Influence of central neuraxial blockade on anesthetic pharmacology and brain function

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Chapter 3

Epidural blockade affects the pharmacokinetics of propofol in surgical patients

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Introduction

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 an hypnotic sparing effect, the sensory blockade from spinal anesthesia itself has been associated with a sedative effect.[4] Lastly, Doherty et al. found that intravenous lidocaine decreased the MAC of halothane in a dose dependent manner in animals, suggesting that the systemic effects of local anesthetics may have direct sedative effects.[5,6]

Epidural blockade, through sympathetic output reduction and the direct vasodilating and myocardial depressant effect of local anesthetics,[7,8] may cause hemodynamic depression. Because sedative agents affect the hemodynamics as well, it is of importance 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 is unclear. The pharmacokinetics of intravenous 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 due to 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 randomized manner.

Materials and 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] American Society of Anesthesiologists status I or II patients, aged 18-65 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 up until the day before the investigation. Patients taking ß-blocking agents and patients taking chronic pain medication were excluded from the study. All patients denied smoking or consumption of more than 20 g of 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 BIS of 60 between epidural ropivacaine doses of 0 and 150 mg with 28 patients9. Patients who dropped out would be replaced.

Study design

This was a randomized double-blind study. The 28 patients were randomly assigned to one of four study groups of 7 patients. The randomization and preparation of the study medication was 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 taken out of 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, again closed, box to the hospital pharmacist.

After arrival in the operating room the un-premedicated 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 intravenous 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. Following 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.

Following 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 Life sciences). A preload of 500 mL of Voluven® was given in 15 min. 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%, ropivacaine 50 mg (7.5 mg/ml), ropivacaine 100 mg (7.5 mg/ml) or ropivacaine 150 mg (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 of NaCl 0.9%, 50 mg of ropivacaine 7.5 mg/ml (6.7 ml), 100 mg of ropivacaine 7.5 mg/ml (13.3 ml), and 150 mg of ropivacaine 7.5 mg/ml (20 ml), respectively. Assessments of the epidural blockade level were performed every 5 minutes during the first 30 min after epidural administration. Hypotension defined as greater than a 30% decrease in systolic blood pressure compared to control, was treated with phenylephrine 100 µg, intravenously. Bradycardia defined as a heart rate less than 40 beats/min was treated with atropine 0.5 mg intravenously.

The propofol infusion was started 30 min after epidural study medication administration using the target controlled infusion pump of Fresenius Vial Infusion Technology; called the Base Primea® using the propofol pharmacokinetic parameters reported by Marsh et al[10]. Patients received a target-controlled infusion 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 µg/ml, 4 µg/ml, and 6 µg/ml, respectively. The target-controlled infusion of propofol was terminated 24 min after its initiation. During the propofol infusion all patients received 100 % oxygen through a non-rebreathing mask.

After termination of the study, 120 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 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 two consecutive 5 min 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 prior to propofol administration. Arterial blood samples for blood propofol concentration determination were taken at 3, 6, 9, 12, 15, 18, 21 and 24 min after the start of the target controlled propofol infusion (the 6-, 12-, 18- and 24-minutes samples were taken just before the change in target concentration), and at 2, 5, 10, 20, 30, 60, 90, 120 and 150 min after termination of the propofol infusion. Blood samples were collected in potassium-oxalate coated syringes and stored at 4 °C. Propofol assays were carried out within 12 weeks in our laboratory. Propofol concentrations in blood were measured by HPLC-fluorescence at an excitation wavelength of 276 nm with emission wavelength of 310 nm.[11] The intra- and inter-assay coefficients of variation were 4.3% and 3.7% for propofol in blood in the concentration range of 0.06 – 14.0 µg/mL.

Pharmacokinetic modelling and covariate selection

The target-controlled infusion 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 Marsh's model10 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 three volumes, V_1, V_2, and V_3, describing the central volume of distribution, and the shallow and deep volumes of distribution, and three 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 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 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. Lastly, the dose of ropivacaine and number of blocked segments were evaluated simultaneously. The ropivacaine dose was incorporated by multiplying the pharmacokinetic parameters by factors $e^{((DOSE/75-1)*\alpha)}$. The number of blocked segments (NBS) was incorporated by multiplying the pharmacokinetic parameters by factors $e^{((NBS/10-1)*\alpha)}$. Parameter alpha denotes covariate coefficients that characterize how strongly the six 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.[14] All possible subsets were sequentially tested for covariates weight, sex, ropivacaine dose and the number of blocked segments.

