Influence of central neuraxial blockade on anesthetic pharmacology and brain function

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Chapter 4

No interactive effect of lumbar epidural blockade and target-controlled infusion of propofol on mean arterial pressure, cardiac output and bispectral index; *A randomised controlled and pharmacodynamic modelling study*

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Introduction

Epidural blockade is offered to patients to provide intra- and postoperative analgesia. In the presence of a neuraxial blockade the intraoperative intravenous hypnotic and volatile anaesthetic agent dose requirements for adequate anaesthesia or sedation are reduced by about 25-62%.[1-9] In prior research a higher level of blocked segments induced by spinal or epidural anaesthesia results in a lower induction and maintenance dose of propofol to reach a certain level of sedation guided by the bispectral index monitor.[1, 3, 5, 7, 8] In animal experiments a transection of the spinal cord resulted in a decrease in anaesthetic requirements.[10] The general proposed explanation is a pharmacodynamic effect of epidural or spinal anaesthesia at supraspinal brain sites, whereby the reduction of afferent sensory input to the central nervous system, also known as deafferentation, is thought to mitigate this hypnotic-sparing effect.[11-14]

We recently studied the influence of epidural blockade on the pharmacokinetics of propofol. We hypothesized that the hemodynamic alterations associated with epidural blockade may affect the distribution, redistribution or clearance of propofol, a drug known for its lipophilicity and high hepatic extraction ratio. At an epidural ropivacaine dose that blocks up to 20 spinal segments, the propofol dosage for adequate hypnosis was reduced by 30% compared to a condition in which no epidural blockade was present. This is mainly the result of an epidural-induced reduction in propofol clearance from 2.6 to 1.9 L/min and consequently higher propofol concentrations in plasma. The reduction of hepatic and renal blood flow by the epidural anaesthetic best explains this pharmacokinetic interaction.[15]

Apart from a pharmacokinetic interaction, an additive pharmacodynamic interaction between epidural anaesthesia and propofol is also plausible, in line with prior research and the concept of spinal epidural-induced deafferentation. In the current analysis, we therefore quantified the influence of epidural blockade on propofol-induced changes in arousal state (as measured by bispectral index) and haemodynamics (mean arterial pressure and cardiac output).
We hypothesize that, apart from the above mentioned pharmacokinetic effect, epidural anaesthesia will affect propofol pharmacodynamics.

Materials and Methods

Subjects

Ethical approval for this study (Ethical Committee Leiden P10.087) was provided by the Ethical Committee of Leiden University Medical Centre, Leiden, The Netherlands (Chairperson Prof. R. Willemze) on 28 July 2010. Written informed consent was obtained from all subjects participating in the trial. Twenty-eight American Society of Anaesthesiologists status I or II patients, aged 18-65 years, scheduled for elective surgical procedures that required epidural anaesthesia, participated in this study, as previously described15. This is a secondary analysis of an earlier published data set on the pharmacokinetic interactive effects of lumbar epidural anaesthesia and propofol TCI.[15]

Study design

The study had a randomized, double-blind, parallel design. The 28 patients were randomly assigned to one of four study groups of 7 patients each. None of the patients received preoperative premedication. An intravenous line was placed in the forearm for administration of medication and fluids, and a second line for the infusion of propofol. Apart from standard monitoring, which included bispectral index monitoring (BIS VISTA) using a head electrode as specified by the manufacturer, an arterial line was placed in the left or right radial artery for blood sampling and continuous measurement of blood pressure. Furthermore, the cardiac output was calculated using the pulse-contour methodology from the intra-arterial blood pressure curve using the Vigileo device (Edwards Life Sciences, USA).

