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Epidural anaesthesia with levobupivacaine and ropivacaine : effects of age on the pharmacokinetics, neural blockade and haemodynamics

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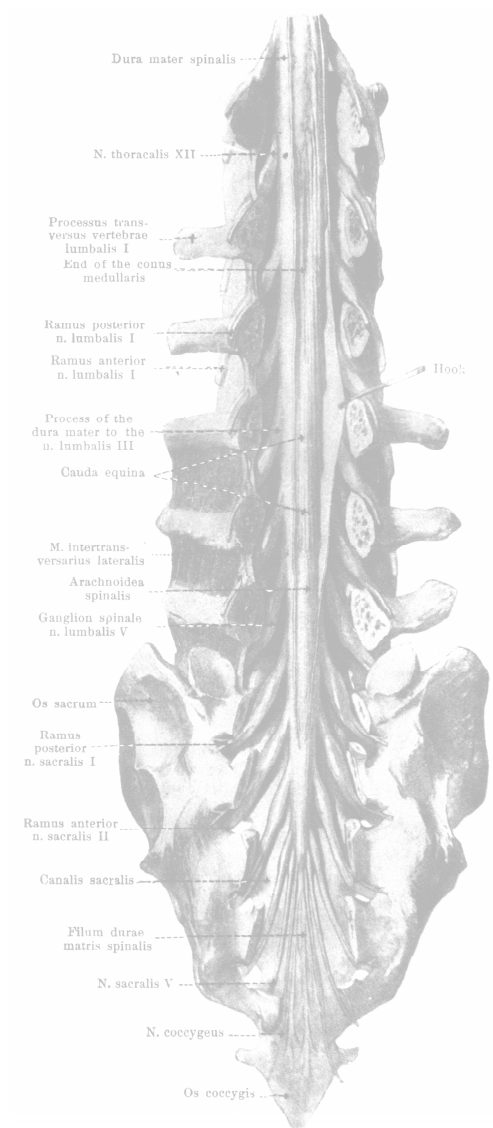
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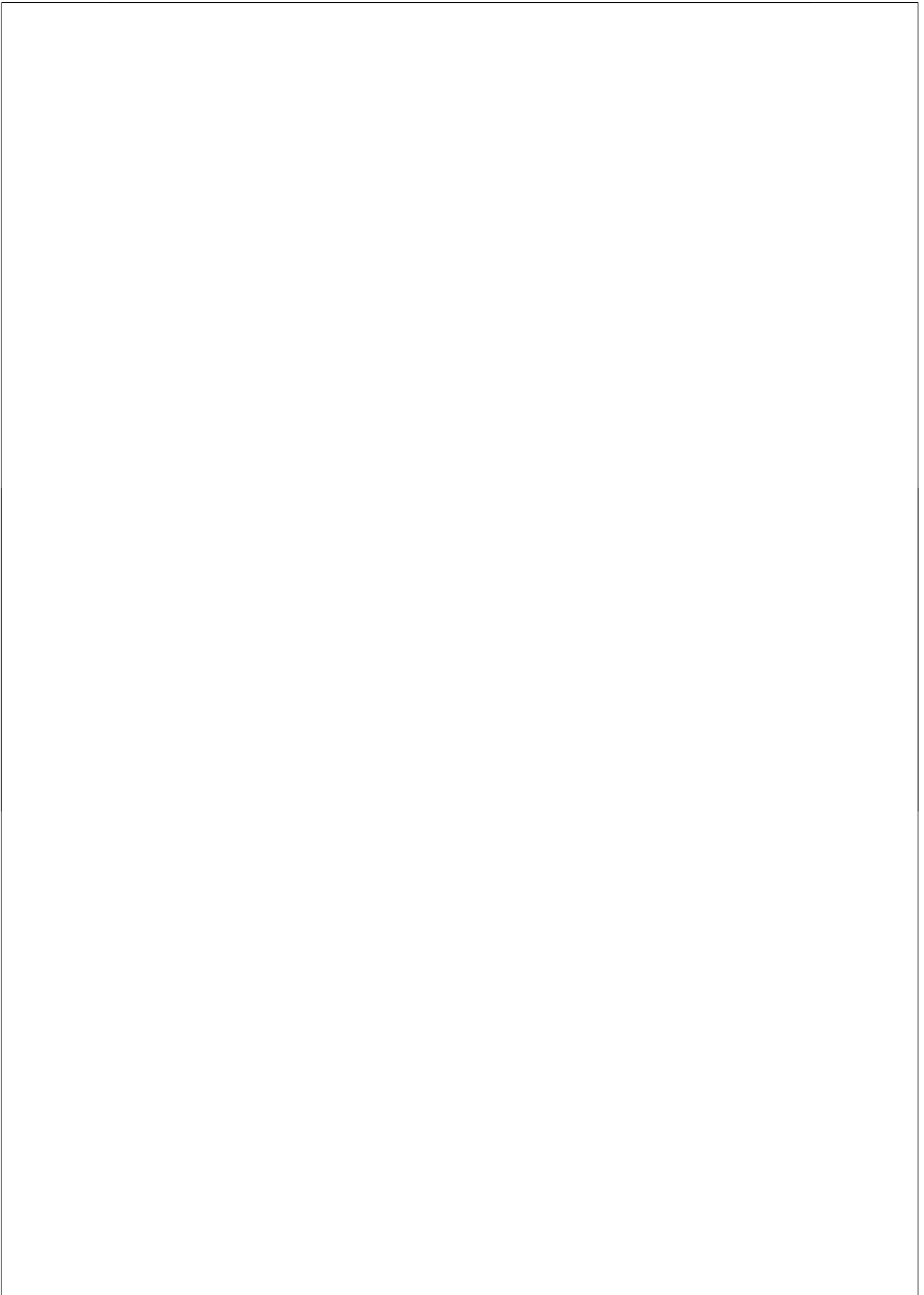
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Section IV