The predictive accuracy of the Base Primea® TCI pump at various target concentration levels was compared between the epidural dose groups (0, 50 mg, 100 mg and 150 mg ropivacaine) with the multi-sample 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 x 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 number of blocked segments (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 (w^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 i-th 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 (E.O.).

Computer simulations.
The influence of the significant covariates (weight, sex and ropivacaine dose or number of blocked segments) 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-1.h-1 for 120 min.

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 yrs., with a body weight of 77.9 + 10.6 kg, a height of 177.6 + 11.1 cm and a BMI of 24.8 + 2.9. All patients were classified as American Society of Anesthesiologists class I or II.

In 3 patients hypotension was treated in total 8 times with intravenous phenylephrine, 100 µg.

In 2 patients intravenous atropine, 0.5 mg, 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 due to a combination of deep sedation and hemodynamic depression. The TCI of propofol therefore was 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 min each, and a total propofol dose of 400-500 mg was given in 24 min. All patients maintained spontaneous ventilation during the study. Patients returned to consciousness 16.3 + 5.2 min after termination of the propofol TCI.

With the ropivacaine dose increasing from 0 to 50, 100 and 150 mg, the number of blocked segments (median and (range)) increased from 0 (0-3) to 9 (3-15), 12 (9-14) and 15.5 (6-21), respectively (Figure 1). In 2 of the 7 patients who received 0 mg ropivacaine, 1 or more blocked dermatomes were recorded in the 30 min after the epidural administration of 10 ml of NaCl 0.9%, suggestive of an epidural induced placebo effect but which we consider a measurement error.

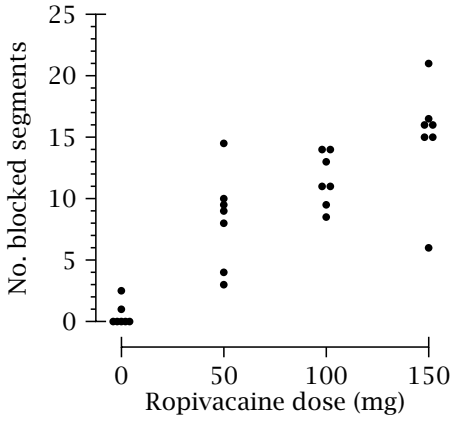

Fig. 1: The number of blocked segments of the individual patients in the 4 groups receiving 0, 50, 100 and 150 mg of ropivacaine in the epidural space.

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 number of blocked segments) 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; MDPE (25th - 75th %) increased in the patients that had received a ropivacaine dose of 0, 50, 100 and 150 mg from 1% (-10 to 16%), to 13% (-9 to 30%), 13% ((2 to 27%), P = 0.001 compared to placebo) and 32% ((6 - 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 to placebo), 18% (9 to 32%), (P = 0.033 compared to placebo) and 37% (19 to 62%), (P<0.0001 compared to 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 (Figure 2).