A lumbar epidural catheter was inserted at spinal level L2-L3 or L3-L4; the catheter was placed 5 cm into the epidural space. After baseline data were collected, the study drug was injected through the epidural catheter. Patients were randomized according to a computer-generated randomization list to receive placebo or one of three doses of the study drug (ropivacaine 7.5 mg/mL): Group 1, placebo (10 ml NaCl 0.9%); group 2, ropivacaine 50 mg; Group 3 ropivacaine 100 mg, Group 4 ropivacaine 150 mg. The study drug was administered by an anaesthesia nurse who took no further part in the study. After epidural anaesthetic level had stabilized, propofol was infused using a Base Primea® TCI system (Fresenius Vial Infusion Technology, France). The infusion algorithm was based on the propofol pharmacokinetic parameters reported by Marsh et al[16]. The initial propofol plasma concentration target was 1 µg/mL. After 6, 12 and 18 min the target concentration was increased to 2.5 µg/mL, 4 µg/mL and 6 µg/ml. The propofol infusion ended 24 min after its start. During the study period, 1-min averages of the three study endpoints, mean arterial pressure, bispectral index and cardiac output, were collected from baseline (prior to the epidural injection) until 2 hours after the start of the propofol infusion and stored in the patient data monitoring system (Metavision, iMD-Soft, Netherlands) for later analysis. Surgery started after the patients finished the study.

Arterial blood samples for blood propofol concentration measurement were taken at 3, 6, 9, 12, 15, 18, 21 and 24 min after the start of the propofol infusion, and at 2, 5, 10, 20, 30, 60, 90, 120 and 150 min after infusion ended. A blank blood sample (10 ml) was first obtained and used for calibration purposes. Propofol concentrations in blood were measured as described previously.[15]

Pharmacodynamic modelling and covariate selection

The data were analysed using NONMEM version 7.4.1 (Icon plc., Gaithersburg, MD, USA) using the First-Order Conditional Estimation with Interaction method. Blood concentration versus time profiles were calculated for each subject using the empirical Bayesian parameter estimates from the earlier published pharmacokinetic study.[15] These were linked to the sedative and hemodynamic parameters using a sigmoid-E_{MAX} model of the form:

$$Effect(t) = BLN + (E_{MAX} - BLN) \times [C_E(t)^{\gamma}/(C_{50}{}^{\gamma} + C_E(t)^{\gamma})]$$

where BLN is the effect at baseline, E_{MAX} the maximum predicted effect, C_{50} the concentration where the effect is halfway between BLN and E_{MAX}, and γ a steepness parameter. Relative to the plasma propofol concentration, the effect-site concentration C_E (t) was assumed to be delayed with half-life factor $t_{1/2}k_{eo}$, *i.e.* the blood-effect site half-life. Because of effects on haemodynamics of waking up, hemodynamic data were excluded when BIS exceeded baseline minus one.

The influence of two covariates was explored: the ropivacaine dose (ROPI), and the number of blocked segments (NBS). These were assumed to possibly affect parameters C_{50}, BLN, E_{MAX}, or shift the curve (affecting both BLN and E_{MAX}) by multiplying these parameters by factors exp(α*(NBS/10-1)) or exp(α*(ROPI/75-1)), where **α** is a covariate coefficient measuring the strength of the covariate influence. A change in the minimum value of the objective function (MVOF) of 6.61 was required for a covariate coefficient to have statistically significant influence (corresponding to P < 0.01).

Simulations

The influence of epidural blockade on the effect of propofol on mean arterial pressure and bispectral index was explored by simulating a single intravenous bolus dose of 2 mg/kg propofol, and a propofol bolus dose (2 mg/kg) followed by a 120 min propofol infusion of 8 mg.kg-1.h-1 for a 70 kg patient.