Modelling



**POPULATION PHARMACOKINETIC/PHARMACODYNAMIC
MODELING OF EPIDURAL ANESTHESIA**

CHAPTER 13

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Epidural anaesthesia is obtained by the administration of local anaesthetic drugs into the epidural space. The characteristics of the ensuing neural blockade such as onset, intensity and duration of sensory blockade depend directly on the changes in the concentration of the local anaesthetics at the axonal membrane, which are dependent on pharmacokinetic factors. The rate of systemic absorption of local anaesthetic gives some indication of the relationship between neural blockade and the amount of drug remaining at or near the site of injection. In the last two decades we measured indirectly residual epidural drug concentrations by estimation of the time course of systemic absorption from the epidural space in humans.¹⁻⁵ These data were analysed on an individual basis and enabled the characterization of individual anaesthetics (including the effect of various covariates, such as age) but did not allow the development of predictive pharmacokinetic/pharmacodynamic (PK/PD) models.

The development of population PK/PD models of epidural anaesthesia is important since it enables the description of both within and between subject variability, enables the development of predictive models, and may improve therapeutic outcome of future patients.⁶ Schnider *et al.*⁷ developed a population PD model to describe the time course and blockade level of spinal anaesthesia. The objective of our study was to develop a population PK/PD model that will predict more precisely the dose requirements of local anaesthetics for epidural anaesthesia. In the analysis the amount of the drug present at the site of action at each dermatome based on the absorption kinetics was estimated allowing for the reduction of the variability of the PD part of the model. A population-based pharmacokinetic re-evaluation was performed to obtain optimal individual absorption parameters for the pharmacodynamic part of the model. The local anaesthetic agents bupivacaine, ropivacaine and levobupivacaine were investigated. Various covariates, such as age, weight, height and sex, were entered into the model.

Methods

The data described in this paper are derived from five previous studies from our department on the epidural single-shot administration (1 ml.s⁻¹) of bupivacaine (two studies),^{1,2} levobupivacaine (two studies)^{3,4} and ropivacaine (one study)⁵ (Table 1). In the studies central venous (bupivacaine) or arterial (ropivacaine and levobupivacaine) blood samples were obtained before, during and after the epidural administration of the local anaesthetic up to 24 h. When after the epidural administration of the unlabelled local anaesthetic agent satisfactory anaesthetic conditions (*i.e.*, the presence of a bilateral sensory blockade, assessed by pinprick) were obtained (usually 15–20 min after the epidural administration) a stable-isotope-labelled analogue (in abovementioned studies: deuterium- or ²H₃-) of the local anaesthetic under investigation was infused intravenously

for the estimation of the disposition kinetics of that local anaesthetic. Absorption kinetics were determined by deconvolution with the use of the disposition kinetics and the plasma concentration of the epidurally administered unlabelled local anaesthetic. In addition, neural block characteristics of sensory blockade were obtained, using pinprick, every 15 min during the first 4 h, thereafter every 0.5 h until the sensory block had completely resolved.

Table 1. Number of patients and observations included in the PK/PD-modelling.