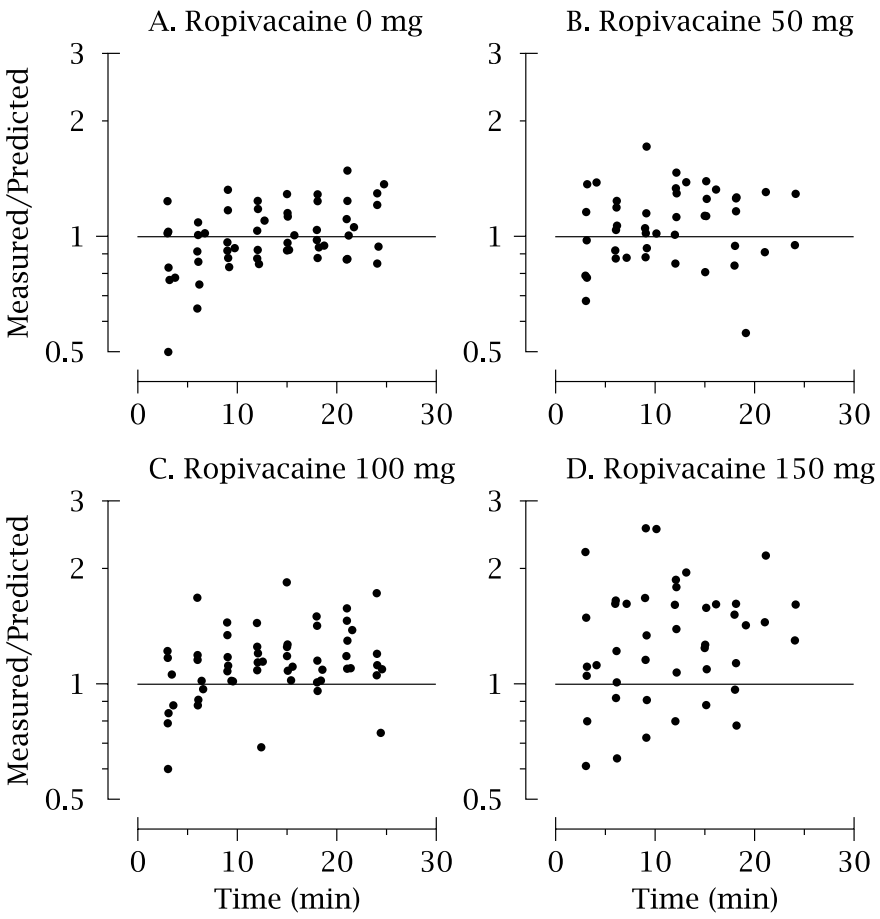

Fig. 2: The measured versus predicted propofol ratio's during a TCI of propofol using the Marsh parameter set in the patients of the 4 groups receiving 0, 50, 100 and 150 mg of epidural ropivacaine. The MDPE in patients of group A (1%) who received no epidural ropivacaine, increased to 13%, 13% and 29% in the patients of group B, C and D who received 50, 100 and 150 mg of 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 as based on the Marsh pharmacokinetics.

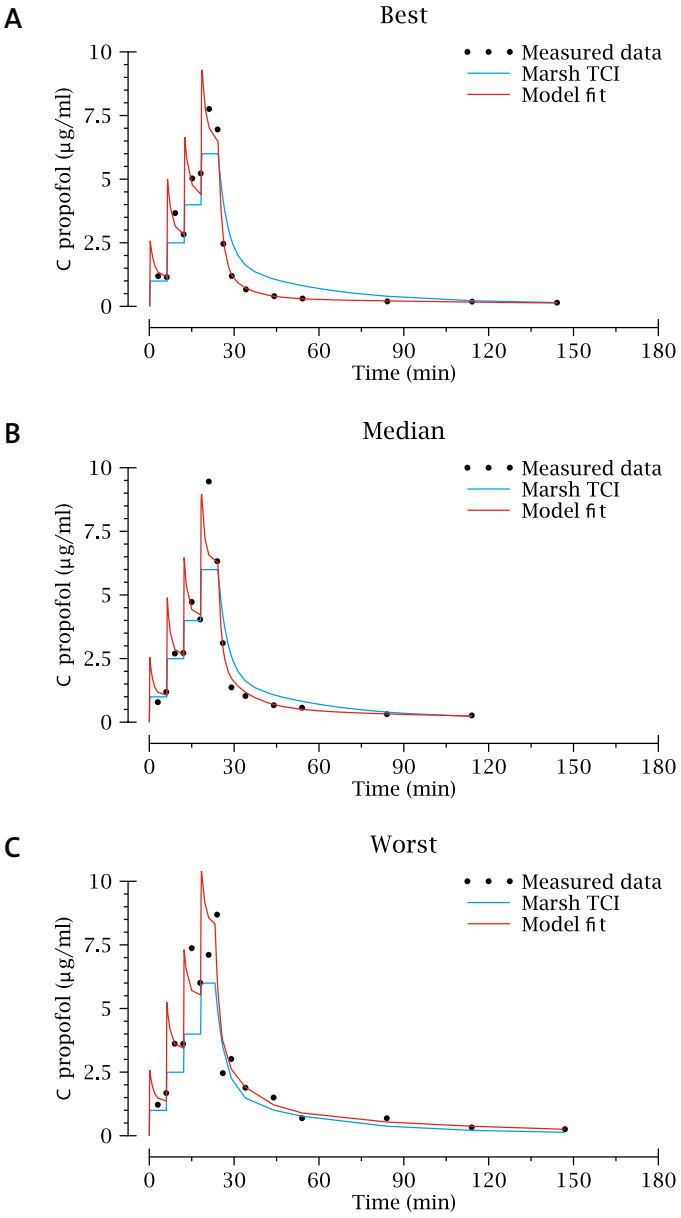

Fig. 3: The measured blood propofol concentrations in time in 3 patients that represent the best (panel A), median (panel B) and worst (panel C) fitted data according to the individual objective function values. The dots represent the measured blood propofol concentrations, the solid red line represents 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 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 if 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 an objective function value of -495.466, demonstrating that our data significantly support scaling propofol pharmacokinetics by weight.