Results

The patients were recruited between December 2010 and February 2012. All 28 patients (17 men, 11 women) completed the study without adverse events and surgery started after the study period. The patients were aged 44.9 ± 15.1 years (mean ± SD), with body weight of 77.9 ± 10.6 kg, height of 177.6 ± 11.1 cm and body mass index of 24.8 ± 2.9 kg/m^2. All patients were classified as American Society of Anaesthesiologists class I or II. With the epidural ropivacaine dose increasing from 0 to 150 mg, the number of blocked segments (median [range]) increased from 0 [0-3] after placebo to 9 [3-15] after 50 mg ropivacaine, 12 [9-14] after 100 mg ropivacaine and 15.5 [6-21] after 150 mg ropivacaine. In Figure 1 the individual data of the effect of propofol on mean arterial pressure, cardiac output and bispectral index without epidural anaesthesia (panels A-C), following epidural injection of 50 mg ropivacaine (panels D-F), following epidural injection of 100 mg ropivacaine (panels G-I) and following epidural injection of 150 mg ropivacaine (panels J-L) are given. Prior to propofol infusion, the epidural blockade reduced mean arterial pressure from 103 ± 17 mmHg (0 mg ropivacaine) to 76 ± 18.7 mmHg (150 mg ropivacaine), without affecting bispectral index and cardiac output (Fig. 1 panels D-L, t = -30 to 0 min). In patients that received placebo rather than ropivacaine, propofol reduced the bispectral index from 97.6 ± 0.5 to 25.7 ± 7.5, mean arterial pressured from 100 ± 20.8 to 59 ± 10.1 mmHg, and cardiac output from 9.8 ± 2.7 to 5.65 ± 2.1 L/min (Fig. 1A-C). We compared the decrease of the mean of CO, MAP and BIS values of the 4 groups from reference value before epidural injection till end of propofol infusion. The ropivacaine dose does not significantly influence the final decrease.

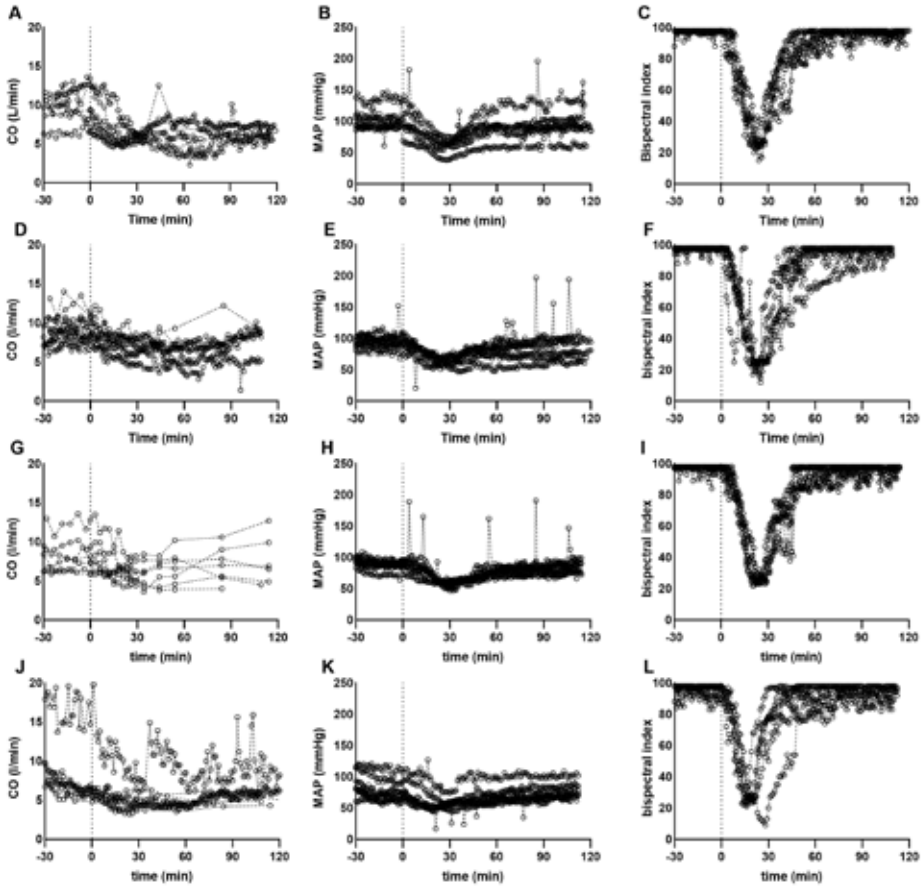

Figure 1. Individual 1-min averages of cardiac output (CO), mean arterial pressure (MAP) and bispectral index following epidural placebo (A-C), 50 mg epidural ropivacaine (D-F), 100 mg ropivacaine (G-I) and 150 mg ropivacaine (J-L).

