Epidural Blockade Affects the Pharmacokinetics of Propofol in Surgical Patients

Elske Sitsen, MD, Erik Olofsen, MSc, Agnes Lesman, MD, Albert Dahan, MD, PhD, and Jaap Vuyk, MD, PhD

BACKGROUND: Neuraxial blockade reduces the dose requirements of sedative agents. It is unclear whether neuraxial blockade affects the pharmacokinetics and/or the pharmacodynamics of IV hypnotics. We therefore studied the influence of epidural blockade on the pharmacokinetics of propofol in patients scheduled for general surgery.

METHODS: Twenty-eight patients were randomly divided into 4 groups, in a double-blind manner, to receive 0, 50, 100, or 150 mg epidural ropivacaine. When the epidural blockade had stabilized, a target-controlled infusion of propofol was started at a target concentration of 1, 2.5, 4, and 6 μg/mL at 0, 6, 12, and 18 minutes, respectively. The infusion was terminated at 24 minutes. Arterial blood samples for blood propofol concentration determination were taken during and up to 150-minute postinfusion. The influence of epidural blockade on propofol pharmacokinetics was determined by mixed-effects modeling.

RESULTS: With a ropivacaine dose increasing from 0 to 150 mg, the number of blocked segments (median [range]) increased from 0 (0–3) to 16 (6–21). With increasing epidural dose, blood propofol concentration increasingly exceeded target concentration. An epidural blockade of 20 segments reduced propofol's elimination clearance from 2.64 ± 0.12 to 1.87 ± 0.08 L/min. Adjusting for weight and sex further improved the propofol pharmacokinetic model.

CONCLUSIONS: Epidural blockade affects the pharmacokinetics of propofol and the performance of a target-controlled infusion of propofol. At an epidural ropivacaine dose that blocks 20 segments, the propofol dosage or target concentration may be reduced by 30% compared with when no epidural blockade is present. An epidural-induced reduction in hepatic and/or renal blood flow may explain this pharmacokinetic interaction. (Anesth Analg 2015;XXX:00–00)

Epidural anesthesia provides surgical analgesia and reduces postoperative pain. Intraoperatively, epidural anesthesia is often used in combination with general anesthesia to reduce anesthetic requirements. Neuraxial blockade has been shown to affect the dose requirements of hypnotic agents required to achieve a given sedative or anesthetic effect.[1] In the presence of epidural blockade, the dose of midazolam and propofol needed to induce loss of consciousness was reduced by up to 25%.[1,2] A similar reduction in dose requirement has been described for volatile anesthetics in the presence of epidural anesthesia.[3] In addition to a hypnotic-sparing effect, the sensory blockade from spinal anesthesia itself has been associated with a sedative effect.[4] Last, Valverde et al.[5] and Doherty and Frazier[6] found that IV lidocaine decreased the minimum alveolar concentration of halothane in a dose-dependent manner in animals, suggesting that the systemic effects of local anesthetics may have direct sedative effects.

Epidural blockade, through sympathetic output reduction, and the direct vasodilating and myocardial depressant effect of local anesthetics[7,8] may cause hemodynamic depression. Because sedatives affect the hemodynamics as well, it is important to determine the interaction between epidural blockade and sedative agents to allow analgesia and sedation in the presence of optimal hemodynamic stability.

The mechanism and the magnitude of the sedative-sparing effect of central neuraxial blockade are unclear. The pharmacokinetics of IV sedatives may be affected by epidural-induced changes in cardiac output and regional blood flow. For example, reductions in liver blood flow reduce propofol clearance, as a consequence of its high extraction ratio.

We hypothesized that epidural blockade affects the pharmacokinetics of propofol because of the hemodynamic alterations that result from epidural blockade. We therefore studied the influence of epidural blockade on the pharmacokinetics of propofol in a double-blind randomly assigned manner.

METHODS

Subjects

After obtaining approval of the Medical Ethics Committee of the Leiden University Medical Centre, registration in National Ethics Registry CCMO, NL32295.058.10, and written informed consent, 28 ASA physical status I or II patients, aged 18 to 65 years, scheduled for surgical procedures requiring epidural anesthesia, participated in the study. All patients were within 30% of ideal body weight; had no history of cardiac, hepatic, or renal disease; and were allowed to take their usual medication until the day before the

From the Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands.

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Address correspondence to Elske Sitsen, MD, Department of Anesthesiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands. Address e-mail to mesitsen@lumc.nl.

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investigation. Patients taking β-blocking drugs and patients taking chronic pain medication were excluded from the study. All patients denied smoking or consumption of >20 g alcohol per day. The study was conducted in an operating room and was completed before the start of the surgical procedure.

The study was powered at 80% to detect a difference of 15% in the blood propofol concentration associated with a level of (un)consciousness equal to a bispectral index of 60 between 0 and 150 mg epidural ropivacaine doses with 28 patients.[9] Patients who dropped out would be replaced.

Study Design

This was a randomly assigned double-blind study. The 28 patients were randomly assigned to 1 of the 4 study groups of 7 patients. The randomization and preparation of the study medication were performed by the hospital pharmacist who took no further part in the study. Randomization was performed in blocks of 4 by a computerized randomization program. Patients were allocated to sequentially numbered boxes. The study medication was delivered in a closed box. The ropivacaine dose was removed from the box and administered via the epidural catheter to the patient by a qualified anesthesia nurse who took no further part in the study. This anesthesia nurse then signed the medication form and returned the box, again closed, to the hospital pharmacist.

After arrival in the operating room, the unpremedicated patients received the standard perioperative monitoring, including the electrocardiogram, end-tidal carbon dioxide, peripheral oxygen saturation, bispectral index, and intra-arterial blood pressure. These were monitored continuously throughout the study. An IV cannula was inserted into a large forearm vein for the infusion of propofol. An intra-arterial cannula was placed in the radial artery for continuous hemodynamic monitoring and blood sampling. After placement of monitors, patients were moved to a sitting position for placement of the epidural catheter. After skin infiltration with lidocaine, patients received a lumbar epidural catheter at the L2-L3 or L3-L4 level, placed 5 cm in the epidural space.