Sex was added as 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 number of blocked segments were introduced concurrently in the analysis. The number of blocked segments (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 number of blocked segments 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 number of blocked segments.

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 number of blocked segments 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 . $e^{(-0.173 \cdot (NBS/10-1))}$. $(WT/70)^{0.75}$, 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.

Table 1. Pharmacokinetic parameters of propofol of the base model without covariates, model with weight, gender and dose as covariates and model with weight, gender and number of epidural ropivacaine-blocked segments as covariates.

Base Model	**Typical value**	**SEE**	**ω^2**	**SEE**
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	**Typical value**	**SEE**	**ω^2**	**SEE**
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	**Typical value**	**SEE**	**ω^2**	**SEE**
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		

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 and Cl_3: slow distribution clearance. M: male and F: female. SEE: standard error of the estimate in the preceding column; SDE: standard deviation of relative residual error(absolute error was not significant); - : not estimable; ω^2: interindividual variance (of log normally distributed parameters); αDOSE: covariate coefficient for dose ropivacaine. αNBS: covariate coefficient for number of blocked segments. The clearance and volume values for the dose model and the blocked segments model are standardized for a ropivacaine dose of 75mg or standardized NBS of 10.

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:
V_1 = 5.98 . (80/70) = 6.83 L; V_2 = 4.19 . (80/70) = 4.79 L; V_3 = 65.8 . (80/70) = 75.2 L
Cl_1 = 2.22 . $e^{(-0.173 \cdot (8/10-1))}$. $(80/70)^{0.75}$ = 2.54 L/min; Cl_2 = 0.724 . $(80/70)^{0.75}$ = 0.80 L/min; Cl_3 = 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 (Figure 4B).

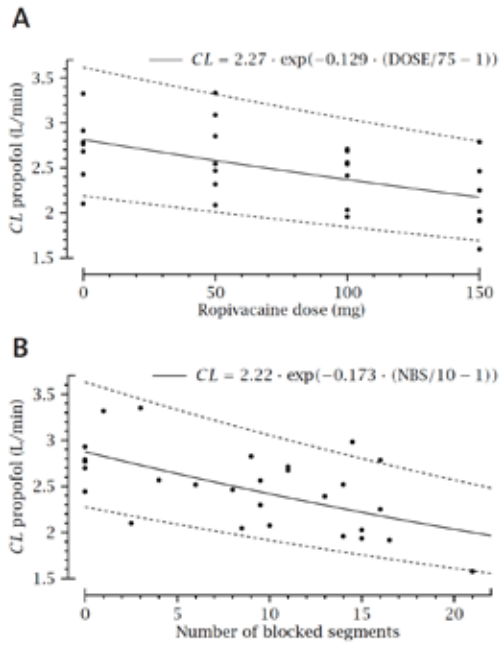

Fig 4: The influence of dose (Panel A) and the number of blocked segments (Panel B) on the clearance of propofol according to the final model fit. An epidural dose of 150 mg ropivacaine decreases the clearance from 2.58 to 2.0 L/min, 20 blocked segments reduces the clearance of propofol from 2.64 to 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 clearance for each patient.