Pharmacodynamic model analyses

Best, median and worst data fits of three patients are given in Figure 2, based upon the coefficient of determination (R^2) obtained from mean arterial pressure. Goodness of fit plots are given in Figure 3. Based upon the data fits and goodness of fit plots we conclude that all three endpoints were well described by the pharmacodynamic models. Table 1 gives the pharmacodynamic model estimates. For mean arterial pressure, adding covariates NBS or ROPI resulted in a decrease of the objective function value by 17 and 13 points, respectively. The best model was obtained with covariate NBS affecting BLN and E_{MAX} simultaneously with $\alpha = -0.17 \pm 0.03$ (Table 1); combining NBS and ROPI did not further improve the model. This indicates that the epidural blockade caused a downward shift of the propofol concentration-mean arterial pressure data without affecting propofol potency parameter C_{50}. Similarly, the two covariates had no effect on propofol C_{50} for bispectral index or cardiac output. C_{50} values

for bispectral index and mean arterial pressure were of the same order of magnitude, while the effect of propofol on cardiac output was more potent (C_{50} value about one-fifth of the values of bispectral index and mean arterial pressure). The absence of significant interactions between epidural anaesthesia and propofol pharmacodynamics is further illustrated by the response surfaces analyses (Figure 4). Finally, epidural blockade had no effect on the effect-site equilibration half-life of propofol for its hemodynamic effects ($t_{1/2}k_{e0}$ 11.5 ± 0.5 min), nor for its effects on the bispectral index ($t_{1/2}k_{e0}$ = 4.6 ± 0.4 min).