After placement of the epidural catheter, cardiac output was determined using the pulse contour methodology on the basis of the intra-arterial blood pressure curve with the Vigileo (Edwards Lifesciences, Irvine, CA). A preload of 500 mL of Voluven® was given 15 minutes before the epidural medication was given.

Drug Administration

After the gathering of baseline measurements, an anesthesia nurse, not otherwise involved in the study, administered the study medication of 10 mL NaCl 0.9%, 50 mg ropivacaine (7.5 mg/mL), 100 mg ropivacaine (7.5 mg/mL), or 150 mg ropivacaine (7.5 mg/mL) via the epidural catheter, according to the randomization protocol. After aspiration, a test dose of 2 mL of the blinded medication was given to exclude a spinal position of the catheter. Then, 3 minutes thereafter, in the absence of significant sensory or motor blockade, the remaining dose was given. The study nurse had no further involvement in the study to maintain the double blinding of the patient and investigators.

Patients in groups 1, 2, 3, and 4 received an epidural dose of 10 mL NaCl 0.9%, 50 mg ropivacaine 7.5 mg/mL (6.7 mL), 100 mg ropivacaine 7.5 mg/mL (13.3 mL), and 150 mg ropivacaine 7.5 mg/mL (20 mL), respectively. Assessments of the epidural blockade level were performed every 5 minutes during the first 30 minutes after epidural administration. Hypotension, defined as greater than a 30% decrease in systolic blood pressure compared with control, was treated with phenylephrine 100 µg, IV. Bradycardia, defined as a heart rate <40 beats/min, was treated with atropine 0.5 mg, IV.

The propofol infusion was started 30 minutes after administration of the epidural study medication using the target-controlled infusion (TCI) pump of Fresenius Vial Infusion Technology called the Base Primea® (Fresenius Vial, Brezins, France) using the propofol pharmacokinetic parameters reported by Marsh et al.[10] Patients received a TCI with propofol with an initial target concentration of 1 µg/mL. After 6, 12, and 18 minutes, this target propofol concentration was increased to 2.5, 4, and 6 µg/mL, respectively. The TCI of propofol was terminated 24 minutes after its initiation. During the propofol infusion, all patients received 100% oxygen through a non-rebreathing mask.

After termination of the study, 150 minutes after cessation of the propofol infusion, the level of epidural blockade was determined again and an additional epidural dose of ropivacaine was given as required to assure adequate sensory blockade for surgery.

Assessment of Clinical Response

The level of sensory loss was determined by loss of cold sensation bilateral in the anterior axillary line. All patients were tested while in a supine position; the upper and lower limits of the blockade were registered. A stable level of sensory loss was defined as an unchanged upper blockade level during 2 consecutive 5-minute assessments. Motor function loss was scored using the Bromage scale (0 = no motor function loss, 1 = patient is able to flex the ankle and knee, 2 = patient is able to flex the ankle, 3 = complete motor loss).

Arterial Blood Samples and Assays

A blank blood sample (10 mL) was obtained for calibration purposes before propofol administration. Arterial blood samples for blood propofol concentration determination were taken at 3, 6, 9, 12, 15, 18, 21, and 24 minutes after the start of the target-controlled propofol infusion (the 6-, 12-, 18-, and 24-minute samples were taken just before the change in target concentration), and at 2, 5, 10, 20, 30, 60, 90, 120, and 150 minutes after termination of the propofol infusion. Blood samples were collected in potassium oxalate–coated syringes and stored at 4°C. Propofol assays were performed within 12 weeks in our laboratory. Propofol concentrations in blood were measured by high performance liquid chromatography-fluorescence at an excitation wavelength of 276 nm with emission wavelength of 310 nm.[11] The intra- and interassay coefficients of variation were 4.3% and 3.7%, respectively, for propofol in blood in the concentration range of 0.06 to 14.0 µg/mL.

Pharmacokinetic Modeling and Covariate Selection

The TCI regimens of the individual patients were used as the input ("the dose") in the pharmacokinetic analysis. The

TCI log files of the Base Primea TCI pump in combination with simulations using the model by Marsh et al.[10] allowed for an accurate representation of the individual infusion rates over time in each individual patient.

The pharmacokinetics were based on a 3-compartment mammillary model. The parameters were estimated using the measured blood propofol concentration-time data alone (without covariates) of the 28 sessions. This model was parameterized using volumes and clearances. These included 3 volumes, V_1, V_2, and V_3, describing the central volume of distribution, and the shallow and deep volumes of distribution, and 3 clearances, Cl_1, CL_2, and Cl_3, describing elimination clearance, clearance to the shallow compartment, and clearance to the deep compartment.

Weight, sex, ropivacaine dose, and number of blocked segments (NBS) were tested as possible covariates improving the model (see Statistical Analysis). We first estimated the volumes and clearances without covariates. We then added weight as a covariate. Weight was incorporated in the model by multiplying volumes and clearances by factors WT/70 and $(WT/70)^{0.75}$, respectively.[12] These powers were tested for significant differences from 1 and 0.75 for volumes and clearances, respectively. Then, sex was added as a covariate so that the pharmacokinetic parameters could have different values for males and females. This was tested for significant improvement versus the same value for males and females. Last, the dose of ropivacaine and NBS were evaluated simultaneously. The ropivacaine dose was incorporated by multiplying the pharmacokinetic parameters by factors $e^{((DOSE/75-1)\times\alpha)}$. The NBS was incorporated by multiplying the pharmacokinetic parameters by factors $e^{((NBS/10-1)\times\alpha)}$. Parameter α denotes covariate coefficients that characterize how strongly the 6 pharmacokinetic parameters are influenced by the covariate (ropivacaine dose or NBS). These were tested for significant difference from zero.

To determine whether to incorporate a covariate in the model, each of the 64 possible combinations was evaluated ($64 = 2^6$, 2 referring to the presence or absence of the covariate, 6 referring to the 6 possible pharmacokinetic parameters).

Statistical Analysis

Data are described as mean ± standard error unless stated otherwise. The pharmacokinetic models were fit to the data using NONMEM[13] (version 7.2.0 ADVAN 6). The pharmacokinetic parameters were assumed to be lognormally distributed across the population. Constant relative and/or additive residual error models were tested. Model discrimination was done using the Bayesian information criterion (BIC).[14] All possible subsets were sequentially tested for covariates weight, sex, ropivacaine dose, and the NBS.

