Population pharmacokinetics and pharmacodynamics of propofol in morbidly obese patients

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Simone van Kralingen*, Jeroen Diepstraten*, Mariska Y.M. Peeters,
Vera H.M. Deneer, Bert van Ramshorst, René J. Wiezer,
Eric P.A. van Dongen, Meindert Danhof, Catherijne A.J. Knibbe
both authors contributed equally

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Abstract

Background and objectives
In view of the increasing prevalence of morbidly obese patients, the influence of excessive total body weight (TBW) on the pharmacokinetics and pharmacodynamics of propofol was characterized in this study using bispectral index (BIS) values as pharmacodynamic endpoint.
Methods
A population pharmacokinetic and pharmacodynamic model was developed with the nonlinear mixed-effects modelling software NONMEM VI, on the basis of 491 blood samples from 20 morbidly obese patients (TBW range: 98 - 167 kg) and 725 blood samples of 44 lean patients (TBW range: 55 - 98 kg) from previously published studies. In addition, 2246 BIS values from the 20 morbidly obese patients were available for pharmacodynamic analysis.
Results
In a three-compartment pharmacokinetic model, TBW proved to be the most predictive covariate for clearance (CL) in 20 morbidly obese patients ($CL = 2.33\ L/min * (TBW/70)^{0.72}$). Similar results were obtained when the morbidly obese patients and 44 lean patients were analysed together ($CL = 2.22\ L/min * (TBW/70)^{0.67}$). No covariates were identified for other pharmacokinetic parameters. The depth of anaesthesia in morbidly obese patients was adequately described by a two-compartment biophase-distribution model with a sigmoid maximum possible effect (E_{max}) pharmacodynamic model (concentration at half-maximum effect (EC_{50}) 2.12 mg/L) without covariates.
Conclusion
We developed a pharmacokinetic and pharmacodynamic model of propofol in morbidly obese patients, in which TBW proved to be the major determinant for clearance, using an allometric function with an exponent of 0.72. For the other pharmacokinetic and pharmacodynamic parameters, no covariates could be identified.

Background

In Western countries, the prevalence of obesity is increasing, resulting in percentages of 20% in men and 25% in women in the US, respectively (1). The prevalence of morbidly obese patients is also rising (2-3). However, there have been a few studies on the influence of (morbid) obesity on the pharmacokinetics and pharmacodynamics of commonly used drugs (4-5). Therefore, systematic pharmacokinetic and pharmacodynamic studies in this special group of patients are urgently needed.

Propofol is widely used for induction and maintenance of anaesthesia in both lean and (morbidly) obese patients. There have been few reports focusing on the influence of excessive total TBW (TBW) on the pharmacokinetics of propofol. Servin et al. (6) originally used an adjusted TBW to dose propofol in morbidly obese patients, and upon pharmacokinetic analysis they observed a linear relationship between TBW and clearance. Schuttler and Ihmsen (7) found that propofol clearance depend on TBW, using an allometric equation with an exponent of 0.71; however, no morbidly obese patients were included in their study. Another study used simulations to propose lean body weight (LBW) as weight input for propofol dosing (8). More recently, it was reported that TBW was the size descriptor for all clearances and volume values of propofol in obese patients (9). While these conflicting reports on the pharmacokinetics of propofol may be a result of an unbalanced range in body weight and/or inclusion of only a limited number of morbidly obese patients in the analyses, there are still no reports available on the pharmacodynamics of propofol in morbidly obese patients.

Therefore, the aim of this study was to evaluate the pharmacokinetics and pharmacodynamics of propofol in morbidly obese patients, using the Bispectral index (BIS) as a pharmacodynamic endpoint. For both the pharmacokinetics and pharmacodynamics, a systematic covariate analysis was performed using TBW, body mass index (BMI), ideal body weight (IBW) and LBW as weight covariates. For the pharmacokinetic analysis, data of 44 lean patients were available from previously published studies (10-11).

Methods

Patients

Twenty morbidly obese patients who were scheduled to undergo laparoscopic gastric banding or gastric bypass surgery were enrolled in a prospective study (ClinicalTrials.gov identifier NCT00395681). Patients were included if they were aged between 18 and 60 years, had an American Society of Anesthesiologists (ASA) physical status classification of II or III, had a BMI of over 40 kg/m^2 at inclusion, and normal renal and hepatic function as assessed by routine laboratory testing. All patients undergoing bariatric surgery were asked to lose weight preoperatively, as this has shown to improve the outcome. Therefore, patients were not excluded from the study as long as their BMI was higher than 35 kg/m^2 on the day of surgery and on the day of study. The exclusion criteria included pregnancy, breastfeeding, epilepsy and known allergy for propofol, soy bean oil or egg lecithin. The study protocol was approved by the hospitals ethics committee, and written informed consent was obtained from by each participating patient.

Forty-four lean patients had been enrolled earlier as part of two other studies; detailed information can be found in the references (10-11). Four patients from one of these studies (10) were excluded from the covariate analysis of the combined dataset of morbidly obese and lean patients, because there was no information available on the height of those patients.

Anaesthetic Procedure

All morbidly obese patients received standardized anaesthesia without premedication. Before induction, an antecubital infusion line, an indwelling arterial blood pressure line and leads for a three-lead ECG were installed, and a BIS electrode was placed on the patient's forehead. Patients were randomized to receive a bolus injection of propofol 200 mg or 350 mg over 60 seconds using total intravenous anaesthesia (TIVA) pump (Asena target-controlled infusion (TCI) and TIVA; Alaris Medical Systems) for induction of anaesthesia, together with 1% lidocaine 2 ml to avoid pain during injection (12). Thereafter, upon administration of fentanyl 250 µg and atracurium besilate 50 mg, the trachea was intubated and mechanical ventilation was initiated by the anaesthesiologist. Anaesthesia was maintained with a continuous infusion of 2% propofol at an initial infusion rate of 10 mg/h/kg TBW, which was started between 2 and 7 minutes after the propofol induction dose. Remifentanil was administrated 25 µg/h/kg IBW (13) and atracurium besilate at 0.3 mg/h/kg TBW, according to local practice. The propofol infusion rate was subsequently adjusted in order to keep BIS values between 40 and 60, the systolic arterial blood pressure between 80 and 160 mmHg, and the heart rate between 60 and 90 beats per minute. Propofol infusion rate adjustments of 50 – 150 mg/h could be made at the discretion of the anaesthesiologist, with no more than one infusion rate adjustment per 5 minutes. The remifentanil infusion rate was kept constant throughout the procedure, in order to rule out any influence of changes in remifentanil concentrations on BIS values or haemodynamic parameters.