Patients (<i>n</i>)			
	Pharmacokinetic analysis	Pharmacodynamic analysis	Male/Female
Bupivacaine ^{1,2}	25	25	24/1
Levobupivacaine ^{3,4}	42	39	28/14
Ropivacaine ⁵	24	24	22/2
Total	91	88	
Observations (<i>n</i>)			
	Pharmacokinetic		Pharmacodynamic
	Epidural	Intravenous	
Bupivacaine ^{1,2}	561	422	721
Levobupivacaine ^{3,4}	1003	598	994
Ropivacaine ⁵	525	341	725
Total	2089	1361	2440

Pharmacokinetic Analysis

The data were pooled to three treatment groups (bupivacaine, levobupivacaine and ropivacaine) despite some differences in dose, sampling schedules and patient characteristics. The pharmacokinetic analysis was performed in four steps:

1. two- and three-compartment models were fitted to the $^2\text{H}_3$ -concentration data;
2. a model including covariates was developed;
3. a model consisting of two parallel absorption compartments and two- or three-disposition compartments (*i.e.*, the model of disposition, which was developed in step 2) was fitted to the epidurally administered unlabelled local anaesthetic concentration-time data. The disposition parameters were fixed to their Bayesian values obtained in step 2;
4. a model including covariates was developed.

The absorption compartments were characterized by the following parameters: F_1 and F_2 (the fractions absorbed during the fast and slow absorption phase, respectively), and $t_{1/2,a1}$, $t_{1/2,a2}$ (the absorption half-lives of the fast and slow absorption phase, respectively).

Statistical analysis was performed with the NONMEM software package (a data analysis program for non-linear mixed effects modelling)* using a population approach.

Pharmacodynamic Analysis

Each segment is modelled by its own central and peripheral absorption compartments (Figure 1). The absorption parameters describe the transport between these compartments and the central disposition compartment. Furthermore, an effect-site is postulated. The effect-site concentration is assumed to lag behind the central absorption compartment concentration with rate constant k_{e0} . Finally, it is assumed that a sensory blockade occurs when the effect-site concentration ($C_e(t)$) exceeds a certain effect-site concentration threshold C_{thr} .

Each segment is described by the following six parameters: F_1 , F_2 , $t_{1/2,a1}$, $t_{1/2,a2}$, $t_{1/2,k_{e0}}$ and C_{thr} . Furthermore, rate constants between the segments need to be defined that describe the transport of the anaesthetic between segments. However, there are only two observations per dermatome, and there are only global rather than local absorption process parameters available from the PK analysis. So, there are more parameters than observations. The following assumptions allow us to proceed:

- The longitudinal spread of the epidural space across segments occurs instantaneously;
- The parameters F_1 , F_2 , $t_{1/2,a1}$ and $t_{1/2,a2}$ are equal for each segment, albeit F_1 and F_2 are interpreted with respect to the fraction of the dose that is present in each segment after the initial spread.

Under these assumptions, both the local and global (obtained by adding all local absorption profiles) processes are described by the same parameters as those obtained

* Beal SL & Sheiner LB. University of California San Francisco (1999).

from the PK analysis. If the local absorption processes would be subject to large variability, it is unlikely that the global absorption profile (obtained from deconvolution) would display such a clear biphasic pattern. We therefore believe that the above stated assumptions are reasonable.

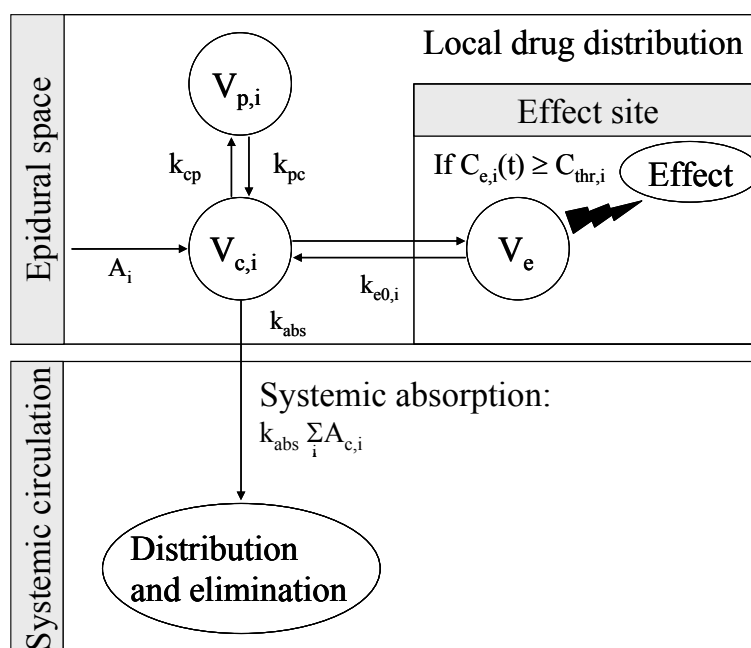


Figure 1. Graphic representation of the epidural PK/PD model, as described in this chapter. Note that this represents the processes that take place at one spinal segment. The global epidural model is the sum of the local processes occurring in the epidural space at each segmental level (see text).