The predictive accuracy of the Base Primea TCI pump at various target concentration levels was compared between the epidural dose groups (0, 50, 100, and 150 mg ropivacaine) with the multisample median test followed by a Mann-Whitney *U* test.

A visual prediction-corrected predictive check[15] was constructed by simulating the designed TCI drug administration schedule for 28 × 357 subjects; 28 equals the number of subjects in the study and their values of the covariates were retained. From the 9996 simulated concentration-versus-time profiles, 95% prediction intervals were calculated. The prediction-corrected predictive check was required because not all patients received the same dosing regimen.

The standard error of clearance as a function of the NBS (Abstract and Results section) was assessed by calculating the standard deviation of (1,000,000) simulated values based on the population clearance and covariate coefficient estimates and standard errors, assuming the estimates are normally distributed. In plots of clearance versus covariates, 95% confidence intervals were plotted based on the interindividual variability estimate (ω^2) of the population clearance.

A cross-validation method using the "leave-one-out" procedure, as described by Fiset et al.,[16] was used to determine the predictive power of the model. In short, a population model is constructed from $n - 1$ patients by leaving patient i out and used to predict the concentration-time data of the ith patient. This is repeated for all n patients. This procedure provides almost unbiased estimates of the performance of the population model. From the measured and predicted data, the median and 95% relative prediction error interval were calculated. The software to automate covariate selection and the jackknife procedure was written by one of the authors (EO).

Computer Simulations

The influence of the significant covariates (weight, sex, and ropivacaine dose or NBS) on propofol pharmacokinetics was explored by computer simulation using NONMEM. The final model as displayed in Table 1 was used for this purpose in a typical patient receiving a propofol regimen of 2 mg/kg bolus followed by a continuous infusion of 8 mg/kg/h for 120 minutes.

RESULTS

The patients were recruited between December 2010 and February 2012. All 28 patients (17 males, 11 females) completed the study without adverse events. The patients were (mean ± SD) aged 44.9 ± 15.1 years, with a body weight of 77.9 ± 10.6 kg, a height of 177.6 ± 11.1 cm, and a body mass index of 24.8 ± 2.9. All patients were classified as ASA physical status I or II.

In 3 patients, hypotension was treated for a total of 8 times with 100 µg IV phenylephrine. In 2 patients, 0.5 mg IV atropine was given to treat bradycardia during the insertion of the epidural catheter. In 5 patients in the 150-mg ropivacaine group, the highest target propofol concentration of 6 µg/mL was not reached because of a combination of deep sedation and hemodynamic depression. The TCI of propofol was therefore terminated at a maximum target concentration of 2.5 µg/mL in 1 patient and at a maximum target concentration of 4.0 µg/mL in 4 patients. In all other patients, the 4 targets of propofol were maintained for 6 minutes each, and a total of 400 to 500 mg propofol dose was given in 24 minutes. All patients maintained spontaneous ventilation during the study. Patients returned to consciousness 16.3 ± 5.2 minutes after termination of the propofol TCI.

With the ropivacaine dose increasing from 0 to 50, 100, and 150 mg, the NBS (median [range]) increased from 0 (0–3) to 9 (3–15), 12 (9–14), and 15.5 (6–21), respectively (Fig. 1). In 2 of the 7 patients who received 0 mg ropivacaine, 1 or more blocked dermatomes were recorded 30 minutes after the epidural administration of 10

Table 1. Pharmacokinetic Parameters of Propofol of the Base Model Without Covariates, Model with Weight, Sex, and Dose as Covariates and Model with Weight, Sex, and Number of Epidural Ropivacaine-Blocked Segments as Covariates

	Typical value	SEE	ω²	SEE
Base model				
V_1 (L)	6.23	0.297	—	—
V_2 (L)	6.53	0.790	—	—
V_3 (L)	70.0	5.58	0.0581	0.0203
Cl_1 (L/min)	2.45	0.0797	0.0307	0.00758
Cl_2 (L/min)	1.21	0.128		
Cl_3 (L/min)	1.27	0.0894	—	—
SDE	0.197	0.00995	0.104	0.0320
Dose model				
V_1 (L/70 kg)	6.00	0.124	—	—
V_2M (L/70 kg)	8.72	0.303	—	—
V_2F (L/70 kg)	4.21	0.929	—	—
V_3 (L/70 kg)	65.8	3.08	0.0781	0.0193
Cl_1 (L/(70 kg)$^{0.75}$/min)	2.27	0.0559	0.0164	0.00369
Cl_2M (L/(70 kg)$^{0.75}$/min)	1.43	0.106	—	—
Cl_2F (L/(70 kg)$^{0.75}$/min)	0.720	0.143	—	—
Cl_3 (L/(70 kg)$^{0.75}$/min)	1.13	0.0654	0.0915	0.0311
SDE	0.192	0.00939		
αDOSE	−0.129	0.0269		
Blocked segments model (final model)				
V_1 (L/70 kg)	5.98	0.446	—	—
V_2M (L/70 kg)	8.71	0.906	—	—
V_2F (L/70 kg)	4.19	0.974	—	—
V_3 (L/70 kg)	65.8	5.93	0.0853	0.0223
Cl_1 (L/(70 kg)$^{0.75}$/min)	2.22	0.0558	0.0142	0.00397
Cl_2M (L/(70 kg)$^{0.75}$/min)	1.42	0.162	—	—
Cl_2F (L/(70 kg)$^{0.75}$/min)	0.724	0.168	—	—
Cl_3 (L/(70 kg)$^{0.75}$/min)	1.13	0.0814	0.0893	0.0302
SDE	0.192	0.00899		
αNBS	−0.173	0.0367		

The clearance and volume values for the dose model and the blocked segments model are standardized for a ropivacaine dose of 75 mg or standardized NBS of 10.

SEE = standard error of the estimate in the preceding column; ω² = interindividual variance (of log normally distributed parameters); V_1 = central volume of distribution; V_2 = shallow peripheral volume of distribution; V_3 = deep peripheral volume of distribution; Cl_1 = elimination clearance; Cl_2 = rapid distribution clearance; Cl_3 = slow distribution clearance; M = male; F = female; SDE = standard deviation of relative residual error(absolute error was not significant); — = not estimable; αDOSE = covariate coefficient for dose ropivacaine; αNBS = covariate coefficient for number of blocked segments.

mL NaCl 0.9%, suggestive of an epidural-induced placebo effect, but which we consider a measurement error.