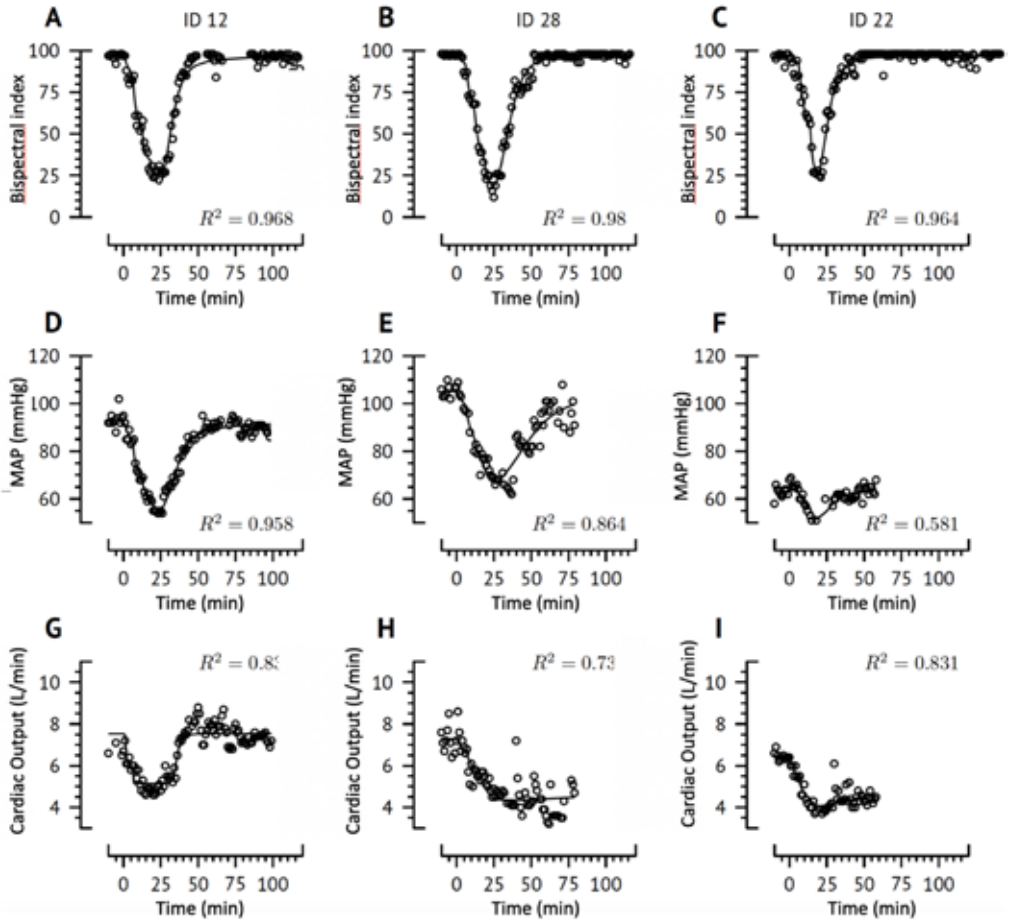

Figure 2. Best, median and worst data fits as determined by the coefficient of variation (R^2) of three patients. A-C: bispectral index, D-F: mean arterial pressure (MAP) and G-I cardiac output. The goodness of fit was determined based on the R^2 for mean arterial pressure. For bispectral index and cardiac output, the data are presented of the same patients as for mean arterial pressure. The dots represent the individual measured data, the solid lines represent the final model fits.

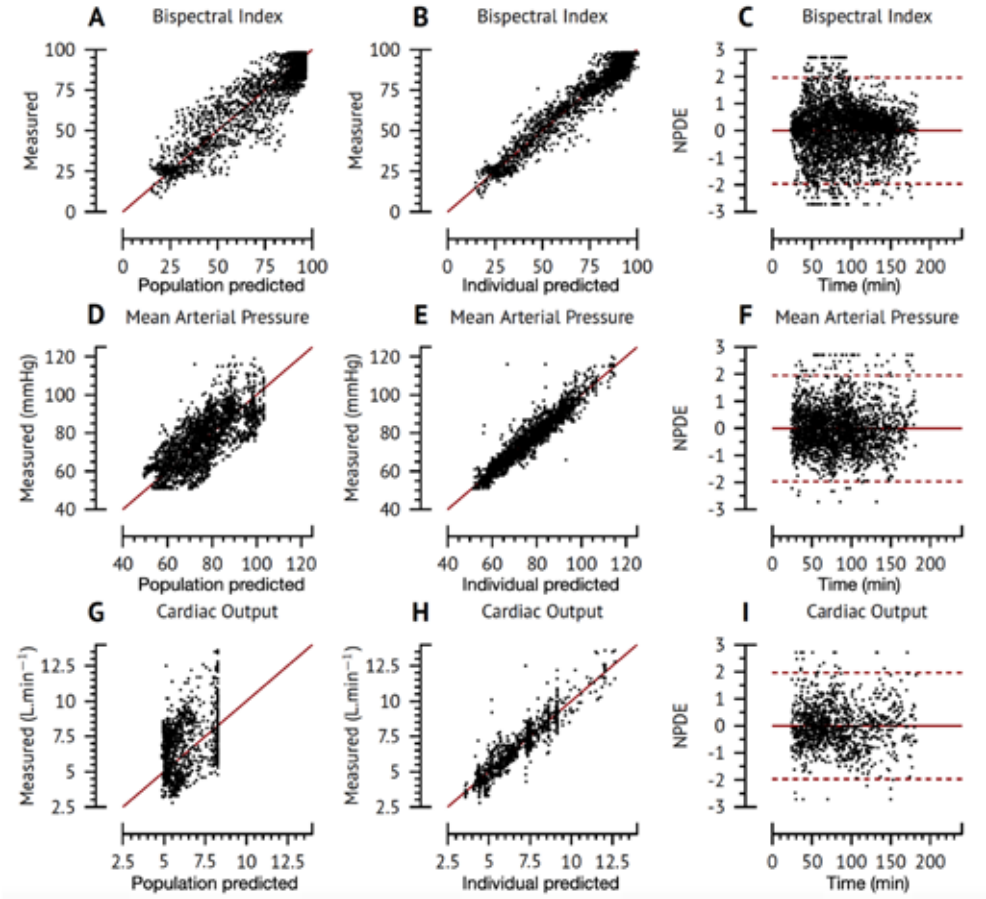

Figure 3. Goodness of fit plots for bispectral index (A-C), mean arterial pressure (D-F) and cardiac output (G-I). A, D and G: measured data versus population predicted data; B, E and H: measured versus individual predicted data; C, F and I: normalized prediction distribution errors (NPDE) versus time. The solid red lines are the lines of identity.