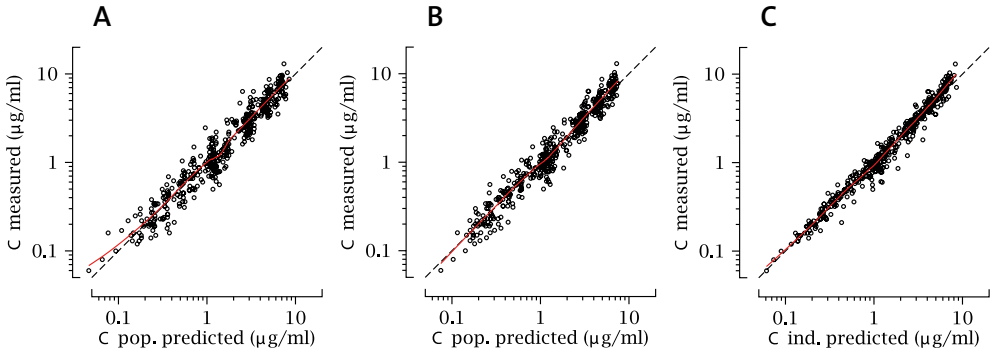

Fig 5: The measured versus population predicted blood propofol concentrations of the model without covariates (Panel A). The measured versus population predicted blood propofol concentrations of the final model including the covariates weight, sex and number of blocked segments (Panel B). The measured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

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 number of blocked segments. Also the super smoother more closely corresponds to the line of identity of the final model after inclusion of the 3 significant covariates.

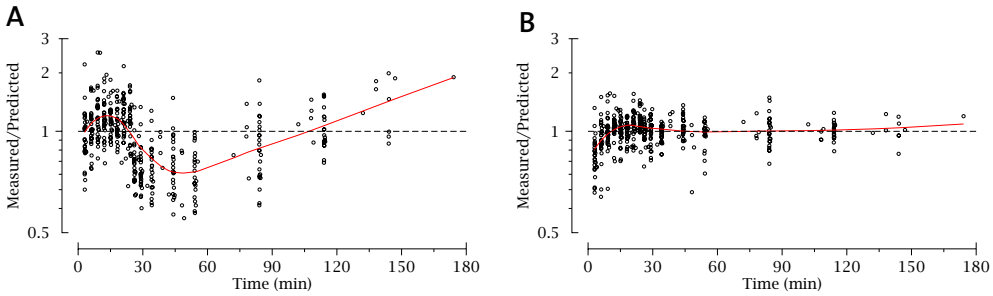

Fig 6: The performance error versus time of all measured blood propofol concentrations as based on the pharmacokinetics of Marsh et al., used in the TCI device in this study (Performance error; panel A) and on the basis of the model fit including weight, sex and number of blocked segments (Performance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