In the 28 sessions, a total of 472 blood samples were drawn for blood propofol concentration determination. With the ropivacaine dose increasing from 0 to 50, 100, and 150 mg (with increasing NBS), the measured blood propofol concentration increasingly exceeded that predicted by the Base Primea TCI pump that based its predictions on the Marsh pharmacokinetics.[17] The bias (= median performance error [25th–75th%]) increased in the patients that had received a 0, 50, 100, and 150 mg ropivacaine dose from 1% (−10% to 16%) to 13% (−9% to 30%), 13% ([2% to 27%], $P = 0.001$ compared with placebo), and 32% ([6% to 62%], significantly different from placebo [$P < 0.0001$], 50 mg [$P = 0.003$], and 100 mg [$P = 0.018$]). The inaccuracy (median absolute performance error: MDAPE [25th–75th%]) increased from 12% (6% to 22%) to 19% ([11% to 31%]; $P = 0.003$ compared with placebo), 18% ([9% to 32%; $P = 0.033$ compared with placebo), and 37% ([19% to 62%]; $P < 0.0001$ compared with placebo), respectively, in these patients. The influence of epidural ropivacaine on the bias and inaccuracy of the Base Primea TCI pump is indicative of a pharmacokinetic interaction between the ropivacaine dose and the corresponding level of epidural blockade and the pharmacokinetics of propofol (Fig. 2).

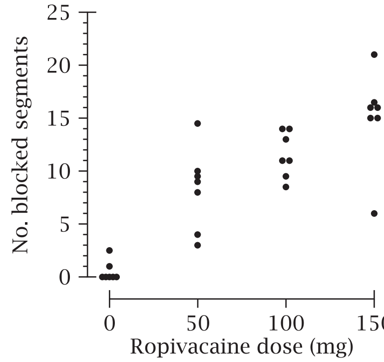

Figure 1. The number of blocked segments of the individual patients in the 4 groups receiving 0, 50, 100, and 150 mg ropivacaine in the epidural space.

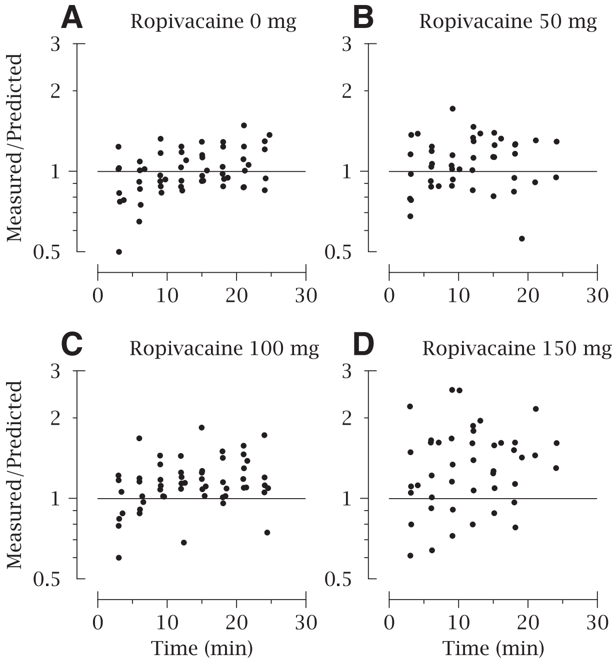

Figure 2. The measured versus predicted propofol ratio's during a target-controlled infusion of propofol using the Marsh parameter set in the patients of the 4 groups receiving 0, 50, 100, and 150 mg epidural ropivacaine. The median performance error in patients of group A (1%) who received no epidural ropivacaine increased to 13%, 13%, and 29% in the patients of groups B, C, and D who received 50, 100, and 150 mg epidural ropivacaine.

This then was confirmed in the pharmacokinetic analysis. A 3-compartment model adequately fitted the data. Figure 3 presents the measured blood propofol concentrations in 3 patients, the best, median, and worst fit of the data, the final model fit of this study, and the predicted propofol concentration by the Base Primea TCI pump based on the Marsh pharmacokinetics.

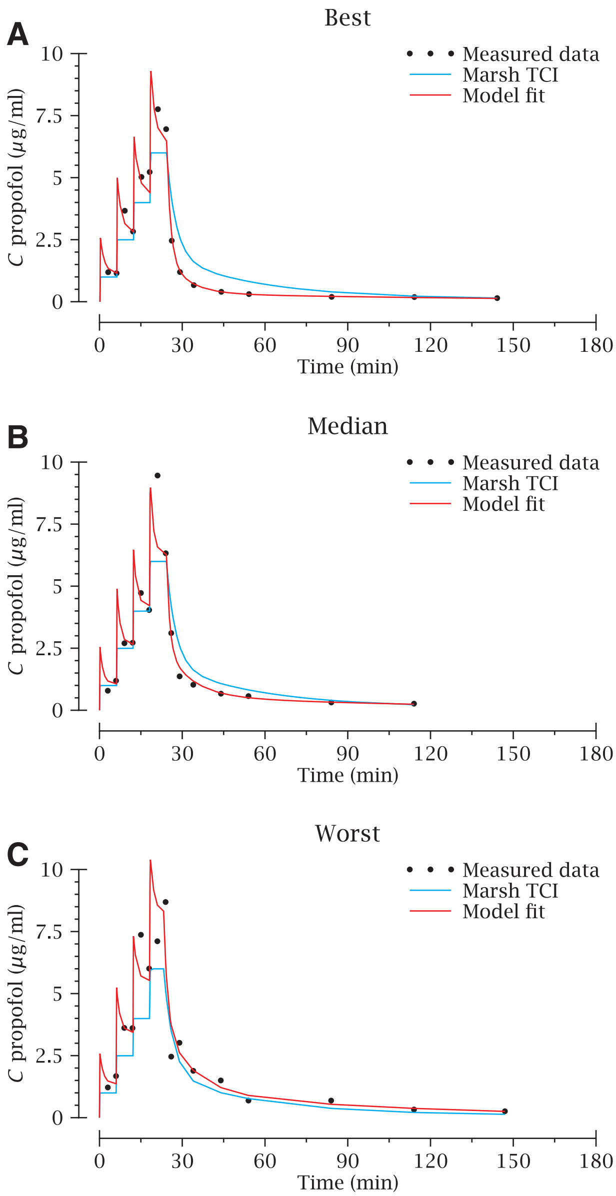

Figure 3. The measured blood propofol concentrations in time in 3 patients that represent the best (A), median (B), and worst (C) fitted data according to the individual objective function values. The dots represent the measured blood propofol concentrations, the solid red line represents the final model fit; the solid blue line represents the propofol concentration as predicted on the basis of the pharmacokinetics of Marsh et al. as used in the target-controlled infusion (TCI) device in this study.

