Modeling the Anesthetic Effect of Ropivacaine after a Femoral Nerve Block in Orthopedic Patients

A Population Pharmacokinetic–Pharmacodynamic Analysis

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ABSTRACT

Background: Even though ropivacaine is frequently used during orthopedic surgery, the relationship between plasma concentrations and degree of sensory anesthesia after a peripheral nerve block is currently unknown. The aim of this study was to characterize this relation using population pharmacokinetic–pharmacodynamic modeling.

Methods: Femoral nerve block was performed by the anterior approach using a single injection (20 ml) of 0.5% ropivacaine hydrochloride in 20 patients scheduled for total knee arthroplasty under spinal anesthesia. Sensory thresholds in response to a gradual increase in transcutaneous electrical stimulation (primary endpoints), loss and recovery of ice-cold sensation, as well as total ropivacaine plasma concentrations were determined up to 4 days after administration of the local anesthetic. Using NONMEM (ICON, USA), sensory block was modeled by assuming an equilibration delay (k_{e0}) between amount in the depot and effect-site compartments.

Results: Mean effect-site amount producing 90% of the maximum possible effect (AE_{90}) was estimated as 20.2 mg. At 2 × AE_{90} , the sigmoid E_{max} model predicted a mean onset time of 23.4 min and mean duration of 22.9 h. Interindividual variability (IIV) for AE_{50} was 49%. Typical k_{e0} half-life was 34.7 min (IIV = 52%) and steepness parameter 8.7 (IIV = 48%). None of the pharmacodynamic model parameters showed sex, age, or body weight dependency.

Conclusions: A population pharmacokinetic/pharmacodynamic model was developed that quantitatively describes the sensory component of a femoral nerve block in orthopedic patients. Further clinical studies will be needed to validate the clinical relevance of this finding. **(ANESTHESIOLOGY 2015; 122:1010-20)**

SINCE its market introduction in 1996, numerous clinical trials have demonstrated the efficacy of ropivacaine in providing prolonged sensory blockade when used for peripheral local anesthesia.[1] Despite this, no research attempted to characterize the pharmacokinetic–pharmacodynamic (PK/PD) relationship of ropivacaine after a peripheral nerve blockade, most probably because of the lack of adequate quantitative pharmacodynamic endpoints. The complex systemic absorption of local anesthetics after a peripheral nerve block[2] certainly represented an additional challenge.

Recently, the authors reported that a current perception threshold (CPT) testing device, previously used to monitor the time course of spinal[3] and epidural[4] anesthesia, not only displays very high reliability in healthy volunteers but is also applicable in a clinical setting to quantitatively assess the onset of a femoral nerve block.[5] We have also demonstrated that the biphasic release of ropivacaine from its perineural (femoral) site of injection can be characterized by a combination of parallel inverse Gaussian and time-dependent inputs in orthopedic patients.[6] This study enabled us to identify an age-related increase in the systemic absorption of ropivacaine. In the current report, we perform a population PK/PD analysis of the sensory component (CPT and ice-cold testing) of the response to ropivacaine (100 mg) using this pharmacokinetic model. The hypothesis is that the estimated rates of systemic absorption can be used to assess the relationship between the sensory response and the estimated

What We Already Know about This Topic

- A pharmacokinetic model with parallel inverse Gaussian and time-dependent inputs describes biphasic absorption of ropivacaine after femoral nerve block in patients undergoing total knee arthroplasty
- A current perception threshold testing device can be used to quantitatively assess the time course of a femoral nerve block

What This Article Tells Us That Is New

- A population pharmacokinetic–pharmacodynamic model was developed that describes the relationship between sensory response and the amount of ropivacaine remaining at the site of injection after single-dose injection for femoral nerve block
- Simulation using the model suggests that following a bolus dose of 100 mg, 0.2% ropivacaine hydrochloride should be infused at least at 3 ml/h to maintain a complete sensory block for 48 h

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amount of drug remaining at the site of injection (depot). Ultimately, such relationship could be used for predicting the clinical course of the block and thus allow for better and more efficient dosing regimens.

Materials and Methods

Subjects

After Research Ethics Board approval (Comité d'éthique de la recherche de l'Hôpital Maisonneuve-Rosemont, Montreal, Canada: protocol No. 07123) and obtaining written informed consent, 20 American Society of Anesthesiologists physical status I–III patients scheduled to undergo unilateral, primary total knee arthroplasty under femoral nerve block and spinal anesthesia were enrolled in the study. Exclusion criteria were as follows: age less than 35 yr or more than 75 yr, repeated surgery, contraindication to femoral nerve block or spinal anesthesia, significant renal or hepatic impairment, and hypersensitivity to ropivacaine, fentanyl, morphine, or acetaminophen.