Table 1. Pharmacodynamic parameters of propofol with respect to its effect on bispectral index, mean arterial pressure and cardiac output.

Bispectral Index				
	Estimate	SEE	ω^2	SEE
BLN	96.6	0.46	0.0006	0.0002
Emax	0	#		
C_{50}	2.92	0.10	0.04	0.01
$t_{½}k_{e0}$ (min)	4.63	0.38	0.17	0.06
γ	1.97	0.11	0.07	0.04
Mean arterial pressure				
	Estimate	SEE	ω^2	SEE
BLN	87.5	0.90	0.008	0.002
Emax	43.1	3.64	0.06	0.03
C_{50}	2.12	0.20	0.08	0.04
$t_{½}k_{e0}$ (min)	11.5	0.50	0.33	0.08
γ	1.49	0.12	0.29	0.09
α	-0.17	0.03		
Cardiac output				
	Estimate	SEE	ω^2	SEE
BLN	8.27	0.37	0.06	0.02
Emax	4.57	0.18	0.17	0.13
C_{50}	0.64	0.02	0.18	0.19
$t_{½}k_{e0}$ (min)	29.8	0.82	1.82	0.59
γ	1.73	0.14	1.31	0.56

BLN = baseline value, Emax = maximal effect, C_{50} = 50% of maximal effect, $t_{½}k_{eo}$ = blood-effect site equilibration half-life, γ = parameter defining the steepness of the Emax curve, α = interaction parameter characterizing the influence of epidural blocked segments, SEE = standard error of the estimate. ω2 = between-subject variability.

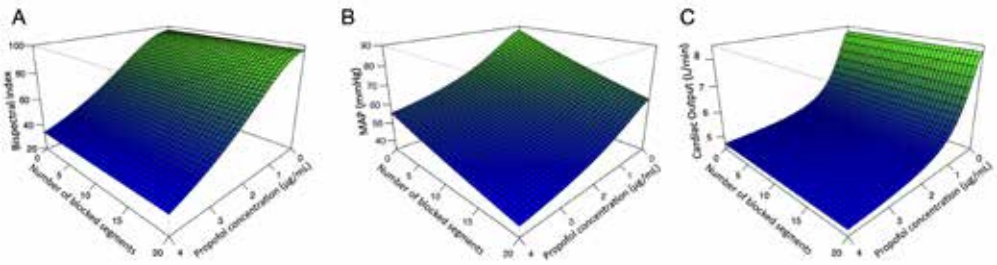

Figure 4. Response surfaces determined from the pharmacokinetic-pharmacodynamic analyses visualizing the interaction between the number of blocked segments (z-axis, NBS) and the measured propofol concentration (x-axis) for bispectral index (A), mean arterial pressure (MAP) (B) and cardiac output (C).

The results of the simulations of a propofol bolus and a bolus following by a 2 h infusion on propofol pharmacokinetics and pharmacodynamics (bispectral index and mean arterial

pressure) at 0, 10 and 20 blocked dermatomes are given in Figures 5. Following a propofol bolus, the epidural anaesthetic intensifies the effect of propofol on both endpoints (Fig. 5A-C). The epidural effect on bispectral index is probably due to the reduced clearance of propofol and thus the higher plasma propofol concentrations. The epidural effect on mean arterial pressure is related to the shift of the concentration-effect response (which is best explained by an epidural anaesthetic-induced reduction in sympathetic tone) and the higher plasma propofol concentrations. This same pattern becomes clear when propofol is given as bolus and continuous infusion (Fig. 5D-F). Bispectral index values are lower in the presence of an epidural block. Similarly, the epidural block causes a significant further reduction in mean arterial pressure, which only recovers slowly and partially after termination of propofol infusion.