Our initial model was a conventional mammillary 3-compartment model with no covariates. This model had an objective function value of −483.876. We then added weight using an allometric approach, multiplying volumes by (WT/70)^1, and clearances by (WT/70)^0.75, respectively. We tested the volume exponent of 1 and the clearance exponent of 0.75 to see whether other exponents provided better fits. Other values for these exponents did not improve the goodness of fit, so in the final model weight is scaled by WT/70, and clearances are scaled by (WT/70)^0.75. This model had an objective function value of −495.466, demonstrating that our data significantly support scaling propofol pharmacokinetics by weight.

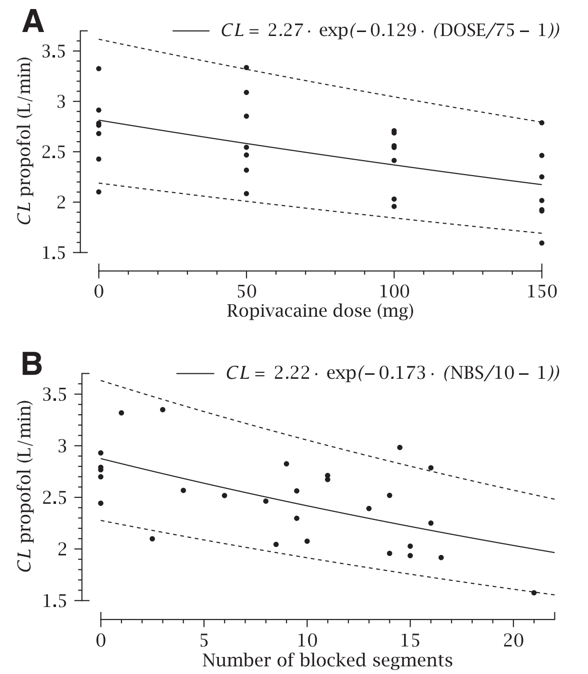

Figure 4. The influence of dose (A) and the number of blocked segments (B) on the clearance (CL) of propofol according to the final model fit. An epidural dose of 150 mg ropivacaine decreases the CL from 2.58 to 2.0 L/min, 20 blocked segments reduces the CL of propofol from 2.64 to 1.87 L/min. The discontinuous line shows the 95% confidence intervals as based on the interindividual variability estimate (ω^2) of the population clearance. The dots are the empirical Bayesian estimates of CL for each patient.

Sex was added as a covariate to have different values for males and females. This resulted in a decrease in the objective function value to −512.742. Dose of ropivacaine and NBS were introduced concurrently in the analysis. The NBS as covariate reduced the objective function value to −526.464. The ropivacaine dose as covariate resulted in a slightly less decrease in the objective function value to −523.496. We therefore selected NBS as the covariate for the model, recognizing that the high correlation between dose and blocked segments precludes assigning the effect of epidural blockade definitively to either dose or NBS.

Table 1 presents the base model (objective function −483.876); the model with weight, sex, and dose as covariates; and the final model with weight, sex, and NBS as covariates. The full equations of the final model for all volumes and clearances are for women: V_1 (L) = 5.98. (WT/70), V_2 (L) = 4.19. (WT/70), V_3 (L) = 65.8. (WT/70), Cl_1 (L/min) = 2.22. $e^{(-0.173.\,(NBS/10-1))}$. $(WT/70)^{0.75}$, Cl_2 (L/min) = 0.724. $(WT/70)^{0.75}$ and Cl_3 (L/min) = 1.13. $(WT/70)^{0.75}$. Males and females have different typical values for V_2 and Cl_2 (see Table 1).

An example of how the parameters of the final model may be calculated for a female patient with a weight of 80 kg and 8 blocked segments is as follows:

V1 = 5.98 . (80/70) = 6.83 L; V2 = 4.19 . (80/70) = 4.79 L; V3 = 65.8 . (80/70) = 75.2 L

Cl_1 = 2.22 . $e^{(-0.173\,.\,(8/10-1))}$. $(80/70)^{0.75}$ = 2.54 L/min; Cl_2 = 0.724 . $(80/70)^{0.75}$ = 0.80 L/min; Cl3 = 1.13. $(80/70)^{0.75}$ = 1.25 L/min.

With the epidural blockade increasing from 0 to 20 blocked segments, the metabolic clearance of propofol was reduced from 2.64 ± 0.12 to 1.87 ± 0.08 L/min (Fig. 4B).

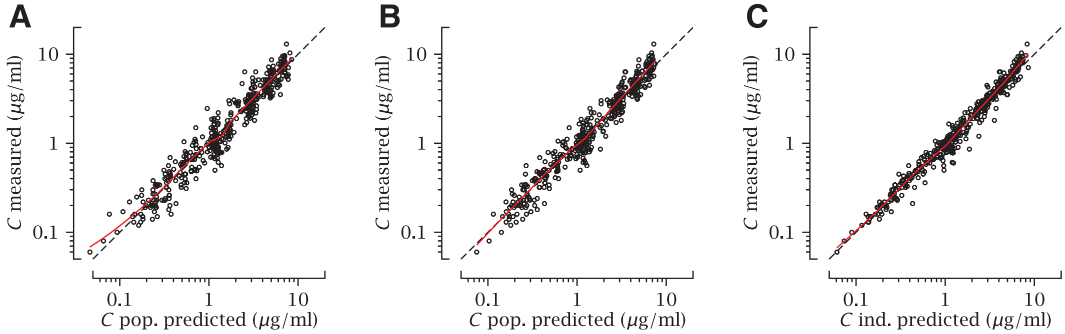

Figure 5. The measured versus population-predicted blood propofol concentrations of the model without covariates (A). The measured versus population-predicted blood propofol concentrations of the final model including the covariates weight, sex, and number of blocked segments (B). The measured versus the individual-predicted blood propofol concentrations of the final model including the covariates weight, sex, and number of blocked segments (C). The dashed lines represent the line of identity (Y = X), the red lines represent the super smoother through the data.