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

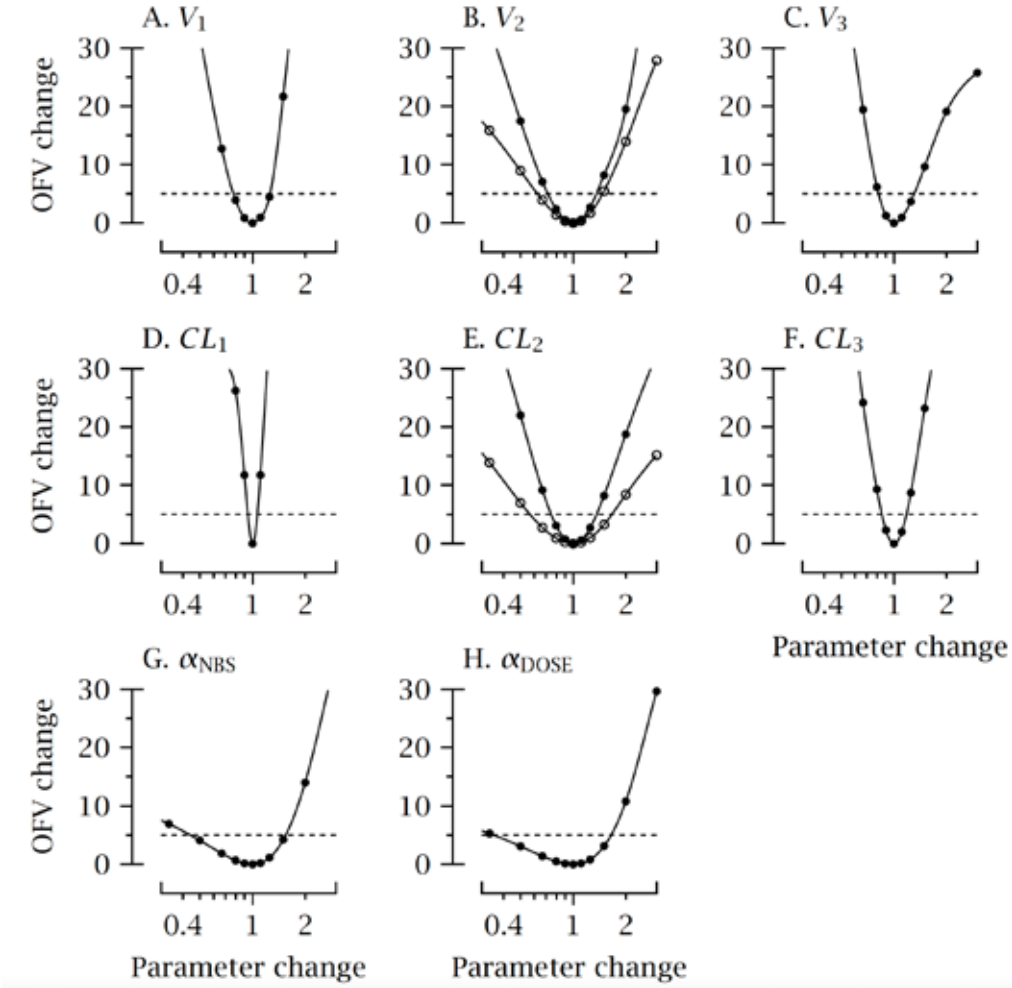

Figure 7: Likelihood profiles showing the change in objective function versus a relative change in the denoted parameter (A-H) while estimating the remaining parameters. The dashed line denotes a change of 5.02 points in objective function, indicating the p = 0.025 level. The crossings of the likelihood profiles with the dashed lines give a parameter range corresponding to a 95% confidence interval. For V2 and CL2 de closed and open dots denote the profiles for males and females, respectively.

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, E) and effect of ropivacaine on

propofol clearance (G, H). The crossings of the likelihood profiles with the dashed lines give a parameter range corresponding to a 95% confidence interval (note that a 99% interval would not include zero for these parameters).

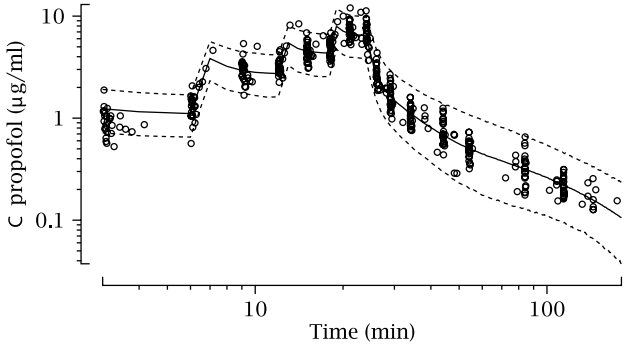

Fig 8: The prediction-corrected Visual Predictive Check of 28 patients. The dashed lines represent the 95% prediction interval

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) %.

Computer simulation

As visible in the raw data, the computer simulations with the final model also revealed (figure 9A) that increasing the level of epidural blockade increased blood propofol concentration up to 30% after a standard propofol administration regimen (propofol bolus of 2 mg/kg followed by 8 $mg.kg^{-1}.h^{-1}$ for 120 min). 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).

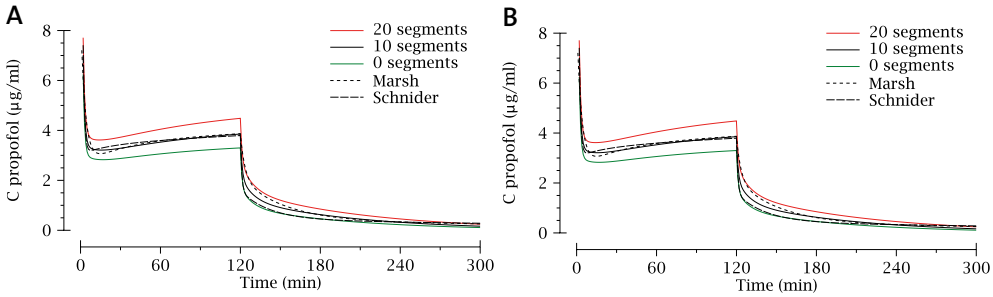

Fig 9A: Computer simulation of the blood propofol concentration in the presence of 0 (green), 10 (black) and 20 (red) blocked segments with a propofol infusion scheme of 2 mg/kg administered in 1 min, followed by 8 mg.kg-1.h-1 for 119 min, using the final model. The discontinuous lines represent the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

Fig 9B: 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-1 for 119 min.