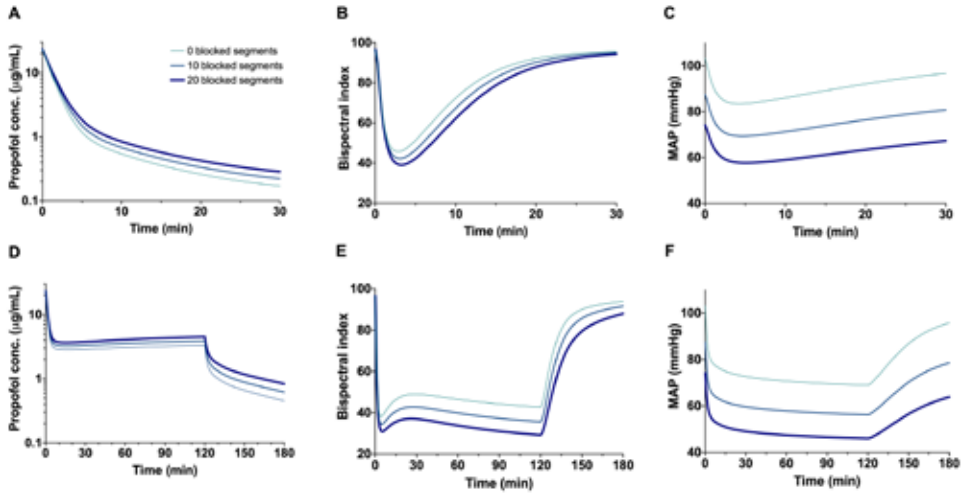

Figure 5. A-C. Simulations of the influence of 2 mg/kg intravenous bolus administration at 0, 10 and 20 blocked spinal segments. D-F. Simulations of the influence of 2 mg/kg intravenous bolus administration followed by a 2 hour infusion of 8 mg.kg^{-1}.h^{-1} at 0, 10 and 20 blocked spinal segments. Thin light green lines: 0 blocked segments, thin blue lines: 10 blocked segments, and thick blues lines 20 blocked segments. A. Propofol concentration; B. Bispectral index; C. mean arterial pressure (MAP).

Discussion

We quantified the interaction of epidural anaesthesia and intravenous propofol by population pharmacokinetic-pharmacodynamic analyses before scheduled surgery (*i.e.* the study was performed without nociceptive stimuli). Epidural anaesthesia, up to 20 blocked dermatomes, did not affect propofol sensitivity (as determined by potency parameter C_{50}) for mean arterial pressure, bispectral index or cardiac output and therefore had no significant pharmacodynamic interaction with propofol. We therefore refute the hypothesis that epidural anaesthesia changes propofol sensitivity for sedation, as measured by bispectral index.
Any effect of epidural anaesthesia on the three studied endpoints is best explained by a pharmacokinetic epidural-propofol interaction.[15]

Several earlier studies showed that epidural anaesthesia is associated with the reduction of volatile agent concentration and propofol requirement for sedative endpoints. For example, these studies showed that in the presence of epidural anaesthesia, the dose of propofol required to reach a certain predetermined BIS level is reduced by up to 64%.[4, 5, 7] A similar reduction in dose requirements was found for volatile anesthetics17-19 In these studies effective analgesia by spinal anaesthesia resulted in a reduction of propofol requirements during surgery but the haemodynamic values were kept in a predetermined range.[3, 8] In other studies that were executed during surgery, in case of insufficient analgesia, opioids were subsequently added. In these cases, nociception with hemodynamic responses were present and also kept within predefined ranges. Also under these circumstances significant less hypnotics were necessary to maintain predefined BIS values. [4-6]

These studies do not allow separation of the underlying cause, *i.e.* we remain uninformed whether the observed reduced anaesthetic requirements are related to epidural anaesthesia-induces changes in anaesthetic pharmacokinetics or pharmacodynamics. The idea that a neuraxial blockade enhances the pharmacodynamic effects of anaesthetics is related to the observation that deafferentation or the disruption of afferent and efferent signals between the central and peripheral nervous system is associated with detectable functional changes at cortical and subcortical sites.[12, 14] For example spinal cord injury produces abrupt irreversible deafferentation of cortical circuits leading to cortical reorganization.[20] These changes occur rapidly upon the induction of deafferentation and are related to neuronal adaptation and plasticity from rebalancing of excitatory and inhibitory neuronal processes upon the loss of afferent input. For example, spinal deafferentation is associated with a reduced pain threshold above the level of the anaesthetic block,[21] improved sensory or motor performance and, in case of maladaptive plasticity, phantom limb pain.[22-24] In case of epidural anaesthesia, e.g. temporary deafferentation, it was hypothesized that central changes in response to epidural deafferentation are responsible for enhanced anaesthetic sensitivity.