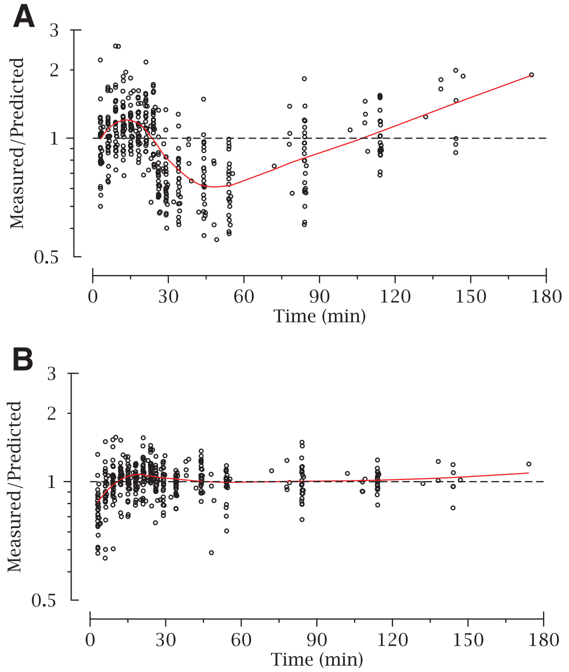

Figure 6. The performance error versus time of all measured blood propofol concentrations as based on the pharmacokinetics of Marsh et al., used in the target-controlled infusion device in this study (performance error; A) and on the basis of the model fit including weight, sex, and number of blocked segments (performance error; B). In red, the median performance error is presented as a continuous line.

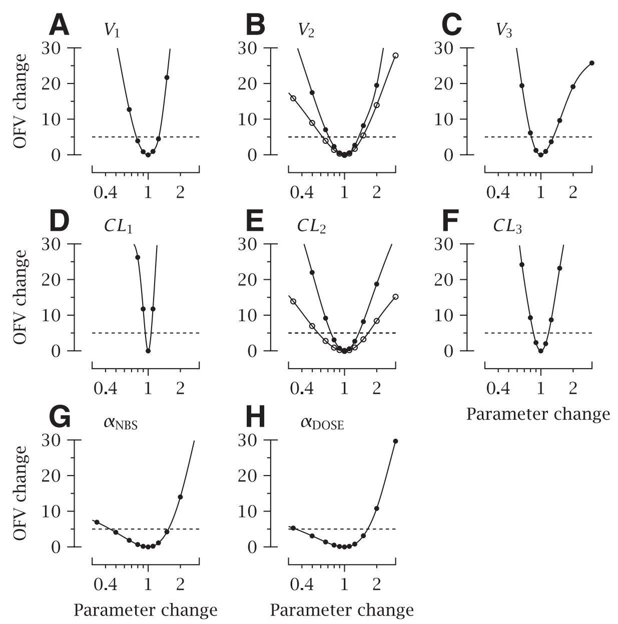

Figure 7. Likelihood profiles showing the change in objective function versus a relative change in the denoted parameter (A–H) while estimating the remaining parameters. The dashed line denotes a change of 5.02 points in objective function, indicating the $P = 0.025$ level. The crossings of the likelihood profiles with the dashed lines give a parameter range corresponding to a 97.5% confidence interval. For V_2 and CL_2, the closed and open dots denote the profiles for males and females, respectively. OFV = objective function value.

Figure 5A displays the measured versus population-predicted blood propofol concentrations without covariates, and Figure 5B displays the measured versus population-predicted blood propofol concentrations with covariates. Figure 5C displays the measured versus the individual-predicted blood propofol concentrations. These figures show that less variability remains after the inclusion of the 3 covariates, weight, sex, and NBS. Also, the super smoother more closely corresponds to the line of identity of the final model after inclusion of the 3 significant covariates.

Figure 6 represents the median performance error over time of the model used in the TCI device by Marsh et al. (A) and our final model based on the population values (B). Compared with the prediction from the TCI device, the final model has a narrower error window and is stable over time.

Figure 7 gives the log-likelihood profiles of the model parameters. The objective function is most sensitive to changes in the structural parameters (volume and clearances, A–F) and less sensitive to changes in the covariate coefficients (females, B and E) and effect of ropivacaine on propofol clearance (G and H). The crossings of the likelihood profiles with the dashed lines give a parameter range corresponding to a 97.5% confidence interval (note that a 99% interval would not include zero for these parameters).

Figure 8 shows the prediction-corrected visual predictive check of all patients as described in the Methods section. To test the power of the study, a leave-one-out procedure was performed, the median prediction error from the leave-one-out procedure (95% prediction error interval) was −10% (−48% to 54%).

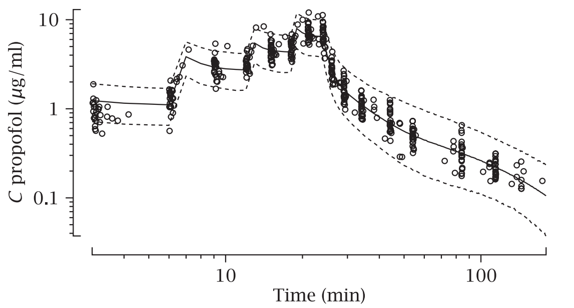

Figure 8. The prediction-corrected visual predictive check of 28 patients. The dashed lines represent the 95% prediction interval.