In the previously published lean patient group, 24 female patients received a bolus injection of propofol 2.5 mg/kg for induction of anaesthesia, and anaesthesia was maintained with isoflurane (10). Another 20 lean intensive care patients received continuous propofol infusions for 2-5 days, with propofol doses based on the Ramsay six-point scale (11). In both previously published studies, no BIS values were available.

Blood sampling and analytical methods

In morbidly obese patients, arterial blood samples (2 mL) were collected at the following timepoints: at baseline prior to the start of the propofol bolus, approximately 1.5, 2.5 and 4 minutes after the propofol bolus; 3, 7, 15, 25 and 45 minutes after the start of the propofol infusion; just before and at 5 or 15 minutes after dose adjustment; just before discontinuation of the propofol infusion; and at 1, 3, 5, 7, 10, 20, 30, 60, 90, 120 and 150 minutes after the end of the infusion.

In one of previously published lean patients (10), arterial blood samples were collected at 1, 1.5, 2, 2.5, 3, 4, 5, 8, 11, 15, 20, 30, 45, 60, 90, 120, 150 and 180 minutes after the induction dose of propofol. In the other previously published study of lean patients (11), arterial blood samples were collected four times daily during propofol maintenance infusion for 2-5 days.

Whole-blood samples for propofol analysis were mixed thoroughly and stored at 4°C until analysis by high-performance liquid chromatography with fluorescence detection at 276 nm and 310 nm. With this method, the coefficients of variation for the intra-assay and inter-assay precision were less than 3.7% and 9.8%, respectively, over the concentration range from 0.05 to 5.0 mg/L, and the lower limit of quantification was 0.05 mg/L (14).

Data analysis and internal validation

The analysis was performed by means of non-linear mixed-effects modelling using NONMEM (version VI, release 1.1; GloboMax LLC, Hanover, MD, USA) (15) with S-plus (version 6.2; Insightful software, Seattle, WA, USA) to visualize the data. Population pharmacokinetic and pharmacodynamic data were sequentially analysed by using the individual pharmacokinetic empirical Bayes estimates as input to the pharmacodynamic model. Discrimination between different models was made by comparison of the objective function value (OFV, i.e. -2 log likelihood (-2LL)). A p-value of < 0.005, representing a decrease of 7.9 in the OFV, was considered statistically significant. In addition, goodness-of-fit plots (observed versus individual-predicted concentration-time, observed versus population-predicted concentration-time, conditional weighted residuals versus time and conditional weighted residuals versus population-predicted concentration-time plots) were used for diagnostic purposes. Furthermore, the confidence interval of the parameter estimates, the correlation matrix and visual improvement of the individual plots were used to evaluate the model. The internal validity of the population pharmacokinetic and pharmacodynamic models was assessed by the bootstrap re-sampling method using 250 replicates (15). Parameters obtained with the bootstrap replicates were compared with the estimates obtained from the original data set.

Pharmacokinetic model

Log-transformed propofol concentration data were described by a three-compartment model (NONMEM VI, ADVAN11, TRANS4) parameterized in terms of the volume of distribution of the central compartment (V1), volume of distribution of the first peripheral compartment (V2) volume of distribution of the second peripheral compartment (V3), inter-compartmental clearance from the central compartment to the first peripheral compartment (Q2) inter-compartmental clearance from the central compartment to the second peripheral compartment (Q3), and clearance from the central compartment (CL) (Figure 1).

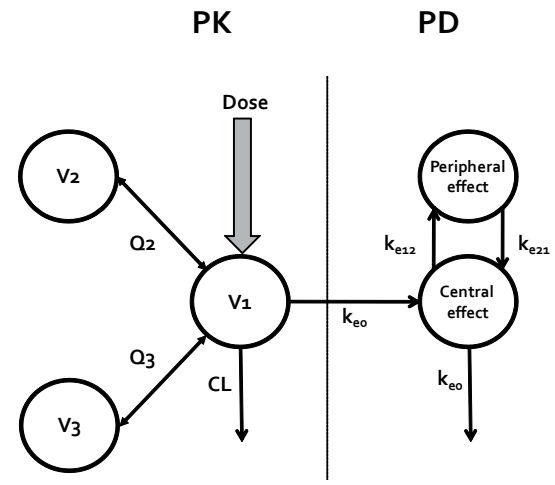


Figure 1 *Schematic representation of the pharmacokinetic and pharmacodynamic model for propofol, based on a three-compartment pharmacokinetic model parameterized using V1, V2, V3, CL, Q2 and Q3 and a two-compartment biophase-distribution model characterizing the pharmacodynamics using k_{e0}, k_{e12} and k_{e21}. The propofol concentration in the central effect-site compartment is responsible for the measured BIS values, as described using equation 4. BIS = bispectral index; CL = clearance from the central compartment; k_{e0} = first-order equilibrium constant linking the central pharmacokinetic compartment to the central effect-site compartment which equalsthe rate constant for drug loss from the central effect-site compartment; k_{e12} = rate constant from the central effect-site compartment to the peripheral effect-site compartment; k_{e21} = rate constant from the peripheral effect-site compartment to the central effect-site compartment; Q2 = inter-compartmental clearance from the central compartment to the first peripheral compartment; Q3 = inter-compartmental clearance from the central compartment to the second peripheral compartment; V1 = volume of distribution of the central compartment; V2 = volume of distribution of the first peripheral compartment; V3 = volume of distribution of the second peripheral compartment.*

The inter-individual value (post hoc value) of the parameters of the i^{th} individual was modelled by (equation 1):

$$\Theta_i = \Theta_{mean} * e^{\eta_i} \quad \text{(Eq. 1)}$$

where θ_{mean} is the population mean and η_i is a random variable with a mean of zero and variance of ω^2, assuming log-normal distribution in the population. The intraindividual variability, resulting from assay errors, model misspecifications and other unexplained sources, was best described with a proportional error model. This means for the j^{th} observed log-transformed propofol concentration of the ith individual, the relation (Y_{ij}) is described by equation 2:

$$Y_{ij} = \log C_{pred,ij} + \varepsilon_{ij} \quad \text{(Eq. 2)}$$

where C_{pred} is the predicted propofol concentration and ε_{ij} is a random variable with a mean of zero and variance of σ^2.