The likelihood of observing the data is the product of the probabilities of all observations per dermatome. By maximizing this likelihood using custom made software written in the computer language C using the free GNU Scientific Library (<http://www.gnu.org/software/gsl>) (E. Olofsen, 2005), the parameters of the PD model can be obtained: $t_{1/2k_{e0,i}}$ and S_i which are the equilibration half-life of segment i and the anaesthetic sensitivity at segment i , which is derived from parameters $C_{thr,i}$, $V_{c,i}$ (the central absorption volume of segment i) and A_i (the amount of anaesthetic in segment i). Note that per dermatome different values for $t_{1/2k_{e0,i}}$ and S_i may be obtained.

Possible improvement of the model fit by inclusion of covariates (age, weight, height and sex) was explored. Covariates were included by multiplying S_i or $t_{1/2k_{e0,i}}$ by the ratio of the covariate value and the median of the covariate to the power α , the value of which was estimated.

95% confidence intervals of the parameters were obtained by using the likelihood profile, *i.e.*, the interval of each parameter was determined for which the increase of the objective function of the data fit remained under 3.84. In this way a measure of significance was obtained for each segment separately.

Results

Pharmacokinetic Analysis

The population pharmacokinetic analyses of the absorption, as well as the disposition parameters yielded similar results as those obtained in individual analyses reported previously.¹⁻⁵

Pharmacodynamic Analysis

Figures 2-4 show the probability of a sensory blockade *versus* time for each dermatome of the three local anaesthetics tested. These graphs were constructed after estimation of the distributions of $t_{1/2k_{e0,i}}$ and S_i .

Parameter values

Parameter $t_{1/2k_{e0}}$ had a value of 0.2 h at the L2 and L3 dermatome levels. At higher and lower segments the value of $t_{1/2k_{e0}}$ showed an increase to 0.4 h at levels L5 to S5 and 0.3 h at levels Th6 to Th4. The between subject variability was about 50% (ranging from 20% at S2 to 70% at Th2). The smaller value of $t_{1/2k_{e0}}$ at levels L2-L3 could be related to differences in distribution of the anaesthetic in the epidural space close to the site of injection. The anaesthetic sensitivity was 3 from segment S5 to Th10 and then showed a gradual decrease to 1 at Th3. Assuming that the sensitivity of the nerves does not vary across segments, the decrease in S_i is due to the smaller amount of anaesthetic (A_i) reaching the higher segments.