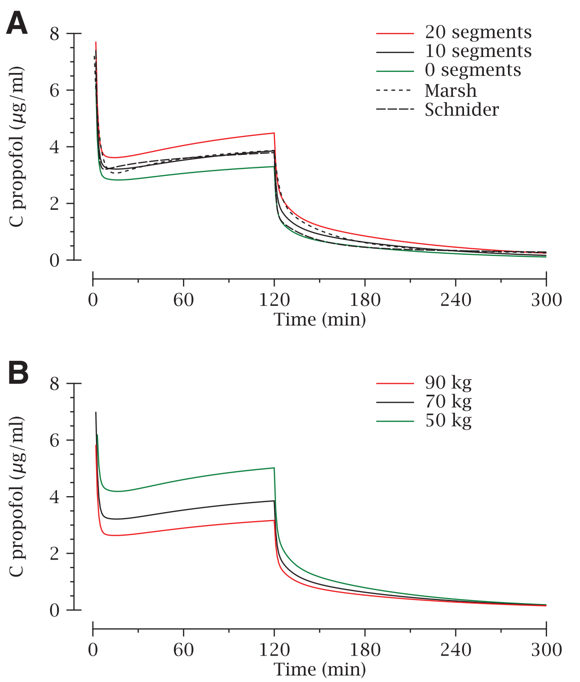

Figure 9. A, Computer simulation of the blood propofol concentration in the presence of 0 (green), 10 (black), and 20 (red) blocked segments with a propofol infusion scheme of 2 mg/kg administered in 1 min, followed by 8 mg/kg/h for 119 min, using the final model. The discontinuous lines represent the blood propofol concentration as predicted on the basis of the pharmacokinetics of Marsh et al. and Schnider et al. B, Computer simulation of the blood propofol concentration using the final pharmacokinetic model in a patient with a weight of 50, 70, and 90 kg with a propofol infusion scheme of 140 mg administered in 1 min, followed by 560 mg/h for 119 min.

Computer Simulation

As visible in the raw data, the computer simulations with the final model also revealed (Fig. 9A) that increasing the level of epidural blockade increased blood propofol concentration up to 30% after a standard propofol administration regimen (2 mg/kg propofol bolus followed by 8 mg/kg/h for 120 minutes). Figure 9B shows the influence of body weight on the pharmacokinetics when the propofol dosing scheme is not weight corrected. Obviously, when a 90-kg and 50-kg patient receive a similar propofol dose, the resulting blood propofol concentration is significantly lower in the 90-kg patient (weight affected all parameters).

Figure 10 shows the 50% plasma decrement time (i.e., the context-sensitive half-time) of propofol in the presence of an epidural blockade of 0, 10, or 20 segments. From this, one may conclude that epidural blockade significantly increases the 50% decrement time of propofol. This suggests that blood propofol concentrations will remain longer at higher levels after termination of the propofol infusion in the presence of epidural blockade. The figure also suggests that the decrement time is smaller in women compared with men.

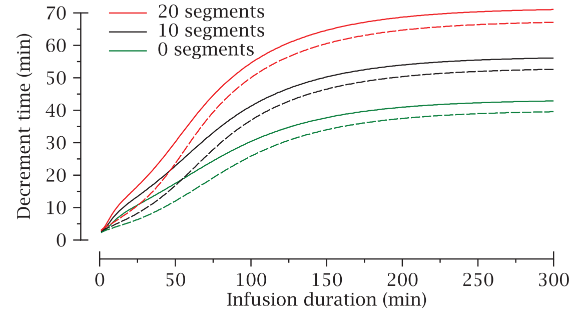

Figure 10. The 50% decrement time (= context-sensitive half-time) of propofol in the presence of 0, 10, and 20 blocked segments based on the final model fit for male (continuous lines) and female (discontinuous lines) subjects.

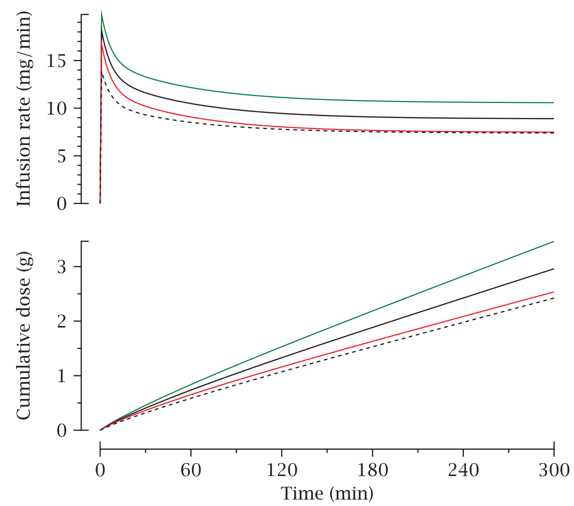

Figure 11. Computer simulation of the propofol infusion rate (upper panel) and cumulative propofol dose (lower panel) required to maintain a constant blood propofol concentration of 4 μg/mL in the presence of 0 (green), 10 (black), and 20 (red) blocked segments using the final model in a 70-kg female. The dashed lines indicate the infusion rate and cumulative dose in the absence of blocked segments times 70%.

In Figure 11, the required propofol infusion rate (mg/min) and cumulative propofol dose (g) to maintain a constant blood propofol concentration of 4 μg/mL are shown in time, in the presence of 0, 10, and 20 blocked segments. In the presence of 20 blocked segments, an approximately 30% lower propofol infusion rate and equivalently lower total propofol dose are required to assure the same blood propofol concentration when no epidural block is present.

DISCUSSION

We studied the influence of epidural blockade on the pharmacokinetics of propofol. The results of this study confirm our hypothesis that epidural blockade affects propofol pharmacokinetics. In the presence of an epidural blockade of 20 segments, blood propofol concentrations are elevated by approximately 30% because of a reduced propofol

elimination clearance. After exploring multiple models, sex was found to affect V_2 and CL_2. Sex and weight further improved the model fit.

Recent reports on the effect of neuraxial blockade on propofol pharmacology suggest that neuraxial blockade mainly affects the pharmacodynamics of propofol. This study, however, shows that epidural blockade affects the pharmacokinetics of propofol through a reduction in propofol clearance.

