitivity to propofol was associated with changes in cardiovascular and respiratory function (Casati and Putzu, 2005; Ingrande and Lemmens, 2010).

The increased CNS sensitivity (i.e., a decreased EC50 value) to propofol was probably responsible for the aggravated anesthetic effects (Fig. 2A). This was because equal or lower propofol concentrations were observed in MO patients (TBW-based dosing of propofol) due to enhanced elimination clearance and increased volume of distribution. Lower systemic exposure to the drug would translate to a diminished drug response. However, the pharmacokinetic change did not predict the alterations in PD. This was because the pharmacodynamic property was also altered by morbid obesity (namely, the drug potency was enhanced). Therefore, our study provides a mechanistic PK/PD explanation as to why dose reduction was required in MO subjects. In addition, our study and a study by Wiczling et al. (2012) highlight that determining the pharmacodynamic parameters is essential to fully assess the effects of diseases on clinical responses of propofol.

In summary, the PK and PD of propofol were characterized in MO subjects. Both elimination clearance and V2 were significantly increased in MO subjects, resulting in an equal or decreased plasma propofol level. Furthermore, the PD parameter EC50 was significantly decreased in MO subjects, which suggests enhanced brain sensitivity to propofol in this population. Moreover, LBW was a better weight-based dosing scalar for anesthesia induction with propofol in MO subjects.

**Authorship Contributions**

Participated in research design: Dong, Peng, Liu, Wu.
Conducted experiments: Dong, Qian, Li.
Contributed new reagents or analytic tools: Peng, Liu.
Performed data analysis: Dong, Peng, Qian, Li Wu.
Wrote or contributed to the writing of the manuscript: Dong, Peng, Wu.