Biophase-Distribution and pharmacodynamic model

Concerning the biophase distribution, the delay in BIS values in relation to the propofol concentration in the central pharmacokinetic compartment was characterized on the basis of a hypothetical 'effect-site' compartment, which is an approach that has been applied previously for propofol-induced BIS values (16). In this approach, it is assumed that the rate of onset and offset of the observed effect is governed by the rate of propofol distribution to and from a hypothetical effect-site compartment. Under this interpretation, the effect-site compartment is linked to the blood compartment by a first-order equilibrium rate constant (k_{eo}), which equals a rate constant for drug loss (k_{eo}) from the effect-site compartment. Under the assumption that in equilibrium, the effect-site concentration equals the blood concentration, equation 3 can be used:

$$\frac{dC_e}{dt} = k_{e0} \cdot (C_b - C_e) \quad \text{(Eq. 3)}$$

where C_b is the blood concentration in the central pharmacokinetic compartment, C_e represents the effect-site concentration and k_{eo} is the first-order equilibration constant.

In addition to this previously applied one-compartment effect-site model, a two-compartment biophase-distribution model was also explored, in which distribution of propofol within the brain was represented by definition of a central effect-site compartment and a peripheral effect-site compartment. In this two-compartment biophase-distribution model, the rate constants from the central effect site to the peripheral effect site and from the peripheral effect site to the central effect site were k_{e12} and k_{e21}, respectively. This two-compartment effect-site model was parameterized in amounts, with the volume of the effect-site compartments set at 1. The full pharmacokinetic-pharmacodynamic model is depicted in Figure 1.

For the pharmacodynamic model, the values of the BIS were related to the propofol concentrations in the central effect-site compartment on the basis of the sigmoidal maximum possible effect (E_{max}) model (equation 4):

$$E = E_0 - \frac{E_{\max,i} \cdot C_{e,ij}^{\gamma}}{EC_{50,i}^{\gamma} + C_{e,ij}^{\gamma}} \quad \text{(Eq. 4)}$$

where E_o is the baseline BIS, $E_{max,i}$ is the E_{max} of propofol on the BIS in the ith individual, $C_{e,ij}$ is the individual-predicted propofol concentration in the central effect-site compartment in the i^{th} individual at the j^{th} timepoint, γ is the Hill coefficient representing the steepness of the concentration-response relation, and $EC_{50,i}$ is the propofol concentration (in mg/L) at half-maximum effect of the BIS in the i^{th} individual.

The interindividual variability (η_i) in the E_{max}, EC_{50} and k_{eo} was assumed to be log-normally distributed with a mean of zero and variance of ω^2 (equation 1). The residual error ε was best characterized by a proportional error model (equation 5):

$$Y_{ij} = E_{pred,ij} \cdot (1 + \varepsilon_{ij}) \quad \text{(Eq. 5)}$$

where Y_{ij} represents the observed Bispectral index in the i^{th} subject at the j^{th} time point.

Covariate analysis

Covariates were plotted independently against the individual post hoc parameter estimates of all pharmacokinetic and pharmacodynamic parameters and the conditioned weighted residuals to visualize potential relations. The following covariates were tested: TBW, BMI , IBW (17) and LBW (18), induction dose (200 versus 350 mg), sex, age, positive end-expiratory pressure, bilirubin level and renal function (serum creatinine levels). Covariates were tested using linear and allometric equations:

$$P_i = P_p \cdot \left(\frac{Cov}{Cov_{standard}}\right)^{z} \quad \text{(Eq. 6)}$$

where P_i and P_p represent individual and population parameter estimates, respectively; Cov represents the covariate; $Cov_{standard}$ represents a

Table I *Baseline characteristics of 20 morbidly obese patients and 44 lean patients (10-11).*

Parameter	Morbidly obese patients (mean (SD))	Lean patients (mean (SD))
Patients (n)	20	44
Sex (M / F)	4/16	16/28
Age (y)	45 (12)	52 (12)
TBW (kg)	124 (20)	74 (11)
IBW (kg)	61 (7)	63 (8)[a]
BMI (kg/m^2)	43 (6)	25 (4)[a]
LBW (kg)	60 (9)	45 (10)[a]

a = value for the 40 patients in whom height data were available.
BMI = body mass index; F = female; IBW = ideal body weight (17); LBW = lean body weight (18); M = male; SD = standard deviation; TBW = total body weight.

standardized (i.e. 70 kg for TBW) or median value of the covariate for the population; and z represents the exponential scaling factor, which was fixed at 1 for a linear function or an estimated value for an allometric equation. Potential covariates were separately entered into the model and statistically tested by use of the OFV and, if applicable, the 95% confidence interval of the additional parameter. When more than one significant covariate for the simple model was found, the covariate-adjusted model with the largest decrease in OFV was chosen as a basis to sequentially explore the influence of additional covariates with the use of the same criteria. Finally, after forward inclusion, a backward exclusion procedure was applied to justify the covariate. The choice of the covariate model was further evaluated as discussed above.