We successfully fitted a 3-compartment model to the data. Covariates were included in the model based on the BIC, evaluated for every possible combination of influence of a covariate on any of the 6 pharmacokinetic parameters. With our data set, the BIC required a change in NONMEM's objective function value of 6.03 points, close to the 6.63 required for a P value of 0.01 for a single test. The probability of finding an effect on any of the 6 parameters is >0.01 because of multiplicity, so likely close to the standard value of 0.05. A standard forward inclusion/backward elimination procedure would have resulted in the same final model (based on inspection of all objective function values). Significant covariates were weight, sex, and NBS (Fig. 5, A and B). Figure 6A and 6B shows the reduction in error and stability of model performance with the final model in comparison with the time-varying error seen with the predictions on the basis of Marsh et al. Note, however, that our data are best described by our model by definition and that any other model is bound to have a larger prediction error.

The likelihood profiles (Fig. 7) show that the elimination clearance of propofol is estimated most accurately as becomes clear from the steep and narrow shaped likelihood profile. This, while there is still some unexplained variability regarding the influence of NBS and ropivacaine dose, is represented by the shallower and wider shaped likelihood profiles. Further studies are needed to gain insight into this variability and obtain a more precise estimate of the effect of central neuraxis blockade on propofol pharmacokinetics. Last, the wider likelihood profile for women for V_2 and Cl_2 compared with men probably results from the smaller number of women included.

The mechanism through which epidural blockade affects propofol's elimination clearance probably is related to the epidurally induced hemodynamic alterations. Epidural blockade reduces systemic vascular resistance resulting from the blockade of the sympathetic nervous system. The consecutive venous pooling of blood results in a reduced preload, and thus reduced cardiac output. As a result of the reduced cardiac output and the altered mesenteric blood flow, epidural blockade is associated with a reduction in hepatic blood flow.[18,19] Because propofol has a high hepatic extraction ratio, changes in hepatic blood flow may readily produce changes in propofol elimination clearance. It may, therefore, well be that the epidural anesthesia-induced reduction in propofol elimination clearance that we observed is the result of a reduction in hepatic blood flow.

In comparison with the pharmacokinetics by Marsh et al.[10] and Schnider et al.,[20] the shallow and deep peripheral volumes of distribution in our parameter set are relatively small. This probably is because of the relatively short period of propofol infusion and the fact that in our study blood samples were taken only 120 minutes after termination of the propofol infusion. The elimination clearance we found exceeds hepatic blood flow, thus confirming that propofol is cleared also at extrahepatic sites like the kidney.[21] Hiraoka et al.[22] determined the elimination of propofol in patients undergoing cardiac surgery in other organs and found a renal extraction ratio of 0.70 ± 0.13. The renal blood flow, and thus renal clearance, may be influenced by epidural-induced sympathetic blockade, just as hepatic clearance may be affected, although renal autoregulation may interfere in this and maintain renal blood flow constant in the presence of a decreasing cardiac output.

With an increase in the epidural dose from 0 to 150 mg ropivacaine, the elimination clearance of propofol was reduced from 2.58 to 2.0 L/min (Fig. 4A). With the inclusion of the NBS as an individual covariate instead of the epidural ropivacaine dose, the elimination clearance of propofol decreased significantly from 2.64 to 1.87 L/min (from 0 to 20 blocked segments; Fig. 4B, objective function decreased from −512.742 to −526.464). In the final model, we included the NBS as an independent covariate. The better fit of the NBS as a covariate is explained by the fact that the hemodynamic response to epidural blockade is probably the driving force behind the influence of epidural blockade on propofol pharmacokinetics, and this is more closely related to the NBS than to the ropivacaine dose.

Figure 9A includes simulations based on our final model, as well as on the pharmacokinetic set by Marsh et al.[17] as based on Gepts et al.[23] and Schnider et al.[20] In the time frame of this study, and with the characteristics of this study population, the Schnider parameter set and Marsh parameter set produce results that are comparable. Both run parallel to the predictions based on our model with 10 blocked segments. In the absence of epidural blockade, like the situation in the patients of the Schnider population, our simulation overestimates the blood propofol concentration by approximately 15% compared with that of Schnider et al. In the presence of an epidural blockade of 10 segments, our simulation closely corresponds to that of Marsh et al. that was based on the data by Gepts et al.[23] who studied patients who received propofol in a majority of cases in the presence of locoregional blockade.

Pharmacokinetic interaction studies of propofol with opioids and other sedatives have shown an increase in the blood propofol concentration by up to 25% after combined administration of propofol with opioids or sedatives.[24,25] The pharmacokinetic interactions between propofol and these opioids or sedatives are, just as we find in this study, predominantly the result of hemodynamic alterations that cause reductions in hepatic blood flow and/or reductions in peripheral propofol distribution. The elimination and rapid and slow distribution clearances ($Cl_{1–3}$) of propofol are reduced in the presence of midazolam.[26] Similarly, the rapid and slow distribution and elimination of propofol are decreased in combination with alfentanil.[25]

In conclusion, the mechanism of action and magnitude of the effect of epidural blockade on the pharmacokinetics of propofol resemble the effect of opioids and other sedatives on propofol pharmacokinetics. Both are the result of hemodynamic alterations, both induce blood propofol concentration elevations by approximately 25% to 30%.

CONCLUSIONS

Epidural blockade affects the predictive accuracy of a TCI of propofol. With an increasing epidural blockade from 0 to 20 blocked segments, the measured blood propofol concentrations exceed those predicted by the Marsh pharmacokinetic parameter set[10] from 1% to 32%.

Epidural blockade affects the pharmacokinetics of propofol, such that with an increasing epidural blockade from 0 to 20 blocked segments the elimination clearance decreases from 2.64 to 1.87 L/min. In the presence of high epidural blockade, propofol dose may be reduced by approximately 30% to assure a similar blood propofol concentration compared with when epidural blockade is absent.

DISCLOSURES

Name: Elske Sitsen, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Elske Sitsen has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Erik Olofsen, MSc.
Contribution: This author helped design the study, analyze the data, and write the manuscript.
Attestation: Erik Olofsen has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Agnes Lesman, MD.
Contribution: This author helped design the study and conduct the study.
Attestation: Agnes Lesman has seen the original study data and approved the final manuscript.
Name: Albert Dahan, MD, PhD.
Contribution: This author helped design the study, analyze the data, and write the manuscript.
Attestation: Albert Dahan has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Jaap Vuyk, MD, PhD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Jaap Vuyk has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
This manuscript was handled by: Steven L. Shafer, MD.

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