An earlier analysis of the current data set showed that epidural anaesthesia changed propofol pharmacokinetics with a 30% reduction of propofol elimination clearance. In the current analysis that focused on the interaction between epidural anaesthesia and propofol pharmacodynamics, the only significant finding was that epidural blockade lowers mean arterial pressure with increasing numbers of blocked segments and thereby aggravates the subsequent cardiovascular depression by propofol. No effect of epidural anaesthesia was observed on propofol sensitivity for its effect on mean arterial pressure, bispectral index or cardiac output. Consequently, we conclude that in our study epidural deafferentation (or any other central effect of epidural anaesthesia) is not causally related to the observation that anaesthetic requirement is reduced during epidural anaesthesia.

Our estimated pharmacodynamic parameters closely correspond with earlier findings.[25-27] In agreement with Kazama et al. the effect-site equilibration half-life of propofol for its effect on mean arterial pressure is considerably longer than for its effect on the bispectral index (11.5 versus 4.6 min). This suggests that after induction of anaesthesia the peak hemodynamic depression is delayed compared to the peak depressant effect of propofol on bispectral index. According to our simulations this delay in the peak depression in mean arterial pressure versus bispectral index is clinically negligible. In contrast, in the recovery phase, the bispectral index rapidly approaches baseline values, whereas mean arterial pressure remains depressed for a prolonged period of time, even at plasma propofol concentrations at which patient may be expected to have regained consciousness. This is partially explained by the prolonged effect-site equilibration half-life for mean arterial pressure depression, but may also related to the small difference in C_{50} between mean arterial pressure and bispectral index (2.12 µg/mL *versus* 2.92 µg/mL, Table 1). Figure 5 furthermore show that this prolonged depression of mean arterial pressure after propofol induction is aggravated by the epidural blockade of 10 and 20 blocked segments. In clinical practice, it is therefore expected that hemodynamic depression will persist even after return of consciousness and that this especially holds true in the presence of epidural blockade.

Our results have an important consequence for the performance of target-controlled infusion systems during epidural anaesthesia. When propofol is infused by TCI, the change in propofol concentration is easiest captured after a long infusion period, when distribution kinetics are no longer relevant and the infusion just compensates the clearance. In that case, the steady-state concentration equals infusion/clearance. The steady-state concentration is equal to the target concentration setting of the TCI system (CTarget) when the clearance is as expected *i.e.*, without epidural anaesthesia. Substituting the covariate equation for the clearance from our pharmacokinetic study, we have:

$$C(NBS) = \text{infusion} / [2.22 \times \exp(-0.173 \times (NBS/10-1))],$$

with CTarget equals the propofol plasma concentration when there is no epidural blockade, C(NBS=0). This may be rewritten as

$$C(NBS) = CTarget * \exp(0.173 \times (NBS/10)).$$

So, with increasing numbers of blocked segments, the attained propofol concentration is increasingly higher than expected based on the TCI setting. At 20 blocked segments, the plasma concentration is 41% greater than expected.

Eleveld at all developed a pharmacokinetic/dynamic model based on a wide range of data from 30 studies, using BIS as endpoint. Local regional or regional techniques were present in 2 of the 30 included studies. The concomitant use of local anaesthetics can differ certain parameters in

the model. Number of blocked segments due to neuraxial blockade is not included as covariate in the model.[28]

In conclusion, in the presence of lumbar epidural blockade 30% less propofol is needed to reach and maintain adequate sedation, in our study conditions performed before surgery. This is unrelated to enhanced propofol sensitivity. The number of blocked segments after ropivacaine lumbar epidural injection aggravates the hemodynamic depressant effects of propofol directly, but also indirectly by reducing propofol elimination clearance leading to higher blood propofol concentration. Pharmacodynamic effects of combined lumbar ropivacaine and propofol TCI, measured by BIS monitoring, is unrelated to enhanced propofol sensitivity but limited to a pharmacokinetic phenomenon.

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Chapter
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