Simulations

On the basis of the final pharmacokinetic and pharmacodynamic model, simulations were performed to keep BIS values between 40 and 60 in morbidly obese patients ranging in TBW between 98 and 167 kg. In addition, BIS values were simulated using a linear dosing regimen (5 mg/kg/h) for these patients (19).

Results

Twenty morbidly obese patients were enrolled and 491 blood samples were available. From 44 lean patients, 725 blood samples were available (10-11). The morbidly obese patients had a mean TBW of 124 kg (range 98–167 kg) compared with 74 kg (range 55–98 kg) in the lean patients. All demographic characteristics of the morbidly obese patients and lean patients are provided in Table I.

Pharmacokinetics

A three-compartment pharmacokinetic model adequately described the time course of the propofol whole-blood concentrations in the morbidly obese patients. Exploratory plots of all tested covariates (see Methods, Covariate Analysis section) against individual post hoc parameter estimates of the simple model showed potential relations between the four weight-related covariates (TBW, LBW, IBW and BMI) and clearance. There were no relations between the explored covariates and other pharmacokinetic parameters. Subsequently, all four weight covariates were incorporated on clearance in the model and tested for significance (Table II). The analysis

Table II *Results of covariate analysis for the pharmacokinetic model of propofol in the dataset of morbidly obese patients and in the combined dataset of morbidly obese and lean patients.*

Model	Relationship of covariate with CL	No. of structural parameters	OFV	
			Morbidly obese	Morbidly obese and lean patients[a]
Simple	-	6	-643	-1557
LBW	$CL_i = CL_{pop} \bullet (LBW_i/55)$	6	-638	-1563
IBW	$CL_i = CL_{pop} \bullet (IBW_i/50)$	6	-640	-1543
BMI	$CL_i = CL_{pop} \bullet (BMI_i/23)^z$	7	-651	-1596
TBW	$CL_i = CL_{pop} \bullet (TBW_i/70)^z$	7	-653	-1599

a = 40 lean patients in whom height data were available.
BMI = body mass index; BMI_i = BMI of the i^{th} individual; CL = clearance from the central compartment; CL_i = CL in the i^{th} individual; CL_{pop} = population mean CL value; IBW = ideal body weight; IBW_i = IBW of the i^{th} individual;; LBW = lean body weight; LBW_i = LBW of the i^{th} individual; NA = not applicable; OFV = objective function value; TBW = total body weight; TBW_i = TBW of the i^{th} individual; z = allometric scaling factor.

showed that body weight TBW and BMI were the most predictive covariates for propofol clearance in morbidly obese patients (Table II).
For both the TBW model and the BMI model, the OFV was more than 7.9 points lower in comparison with the simple model ($p<0.005$). The diagnostic and individual plots of the TBW model proved to be superior to the simple model and the BMI model, particularly with respect to population-predicted concentrations. Therefore, the TBW model was chosen as the final model for morbidly obese patients, in which the equation for clearance was (equation 7):

$$CL_i = CL_{70\,kg} * (TBW_i/70)^z \qquad \text{(Eq. 7)}$$

where CL_i represents CL in the ith individual, $CL_{70\,kg}$ is the population mean CL value in an individual weighing 70 kg, TBW_i is the TBW of the i^{th} individual, 70 is the standard TBW in kilograms, and k is the allometric scaling factor, which was estimated to be 0.72. The pharmacokinetic parameters of the simple model and the final body weight model are shown in Table III. The stability of the final body weight TBW model was shown by the bootstrap analysis (Table III). In Figure 2A and 2B, the diagnostics of the final body weight TBW pharmacokinetic model in the 20 morbidly obese patients are shown.
For the analysis of both the dataset of the 20 morbidly obese patients and the dataset of the 44 lean patients from the previously published studies, a three-compartment pharmacokinetic model most adequately described the data. In Figure 3, the results of the covariate analysis are shown, with individual parameter estimates for clearance in the simple model without covariates versus the four tested weight covariates. For this covariate analysis, 40 lean patients were included instead of 44, as the height of four lean patients was not available. All four weight covariates were incorporated on clearance in the model and tested for significance (Table II). The covariate analysis showed that TBW was the most predictive covariate for propofol clearance in the combined dataset of morbidly obese patients and lean patients, which was similar to the results in the morbidly obese patients alone. In the final TBW model, which included all 20 morbidly obese patients and all 44 lean patients, the OFV decreased by 46 points ($p<0.001$), while the interindividual variability in clearance decreased by 33%, and diagnostic and individual plots of the TBW model improved in comparison with the simple model (Table III). Implementation of fixed exponents of 0.75 for clearance and 1 for volumes, as applied by Cortinez et al. (9), led to worse performance and an unstable model during bootstrap analysis, compared to the final TBW model. For the final TBW model in the 20 morbidly obese patients and all 44 lean patients, the equation for clearance was equation 7, where z was