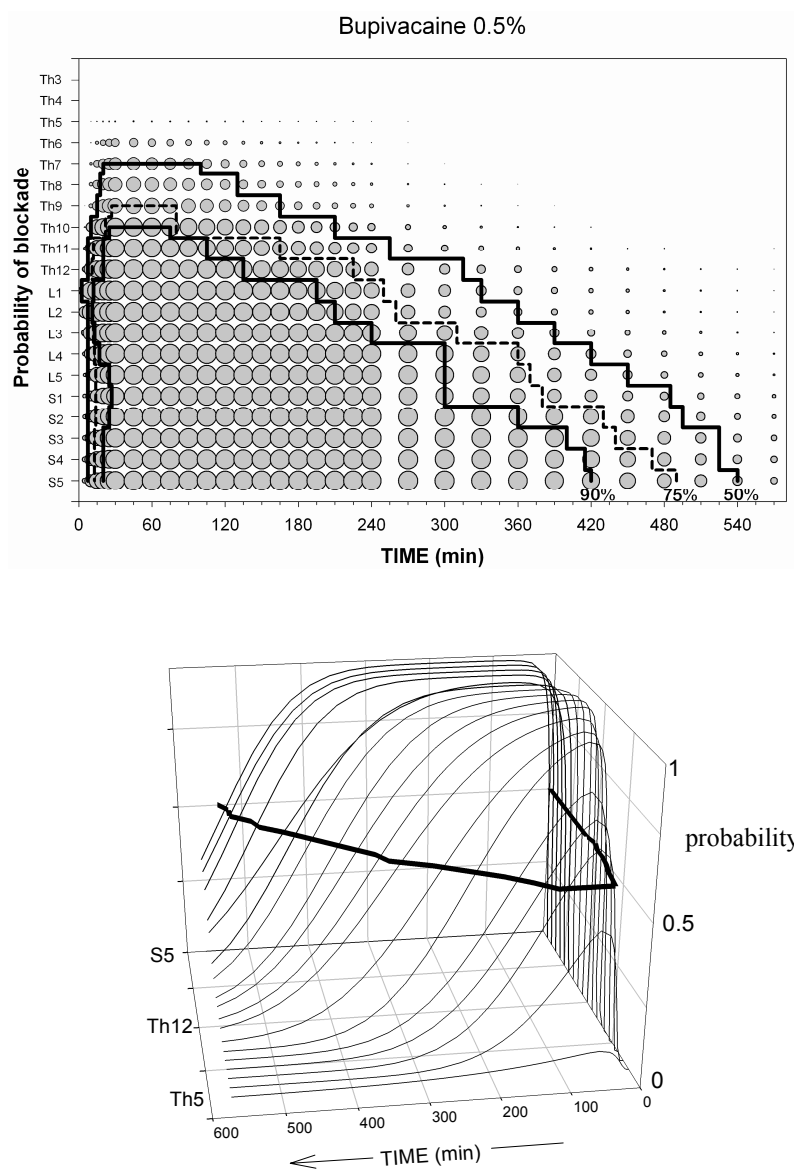


Figure 2. Upper panel: Population pharmacodynamic analysis of the effect of 23 ml of bupivacaine 0.5% on epidural anaesthesia. Each circle represents the probability of blockade where size is linked to the magnitude of the probability. The iso-probability lines represent 50%, 75% and 90% probability of blockade. Lower panel: 3D representation of the bupivacaine effect. Thick line is the 50% iso-probability line. XYZ-axis represent segment level – time – probability of sensory blockade.

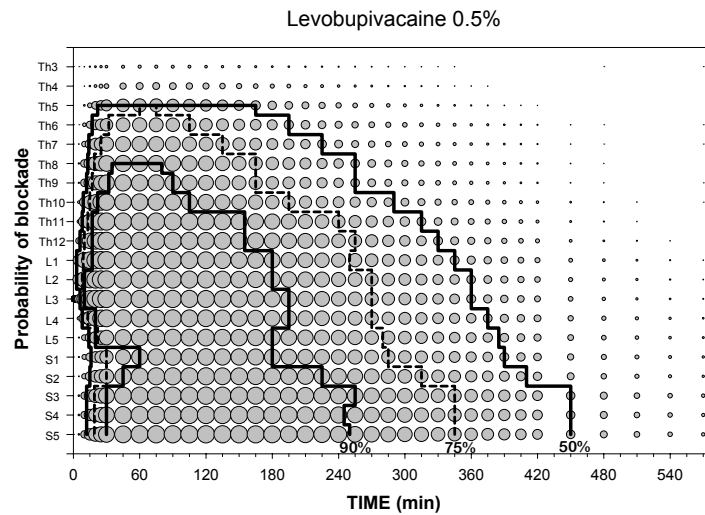


Figure 3. Population pharmacodynamic analysis of the effect of 19 ml of levobupivacaine 0.5% on epidural anaesthesia. Each circle represents the probability of blockade where size is linked to the magnitude of the probability. The iso-probability lines represent 50%, 75% and 90% probability of blockade.

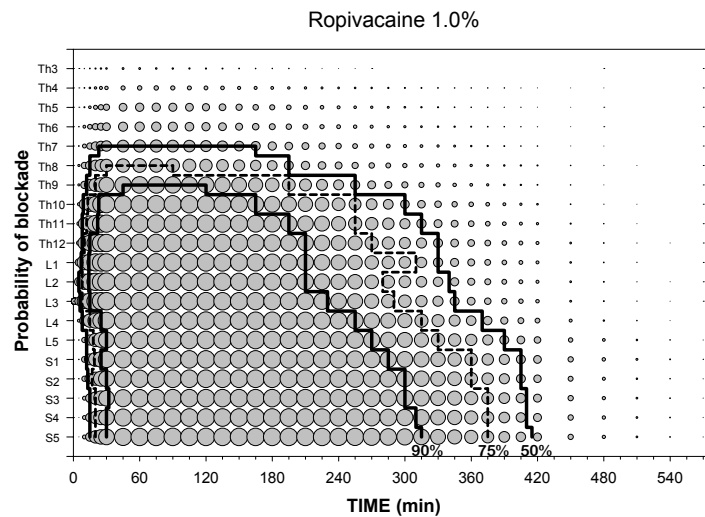


Figure 4. Population pharmacodynamic analysis of the effect of 15 ml of ropivacaine 1.0% on epidural anaesthesia. Each circle represents the probability of blockade where size is linked to the magnitude of the probability. The iso-probability lines represent 50%, 75% and 90% probability of blockade.