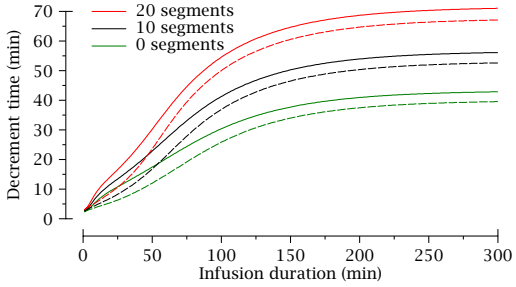

Fig 10: The 50% decrement time (= context-sensitive half-time) of propofol in the presence of 0, 10 and 20 blocked segments based on the final model fit for male (continuous lines) and female (discontinuous lines) subjects.

Figure 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 to men.

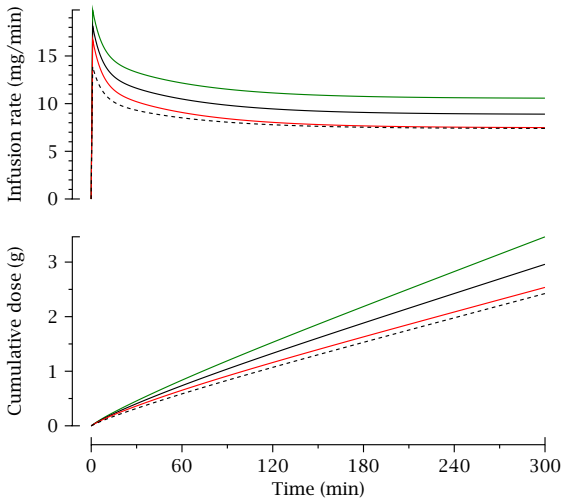

Fig 11: Computer simulation of the propofol infusion rate (upper panel) and cumulative propofol dose (lower panel) required to maintain a constant blood propofol concentration of 4 µg/ml in the presence of 0 (green), 10 (black) and 20 (red) blocked segments using the final model in a 70 kg female.

In figure 11 the required propofol infusion rate (mg/min) and cumulative propofol dose (g) to maintain a constant blood propofol concentration of 4 ug/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 about 30% due to 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 Bayesian Information Criterion (BIC), evaluated for every possible combination of influence of a covariate on any of the six 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 to find an effect on any of the six parameters is

larger than 0.01 due to 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 number of blocked segments (fig. 5A and 5B). Figures 6A and 6B show 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 is best described by our model by definition, and that any other model is bound to have a larger prediction error.

The likelihood profiles (Figure 7) show that the elimination clearance of propofol is estimated most accurately as becomes clear form the steep and narrow shaped likelihood profile. This, while still some unexplained variability exists regarding the influence of number of blocked segments and ropivacaine dose as is represented by the more shallow and wider shaped likelihood profiles. Further studies are needed to gain insight on this variability and obtain a more precise estimate of the effect of central neuraxial blockade (CNB) on propofol pharmacokinetics. Lastly, the wider likelihood profile for women for V2 and Cl2 compared to 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 sympathic 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 to 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 due to the relatively short period of propofol infusion and the fact that in our study setting blood samples were only taken until 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 in patients undergoing cardiac surgery the elimination of propofol 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 sympathic 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 of ropivacaine from 0 to 150 mg, the elimination clearance of propofol was reduced from 2.58 to 2.0 L/min (Figure 4A). With inclusion of the number of blocked segments 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 number of blocked segments as an independent covariate. The better fit of number of blocked segments as a covariate is explained by the fact that the hemodynamic response to epidural blockade probably is the driving force behind the influence of epidural blockade on propofol pharmacokinetics, and this is more closely related to the number of blocked segments than to the ropivacaine dose.

Figure 9A includes simulations based on our final model as well as on the PK set by Marsh[17] as based on Gepts[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 about 15% compared to that by Schnider et al. In the presence of an epidural blockade of 10 segments our simulation closely corresponds to that by Marsh et al. that was based on the data by Gepts et al. who studied patients who received in a majority of cases propofol 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, 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 resembles the effect of opioids and other sedatives on propofol pharmacokinetics. Both are the result of hemodynamic alterations, both induce blood propofol concentration elevations by about 25-30%.

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 set10 from 1% to 32%.

Epidural blockade affects the pharmacokinetics of propofol such that with an increasing epidural blockade from 0-20 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 about 30% to assure a similar blood propofol concentration as compared to when epidural blockade is absent.

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Chapter
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