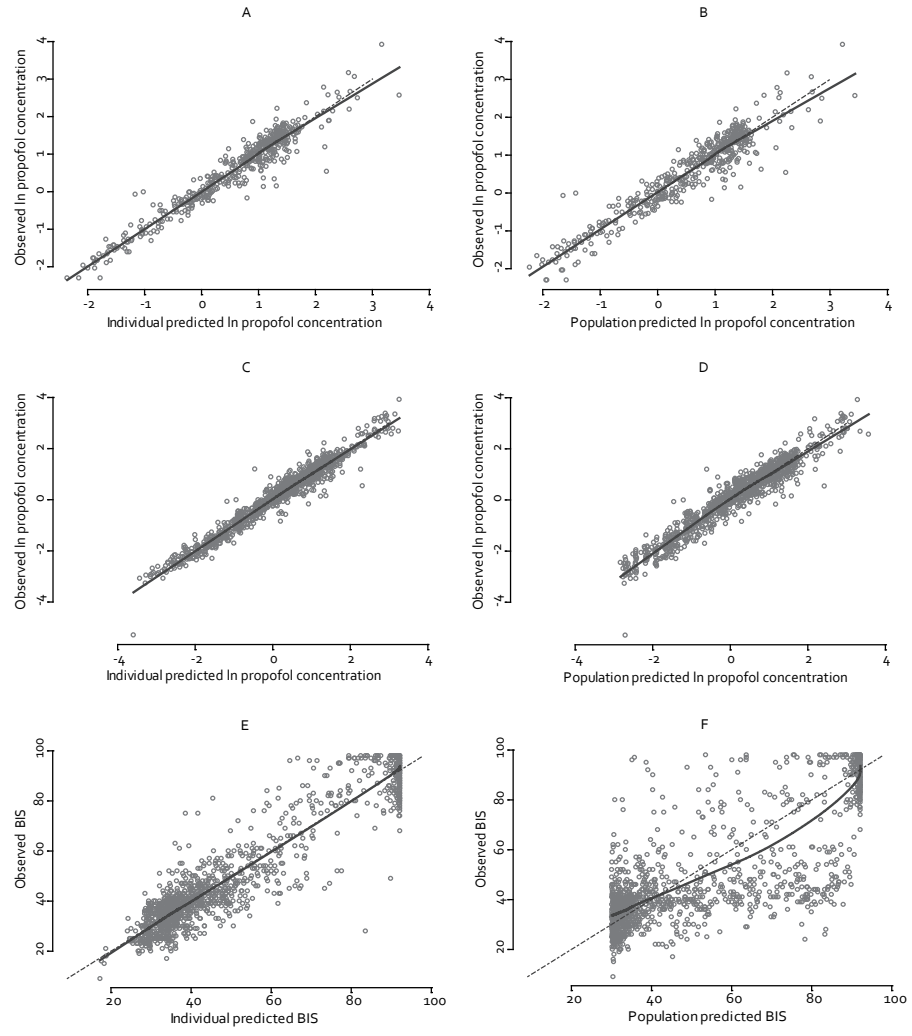


Figure 2 *Diagnostic plots of the final TBW pharmacokinetic model in 20 morbidly obese patients (A and B), the final TBW pharmacokinetic model in 20 morbidly obese patients and 44 lean patients (C and D), and the final pharmacodynamic model using BIS values in 20b morbidly obese patients (E and F), including observed versus individual predictions (A, C and E), and observed versus population predictions (B, D and F). BIS = bispectral index; ln = log-normal; TBW = total body weight. The solid line indicates the trend line, the dashed line represents the line of identity, x = y.*

Table III *Population pharmacokinetic parameters and their bootstrap values for the simple and final pharmacokinetic models for propofol in morbidly obese patients and in the combined dataset of morbidly obese and lean patients.*

Parameter	Morbidly obese patients[a]			Morbidly obese and lean patients[a]		
	Simple model	Final TBW model	Bootstrap final model	Simple model	Final TBW model	Bootstrap final model
Patients (n)	20	20	NA	64	64	NA
CL (L/min)	3.55 (8.8)	NA	NA	2.57 (3.8)	NA	NA
$CL_{70\,kg}$ (L/min)[b]	NA	2.33 (5.11)	2.29 (16.2)	NA	2.22 (2.8)	2.22 (3.3)
Z	NA	0.72 (10.8)	0.76 (36.7)	NA	0.67 (6.0)	0.67 (11.4)
V1 (L)	4.51 (13.0)	4.52 (10.1)	4.41 (14.4)	3.10 (8.3)	3.03 (9.3)	3.15 (11.9)
V2 (L)	22.1 (18.9)	22.2 (17.4)	22.5 (19.6)	5.48 (9.8)	5.34 (9.7)	5.61 (13.4)
V3 (L)	106 (12.6)	107 (12.3)	113 (20.4)	117 (7.6)	116 (7.6)	115 (7.8)
Q2 (L/min)	2.55 (14.3)	2.55 (15.1)	2.57 (14.8)	1.67 (7.6)	1.64 (7.0)	1.64 (9.7)
Q3 (L/min)	1.41 (15.5)	1.41 (14.0)	1.42 (15.2)	1.88 (4.8)	1.86 (5.0)	1.88 (5.6)
OFV	-643	-653	-677	-1726	-1772	-1760
Interindividual variability (%)						
CL	12.6 (36.1)	11.9 (29.7)	10.7 (39.7)	27.1 (14.0)	18.1 (13.5)	17.7 (19.2)
V1	45.0 (42.1)	44.7 (46.7)	50.5 (63.0)	44.5 (45.7)	44.5 (44.0)	47.4 (53.2)
V3	30.7 (46.9)	28.9 (47.3)	31.8 (106)	NA	NA	NA
Proportional intraindividual error (%)	29.4 (15.4)	29.4 (15.9)	29.0 (15.5)	27.9 (19.8)	31.9 (14.9)	27.5 (11.0)

a The data are expressed as mean [%CV] unless specified otherwise.
b $CL_i = CL_{70\,kg} \times (TBW/70)^z$.
CL = clearance from the central compartment; $CL_{70\,kg}$ *= population mean CL value in an individual weighing 70 kg;* CL_i *= CL in the* i^{th} *individual; CV = coefficient of variation; NA = not applicable; OFV = objective function value; Q2 = inter-compartmental clearance from the central compartment to the first peripheral compartment; Q3 = inter-compartmental clearance from the central compartment to the second peripheral compartment; TBW = total body weight; V1 = volume of distribution of the central compartment; V2 = volume of distribution of the first peripheral compartment; V3 = volume of distribution of the second peripheral compartment; z = allometric scaling factor in* $CL_i = CL_{70\,kg} \times (TBW/70)^z$.