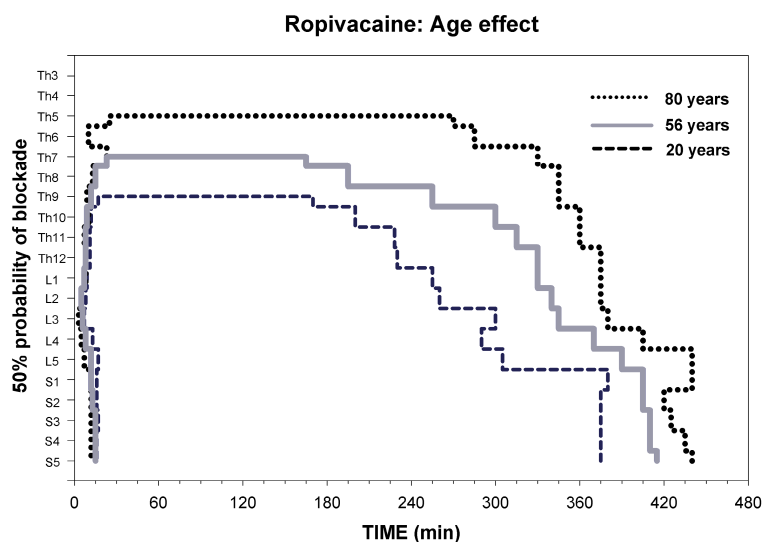


Figure 5. Influence of age on ropivacaine 1.0% induced epidural anaesthesia. Fifty percent isoproability lines represent a 20-years old patient (broken line), a 56-years old patient (continuous line; median age of the study population) and a 80-years old patient (dotted line). Note the age effect on block height and duration of effect.

Covariate analysis

AGE: For all three anaesthetics, age increased anaesthetic sensitivity at segments Th10 and higher ($\alpha = 0.25$ for bupivacaine and levobupivacaine, and about 0.89 for ropivacaine). This indicates, for example for ropivacaine, that the sensitivity is 40% of the median at age 20, and 137% of median at age 80. Age reduced the value of $t_{1/2}k_{e0}$ of bupivacaine at segments L1 and lower ($\alpha = -0.84$) and of levobupivacaine across most segments ($\alpha = -0.76$). However, no significant effect was seen for ropivacaine. In Figure 5 the effect on the probability of blockade at three ages is given for ropivacaine. Note that with increased age the level of sensory blockade increases, as does the duration of anaesthetic effect.

WEIGHT: An effect of weight on S_i was observed for bupivacaine only (average value of $\alpha = -0.56$) across all segments and significant at 7 segments. Height did not affect $t_{1/2}k_{e0}$.

HEIGHT: Height decreased S_i for bupivacaine at Th12 and higher ($\alpha = -3.4$), for ropivacaine at Th8 and higher ($\alpha = -6.3$), but not significantly for levobupivacaine. Height did not affect $t_{1/2}k_{e0}$.

SEX: Only for levobupivacaine sex could be included as a covariate (PD data were available from 23 men and 12 women). Sex did not affect S_i . Across all segments, the value of $t_{1/2k_{e0}}$ was about 20% greater for women and 20% smaller for men relative to the population value. The sex effect was significant at segments L1-Th7.

Discussion

We performed a PK/PD analysis of epidural anaesthesia and successfully developed a predictive model with emphasis on several covariates (*i.e.*, age, sex, weight and height). The population PK analysis yielded similar parameter estimates as obtained from individual data estimates with several significant covariates (data not included). The PK/PD model was able to predict the probability of block and duration of anaesthesia per segment. In addition, covariate analysis showed that age, being the most important factor in this study, influenced the spread and duration of analgesia. However, other covariates, such as height, weight and sex, also significantly influenced the parameters of the model.