Table IV *Population pharmacodynamic parameters for the one compartment effect-site model and two compartment biophase distribution model for propofol induced changes of the Bispectral index during induction, maintenance of and emergence from anesthesia in morbidly obese patients.*

Parameter	One-compartment effect-site model[a]	Final two-compartment biophase-distribution model[a]	Bootstrap final model[a]
E_o (value)	92.0 (1.0)	92.2 (1.0)	92.1 (1.0)
E_{max} (value)	60.3 (4.4)	62.1 (4.3)	62.1 (4.2)
EC_{50} (mg/L)	2.11 (4.6)	2.12 (4.6)	2.09 (5.1)
γ	6.63 (18.6)	8.76 (19.9)	9.16 (9.2)
k_{eo} (min^{-1})	0.089 (8.5)	0.095 (9.0)	0.097 (12.4)
k_{e12} (min^{-1})	-	0.050 (21.5)	0.050 (21.5)
k_{e21} (min^{-1})	-	0.049 (17.5)	0.047 (19.6)
OFV	9879	9712	9700
Interindividual variability (%)			
k_{eo}	39.7 (30.3)	36.6 (26.0)	46.8 (141)
EC_{50}	20.4 (33.6)	20.1 (36.4)	20.1 (39.0)
E_{max}	7.84 (27.6)	9.22 (43.6)	9.08 (40.5)
Proportional intraindividual error (%)	15.5 (9.75)	14.7 (11.4)	14.7 (12.0)

a The data are expressed as mean [%CV] unless specified otherwise.
γ = Hill coefficient; BIS = bispectral index; CV = coefficient of variation; E_o *= baseline BIS;* EC_{50} *= propofol concentration at half-maximum effect;* E_{max} *= maximum possible effect;* k_{e12} *= rate constant from the central to the peripheral effect-site compartment;* k_{e21} *= rate constant from the peripheral to the central effect-site compartment;* k_{eo} *= first-order equilibrium rate constant between plasma and the effect-site compartment; NA = not applicable; OFV= objective function value.*

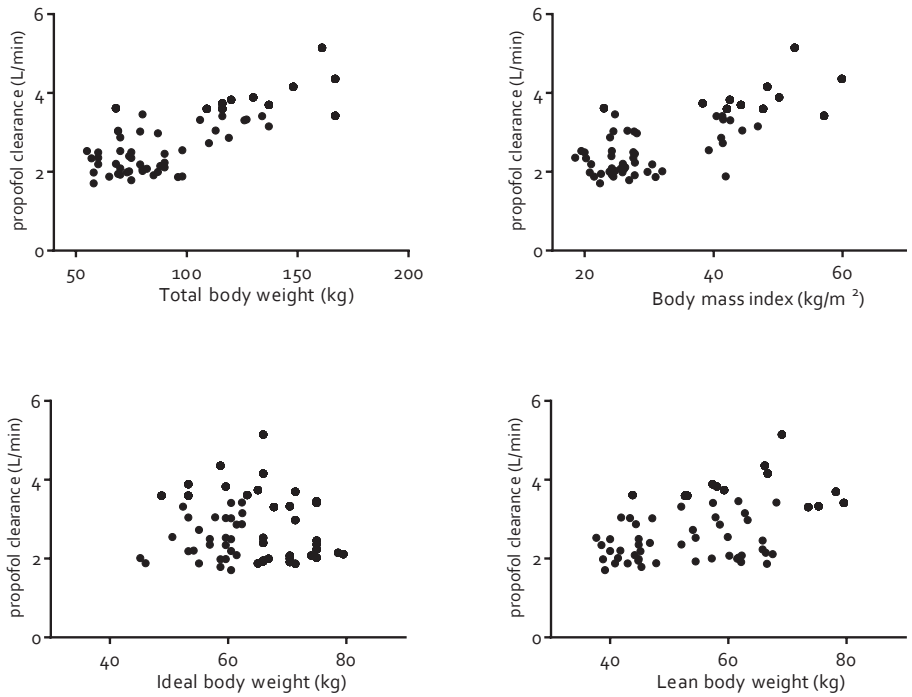


Figure 3 *Individual propofol clearance values versus TBW, BMI, IBW and LBW for the simple three-compartment pharmacokinetic model in 20 morbidly obese patients and 40 lean patients (n = 60). BMI = body mass index; TBW = total body weight; IBW = ideal body weight; LBW = lean body weight.*

estimated to be 0.67. Final diagnostic plots are shown in Figure 2C and 2D, and final pharmacokinetic parameter values are shown in Table III.
Bootstrap analysis of 250 replicates of the dataset of both the morbidly obese patients and the lean patients confirmed the stability of the model.

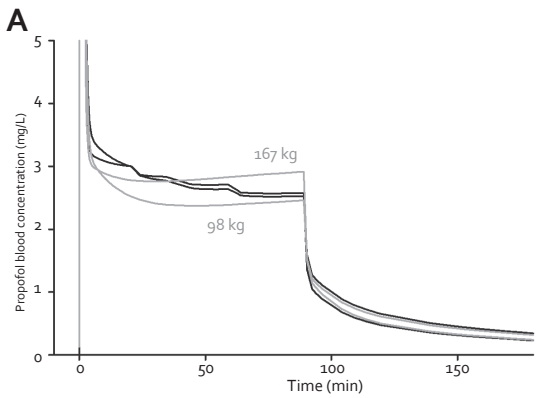
Pharmacodynamics
The pharmacodynamic dataset contained 2246 observed BIS values from the 20 morbidly obese patients. While a one-compartment effect-site model adequately described the BIS values over the time profiles of the patients, a two-compartment biophase-distribution model significantly improved the performance, which was reflected by a reduction in the OFV of 167 points ($p<0.001$). While the differences in concentrations in the central effect-site compartment are generally small during steady state, just after a rapid change in concentration in the central pharmacokinetic compartment, small changes can typically be observed in the conditional weighted residuals

versus time plots of the one-compartment effect-site model versus the two-compartment biophase-distribution model (data not shown). No covariates for the pharmacodynamics of propofol were found. Table IV shows the population parameters of the one-compartment effect-site model and the final two-compartment biophase-distribution model and the results of the bootstrap analysis of 250 replicates of the dataset of the 20 morbidly obese patients, confirming a stable E_{max} model. In Figure 2E and 2F, the diagnostics of the final pharmacodynamic model are shown.