PK/PD modelling of the epidural space may be regarded as a mathematical description of the processes, involved with the local drug distribution in the epidural space.⁶ These processes, occurring after administration of the drug at the site of injection until it reaches the site of action, consist of longitudinal spread and local tissue distribution. They determine the characteristics of the neural blockade, because they influence the changes in the concentration of the local anaesthetics at the axonal membrane. Local anaesthetics reach their sites of action, *i.e.*, the spinal roots and the spinal cord, by penetration of the meninges and by passive diffusion through the CSF. A high initial concentration gradient ensures the exceeding of the threshold value for neural blockade. However, these nerve blocking effects are counteracted by the uptake of the local anaesthetics in epidural fat and vascular structures, lowering the concentration at the effect site. Uptake in the epidural fat lowers the perineural concentration but may also prolong the duration of block. Vascular structures present in the epidural space cause systemic uptake and elimination of the neural blocking action of local anaesthetics.

The systemic absorption is the ultimate result of the processes that are involved with local drug distribution. Thus, the rate of systemic absorption of local anaesthetic contains some information about the relationship between neural blockade and the amount of drug remaining at or near the site of injection. However, the exact concentrations at the effect site are not known. For local anaesthetics the systemic absorption may be described with a two-exponential absorption model in an individual compartmental model.⁸ The initial absorption phase may represent rapid uptake, promoted by the high concentration gradient from the epidural space into the vascular structures that are present in the epidural space.

The much slower secondary phase may represent the slow release from the epidural fat of the highly lipophilic long-acting local anaesthetics and uptake into the systemic circulation.

In our institute, absorption kinetics has been determined after epidural administration of bupivacaine, levobupivacaine and ropivacaine.¹⁻⁵ Stable-isotope-labelled analogues (or deuterium- or $^2\text{H}_3$ -) were intravenously infused to obtain disposition kinetics. Subsequently, with the use of the disposition kinetics and the plasma concentration of the epidurally administered unlabelled local anaesthetic the absorption kinetics could be obtained by deconvolution. The plasma concentration-time curves of individual patients were adequately described by fitting directly the aggregated model of two parallel first-order absorption compartments and its disposition profile (a two or three compartmental model). These analyses allowed the determination of the profiles of the different local anaesthetics, but also the effects of several covariates, such as age.

However, the individual analyses may be hampered by interindividual variability, caused by genetic, environmental and pathophysiologic factors.⁶ A population approach of these data may be attractive, because it can explain a part of the wide variability by incorporating covariates, such as type of local anaesthetic agent, age, sex, height and weight. In addition, it enables the development of models, which are able to make predictions about certain clinically important end-points. This may, consequently, improve therapeutic outcome in future patients. The data obtained in the earlier mentioned studies are suitable to develop a population-based PK/PD model using non-linear mixed-effects modelling, because the data may be collected at different times and the data may be unbalanced.

To our best knowledge, this is the first PK/PD model developed for lumbar epidural administration of local anaesthetics. For spinal anaesthesia, Schnider *et al.*⁷ developed a population based pharmacodynamic model, using mixed-effect modelling. Their model adequately described the time course of central neural blockade in each individual, when using all measurements ($R^2 = 0.9$). In addition, the model was also able to predict offset of effect, using the Bayesian parameters for each individual, calculated from the population parameters and the measurements of level of analgesia up to 30 min ($R^2 = 0.71$). In contrast to their model, that was only able to predict the highest level of anaesthesia, in our model we are able to predict sensory blockade and duration at any segmental level.^{7,9}

Although the Schnider model is applicable to epidural anaesthesia it is unable to predict sensory blockade at lower levels than the maximum block height. Furthermore, since they did not take into account PK data (disposition and absorption) and hence the local anaesthetic concentration, their PD data analysis is contaminated by PK variability. Although this seems of limited importance when treating and predicting epidural

anaesthesia in a new patient, the inclusion of covariates on the PK data will improve the prediction of sensory anaesthesia in this particular patient using our model.

We observed that the sensitivity to the three anaesthetics, expressed by parameter S_i , decreased with segment height. This is probably related to the fact that S_i is a combination parameter and to the lower amount of anaesthetic that reaches the higher segments caused by anatomical (physical) factors. However, this decrease is different for the three anaesthetics. The decrease is steepest for bupivacaine: with adequate anaesthesia at the lower segments, the probability of block at high thoracic segments is lowest for bupivacaine. Furthermore, the sensitivity is smallest for levobupivacaine. So while the absorption characteristics cause this anaesthetic to be concentration-efficient (data not shown), this is counteracted by its lower sensitivity. Ropivacaine was found to have the lowest speed of onset and offset (as expressed by $t_{1/2}k_{e0}$), followed by bupivacaine and levobupivacaine. The physicochemical properties of ropivacaine are similar to those of bupivacaine and levobupivacaine, except for its lower lipid-solubility. As lipid solubility is related to potency, ropivacaine may be less potent.¹⁰

One potential drawback of our model is the underlying essential assumption that rostral and caudal spread of the anaesthetic in the epidural space is instantaneous and subsequently remains unchanged (apart from absorption). In reality, the local anaesthetic spreads with a certain delay. Incorporation of a segment-dependent delay is not feasible as we only have two measurements per dermatome (onset and offset times of blockade). Note that the $t_{1/2}k_{e0}$ is not the delay to the segments but the delay from the segment to the effect-site (*i.e.*, spinal roots and spinal cord). Consequently, we just slightly may have underestimated the value of $t_{1/2}k_{e0}$. Furthermore, the results that we present here are valid for the specific volume of the local anaesthetic given as well as the location of the epidural puncture (L3-L4 interspace). Interestingly, DERNEDDE *et al.*,¹¹ showed that volume *per se* has little or no effect on sensory block height and quality of anaesthesia. We may assume, however, that the epidural spread of the anaesthetic is different for different volumes injected and depends on the site of injection. Dose is the most important factor affecting spread of epidural anaesthesia.¹¹ The higher the dose of a given local anaesthetic, the greater the spread. This is due to the fact that at increased dose the local concentration of anaesthetic at the effect sites is large enough to exceed the threshold for sensory blockade, while at lower dose but increased volume the local concentration is insufficient to exceed the threshold for blockade.

We observed an important age effect for all three anaesthetics, which was that anaesthetic sensitivity increased at the higher segment levels (Th9 and higher). Onset and offset of the sensory blockade, as expressed by parameter $t_{1/2}k_{e0}$, appears to be faster with increased age, possibly due to changes in epidural fat with increased age. Anatomical and physiological changes, associated with advancing age, may affect the nerve block characteristics and the

pharmacokinetics following epidural administration of local anaesthetics. A declining number of neurons, deterioration in myelin sheaths in the dorsal and ventral roots, changes in the anatomy of the spine and intervertebral foramina may contribute to altered nerve block characteristics following an epidural anaesthesia.^{12,13} Furthermore, the number of axons in peripheral nerves decreases with advancing age, and the conduction velocity diminishes, particularly in motor nerves.¹³⁻¹⁵ With increasing age, changes in the connective tissue ground substances may result in changes in local distribution, *i.e.*, in the distribution rate of the local anaesthetic from the site of injection (the epidural space) to the sites of action.¹² The most probable mechanism of an increased anaesthetic sensitivity with age is an age-dependent change in the longitudinal spread of the anaesthetics in the epidural space. This is evident because we observed an increased sensitivity with age at the higher segments only. The reduced loss of anaesthetic *via* sclerotic intervertebral foramina during its rostral spread with increasing age may explain the observed age effect. The higher level of analgesia in older patients may as well be attributed to a greater sensitivity, such that with the same local anaesthetic concentrations at higher thoracic segments, blockade occurs in older, but not in younger patients. Consequently to obtain comparable epidural blocks, smaller doses of local anaesthetic solutions should be administered to older as compared to younger patients.

In earlier studies, the effects of height and weight on epidural spread have not been clearly demonstrated.¹⁶ In the present analysis we found that increased weight decreases the sensitivity for bupivacaine, but not for levobupivacaine and ropivacaine. An increased height decreases the sensitivity to bupivacaine and ropivacaine, but only at the higher (thoracic) segments. Furthermore, we found a sex effect on $t_{1/2k_{e0}}$ with a faster response in men (tested for levobupivacaine only). This is conform the results of Sarton *et al.*,¹⁷ who observed a greater opioid speed of onset/offset in men relative to women. These variations in $t_{1/2k_{e0}}$ are probably caused by changes in the local distribution of the anaesthetic (*i.e.*, kinetic changes), for example due to differences in epidural fat content between the sexes. Uptake into extraneural tissues, such as epidural fat, limits the rate and extent of drug distribution to the nerves and thereby reduces clinical potency.⁸

In conclusion, we successfully developed a predictive PK/PD model of epidural anaesthesia in humans. We were able to demonstrate the importance of age on the spread of the sensory blockade as well as on the speed of onset/offset of blockade. Our model allows us to study various important variables and factors in epidural anaesthesia such as the site of epidural injection, the volume of the injected fluid, combined spinal-epidural injections, anaesthetic-opioid interaction and pregnancy. Furthermore, our model may be used in the development and study of new local anaesthetics for epidural use.

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