Simulations
On the basis of the final pharmacokinetic and final pharmacodynamic model, simulations were performed aiming for BIS values between 40 and 60 for patients ranging in TBW between 98 and 167 kg. The results of the simulation exercise showed that, upon an induction dose of propofol 350 mg (12), the rate of the maintenance propofol infusion should be set to 7 mg/(70 kg * (TBW/70)$^{0.72}$)/h for 20 minutes, followed by 6.5 mg/(70 kg * (TBW/70)$^{0.72}$)/h for 20 minutes, 6 mg/(70 kg * (TBW/70)$^{0.72}$)/h during 20 minutes, and 5.5 mg/(70 kg * (TBW/70)$^{0.72}$)/h until the end of surgery, in order to achieve the desired BIS values. These BIS values can be expected provided that co-analgesia is achieved with remifentanil 25 µg/h times IBW (13) and predictive muscle relaxation is obtained using a continuous infusion of atracurium besilate.
Figure 4 shows blood propofol concentrations, propofol effect-site propofol concentrations and BIS values both with the model-based dosing regimen, as described above, and with a linear 5 mg/kg/h propofol dosing schedule in a 98 kg morbidly obese patient and in a 167 kg morbidly obese patient.

Discussion

In order to study the influence of morbid obesity on the pharmacokinetics and pharmacodynamics of propofol, a population pharmacokinetic-pharmacodynamic model was developed, in which clearance proved to scale with TBW, using an allometric function with an exponent of 0.72. While this allometric scaling factor of 0.72 in morbidly obese patients was fairly similar to the allometric scaling factor of 0.67 identified in both morbidly obese and lean patients, no other differences in pharmacokinetics or pharmacodynamics were identified.
It has been previously reported that variations in propofol clearance between patients are mainly influenced by TBW (6-7, 9). However, these studies evaluated only a limited number of obese (6-7) and morbidly obese patients (6-7, 9). In contrast to these findings, Han et al. suggested that LBW



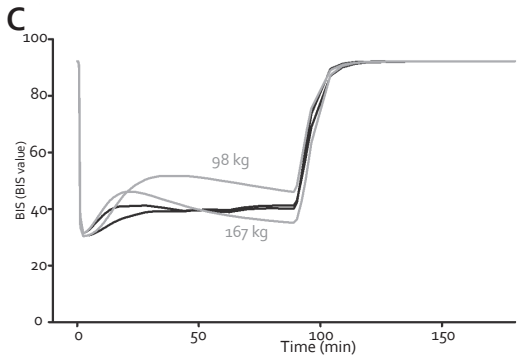


Figure 4 *Model-based predictions of blood propofol concentrations (A), effect-site propofol concentrations (B) and BIS values (C) upon a model-based dosing regimen (black lines) and a linear dosing regimen (grey lines) of propofol in a morbidly obese patient of 98 kg and a morbidly obese patient of 167 kg. The model-based dosing regimen consisted of an induction dose of propofol 350 mg, followed by 7 mg/(70kg * (TBW/70)$^{0.72}$)/h for the first 20 minutes, 6.5 mg/(70kg * (TBW/70)$^{0.72}$)/h for the following 20 minutes, 6 mg/(70kg * (TBW/70)$^{0.72}$)/h for the next 20 minutes, and 5.5 mg/(70kg * (TBW/70)$^{0.72}$)/h until the end of surgery. The linear dosing regimen consisted of an induction dose of propofol 350 mg, followed by 5 mg/kg/h throughout the entire procedure. BIS = Bispectral index; TBW = total body weight.*

is related to clearance of propofol and can therefore be used as a parameter for propofol dosing in obese patients (20). This suggestion was explored by McLeay et al. (8); however, their model was based on simulations and not supported by clinical data in (morbidly) obese patients. In our study in 20 morbidly obese patients and 40 lean patients, the patients' TBW, BMI, IBW and LBW were available and could be studied for their specific influence on any of the pharmacokinetic parameters. In morbidly obese patients, it was found that clearance correlated with TBW and BMI, with no significant difference between the two models in terms of the OFV. However, after analysing both the morbidly obese patient dataset and the lean patient dataset (range 55–167 kg), TBW proved to be superior to BMI as a covariate for clearance of propofol based on the basic goodness-of-fit plots together with the OFV (a decrease in the OFV of 3 points). As both Figure 3 and Table II demonstrate, IBW and LBW could not be identified as predictors of propofol clearance, despite the fact that there is great interest in LBW as a covariate for dosing based on theoretical principles (8, 20).

In morbidly obese patients, we found that the nature of the influence of TBW on clearance was best described by an allometric equation with an exponent of 0.72. This scaling factor was not significantly different from the scaling factor of 0.67 that we reported for the entire TBW range of lean and morbidly obese patients (55 - 167 kg). These results are in accordance with previously reported scaling factors of 0.71 in lean patients described by Schuttler et al. (7) and the fixed value of 0.75 in obese patients described by Cortinez et al. (9). More specifically, the clearance value of 2.22 L/min for a patient weighing 70 kg, as reported in our study, is in good agreement with the clearance of 2.25 L/min for a 70 kg person reported by Cortinez et al. (9). In our opinion, the nonlinearity in the relation between TBW and clearance is important to consider when dosing propofol in morbidly obese patients. In anaesthesia, medication is typically administered in milligrams per kilogram per hour, assuming a linear relation between TBW and clearance. While this dosing paradigm in milligrams per kilogram per hour may lead to overdosing in individuals at the upper TBW range, in this study we propose a nonlinear model-based dosing algorithm. Using this dosing regimen, the nonlinearity of the influence of TBW on clearance is accounted for and, as a result, a fixed dosing schedule (5.5–7 mg per (kg of TBW/70)$^{0.72}$ per hour) can be used for all patients ranging between 98 and 167 kg in TBW. While the proposed dosing regimen, together with the corresponding ABW, deserves further study in the TBW range that was included in this study (98–167 kg), it remains of interest to evaluate the extrapolation capacities of this function at higher TBW values than those that were included in the current study (e.g. >167 kg). It is emphasized that the proposed model-based dosing regimen is to be used in conjunction with full muscle relaxation and remifentanil co-

analgesia, as other co-medication may influence the pharmacokinetics and/or pharmacodynamics of propofol, resulting in lower or higher propofol infusion rates, despite the fact that the influence of TBW on propofol clearance remains the same.

Concerning the other pharmacokinetic parameters, there was a trend towards an increased V1 in morbidly obese patients compared with morbidly obese and lean patients together (4.52 L versus 3.03 L, respectively) (Table II). Previously, linear (6, 9) and allometric (7) relationships between TBW and the volume of distribution have been suggested. In our study, however, even though a large variability in individual values of the volume of distribution was found, incorporation of TBW as a covariate for the volume of distribution in the model did not result in significant improvement of the model according to the criteria described in the Methods section. It seems that larger datasets or different sampling schemes are needed to identify this influence or that factors other than TBW contribute to this large interindividual variability.

Besides the pharmacokinetics of propofol in morbidly obese patients we investigated the pharmacodynamics using the BIS as endpoint. As morbidly obese patients can be considered to suffer from chronic inflammation (21) and are reported to have a lower pain threshold (22), we hypothesized that differences in the pharmacodynamic effects of propofol in these patients compared with lean patients cannot be excluded. However, considering the pharmacodynamic parameters reported in morbidly obese patients in this study, it seems that the EC_{50} and k_{e0} are in accordance with previously reported pharmacodynamic parameters of propofol in lean patients (16, 23). We compared our results with literature values because no BIS data were available in our lean patients datasets for us to do a combined pharmacodynamic analysis on morbidly obese and lean patients. Instead, we studied the influence of TBW within the pharmacodynamic model of our morbidly obese patients, in which no significant covariates could be identified. On the basis of these results, and in the absence of other reports on the pharmacodynamic relation of propofol in morbidly obese patients, we conclude that there are no differences in sensitivity to the propofol effect, measured using the BIS, between lean and morbidly obese patients.

In the pharmacodynamic analysis, a two-compartment biophase-distribution model proved to be superior to a one-compartment effect-site model (a decrease in the OFV of 167 points). While a two-compartment biophase-distribution model has been previously reported for propofol in lean patients (23), plasma-effect-site equilibration is often assumed to be a mono-exponential first-order process (24). This assumption of a mono-exponential first-order process has been firmly adopted in pharmacokinetic and pharmacodynamic modelling, although it was reported as early as 1991 that this assumption appeared to be inadequate for amobarbital and alphaxalone and that a bi-exponential conductance function better described the data (25-26). An explanation for the two-compartment biophase-distribution function is re-distribution of the drug in the central nervous system. Although the differences between the two models are generally small during steady-state situations, just after a bolus injection and a large infusion rate change, differences between the models can be noted. As in to lean patients (23), a bi-exponential function was found to be superior to a one-compartment effect-site model in morbidly obese patients in this study.

The limitations of our study include the characteristics of the lean patient datasets, which were not fully comparable to those of the studied group of morbidly obese patients. One lean patient dataset was obtained in females receiving a single bolus dose of propofol and isoflurane for maintenance of anaesthesia (10), while the second lean patient dataset consisted of critically ill patients receiving a long-term infusion of propofol (11). Furthermore, our study in morbidly obese patients was performed during clinical practice, implying that substantial co-medication was given, which may have influenced the pharmacodynamic estimates. In particular, remifentanil and muscle relaxants are known to influence the pharmacodynamics of propofol, although the literature is conflicting on this issue (27-31). However, an advantage of this approach is that the resulting model-based dosing regimen can be used directly in clinical practice provided that the same anaesthetic protocol is applied. Another issue was the lack of external validation datasets. Furthermore, as a result of the BIS target of 40–60, a limited range of propofol concentrations and BIS values were obtained, resulting in under-studied BIS ranges, e.g. lower than 30. Further study is needed to describe the entire BIS range, although for clinical practice, the current dataset and derived model seems to be adequate.

On the basis of the results of the final pharmacokinetic and pharmacodynamic model of propofol in morbidly obese patients, a dosing schedule with specific rates in milligrams per kilogram per hour with use of an adjusted body weight ($70\ kg \times (TBW/70)^{0.72}$) for a surgical procedure aiming at BIS values between 40 and 60 was derived. An alternative strategy for propofol dosing is to target a specific propofol concentration, using TCI techniques. TCI anaesthesia is controlled by pharmacokinetic models that are based on lean patients, such as the Marsh model (32) and the Schnider model (33). By evaluation of the actual depth of anaesthesia at a specific target concentration by the anaesthesiologist, adjustment of the target concentration can be considered and entered into the TCI system. There are several reports on the performance of TCI in obese and morbidly obese patients. Cortinez et al. suggest that their model for obese patients leads to a performance that is similar to that of the Marsh model (9). Absalom et al. (34) warned that

for an excessive maintenance dose of propofol may be administered when LBW is used for TCI in morbidly obese patients using the Schnider model. Similarly, La Colla et al. (35) reported a clinically unacceptable performance bias with the use of TBW as input for the Marsh model and concluded that titration to target BIS values in morbidly obese patient remains necessary. While TCI can be considered an important approach to dose propofol for anaesthesia, it seems that TCI systems are not yet ready for this approach in morbidly obese patients. The results of this study can be used to fill this gap if implemented into the TCI system and tested in morbidly obese patients with TBW up to 170 kg, in conjunction with remifentanil analgesia. Until then, the dosing paradigm that has been derived from our final pharmacokinetic and pharmacodynamic model can be used to dose morbidly obese patients in clinical practice, with use of an adjusted TBW together with a specific infusion rate regimen, aiming for a BIS between 40 and 60.

Conclusion

A pharmacokinetic model for propofol in morbidly obese patients has been derived, with TBW as the major determinant of clearance, using an allometric function with an exponent of 0.72. No covariates for the other pharmacokinetic parameters were identified. The obtained BIS values in morbidly obese patients were described with a two-compartment biophase-distribution model, with a sigmoid E_{max} pharmacodynamic model without covariates.

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