Ropivacaine Administration and Blood Sampling

After arrival in the operating room, each patient was positioned supine and IV catheters (for pharmacokinetic sampling, drug and fluid administration) were placed at the upper limbs. If deemed necessary by the anesthesiologist, a light sedation using IV fentanyl (0.75 μg/kg) was given. Femoral nerve block was performed by the anterior approach using both ultrasonic guidance and neurostimulation. A linear array ultrasound transducer (L10-5, Zonare Medical System, USA) was used to identify the neurovascular structures. Ultrasound use allowed the anesthesiologist to visualize the site of injection, that is, under the fascia iliaca in a circumferential manner with regard to the nerve. After skin infiltration with 1% lidocaine, a short bevel 50-mm, 22-gauge, Teflon-coated neurostimulation needle (Stimuplex, B Braun, USA) was advanced toward the femoral nerve in order to elicit an ipsilateral quadriceps contraction with upward patellar movement at less than 0.5 mA (extraneural). At this point, after negative aspiration, 20 ml of 0.5% ropivacaine hydrochloride Naropin® (Fresenius Kabi, USA), corresponding to 88.3 mg base, was slowly (5 ml every 10 s) injected. Pharmacokinetic and pharmacodynamic measures were carried out for approximately 30 min. The patient was then placed in the sitting position and, following skin infiltration with 1% lidocaine hydrochloride, a 27 gauge Whitacre spinal needle (Vygon®, SPME Québec, Canada) was introduced into the subarachnoid space *via* the L2-L3 interspace. After free cerebrospinal fluid aspiration, a 2.0-ml bolus dose of 0.5% plain bupivacaine hydrochloride (10.0 mg) was injected. The patient was placed supine until the end of surgery. To avoid excessive bleeding, a tourniquet was used during the surgery. In the recovery room, the patient received patient-controlled analgesia set to deliver IV morphine in 1 mg boluses, with a lockout interval of 6 min (maximum 40 mg) for postoperative pain management. Venous blood sampling was performed before ropivacaine administration (0 h) at 5, 10, 15, 30, 45, 60, and 90 min and 4, 10, 21, 33, 45, 57, 69, 81, and 93 h thereafter. Plasma was separated and stored at −70°C before high-performance liquid chromatography analysis (total concentration).[7] Measurements below the lower limit of quantification (3.9 ng/ml) were excluded from data analysis.

Pharmacodynamic Evaluations

Quantitative Sensory Testing (Biomarker). Transcutaneous electrical stimulation was applied over the skin of the middle anteromedial aspect of both thighs *via* a pair of 1-cm-diameter gold-plated surface electrodes linked to a neurostimulator (Neurotron, Inc., USA). The device can deliver a constant electrical sine wave stimulus at different frequencies (5, 250, and 2,000 Hz) that have been reported to primarily stimulate small (C), medium (Aδ), and large (Aβ) fibers, respectively.[8] Mostly because of its possible association with the pain-conducting C-fibers,[3] the 5-Hz frequency (pulse duration, 100 ms) was used throughout the study. CPT evaluation was performed as previously described with slight modifications.[3,4] Briefly, the intensity of the nonpainful electrical stimulus (5-Hz sine wave pulses, cutoff 9.99 mA) was increased in steps of 20 μA at 3-s intervals from 0 μA until the patient felt any change in sensation (CPT). The current was then turned off, repeated in steps of 10 μA, and the intensity noted. CPT measurements were performed before the injection of ropivacaine (t = 0 or baseline), at approximately 5, 10, 15, 20, and 25 min after injection, then at various times in the postoperative period (up to 2 days after the administration of ropivacaine). This testing sequence was undertaken for both thighs (left and right) on an alternating basis. Baseline values were obtained in triplicate for each patient; the average value was used for data analysis.

In some patients, pain perception threshold (PPT) had to be used instead of CPT to quantitatively assess nerve blockade during the postoperative period. PPT evaluation at L2 (middle anteromedial aspect of the thigh) was performed by increasing the current stepwise[8] (controlled by the device) until the patient reported a painful sensation (PPT) at which time stimulation was stopped and PPT value recorded. This procedure was carried out only in those patients who experienced a successful sensory block (ice-cold testing) despite no significant change in the CPT. The observed change from baseline values was considered significant when higher than the standard error of the measure,[5] expressed as coefficient of variation (SEM_{CV} of 41%). Baseline values were obtained in triplicate after recovery and the average of the three measures was used for data analysis.

Ice Cold-testing (Clinical Endpoint). To corroborate successful block, sensory evaluation, using an ice cube, was assessed up to 30 min after the administration of

ropivacaine. Loss of cold sensation was determined by the patient's verbal response to the stimulus applied to the middle anteromedial aspect of the operated thigh. The response was noted as follows: 0 = normal sensation and 1 = no cold perception. Additional measurements were taken throughout the postoperative period until return of cold sensation.

PK/PD Analysis

Pharmacokinetic Analysis. As previously described,[6] a one-compartment model with parallel inverse Gaussian and time-dependent inputs (fast and slow release, respectively) was fitted to ropivacaine plasma concentration–time data. This combination of input roughly represents absorptions from the interstitial fluid (fast) and fatty tissues (slow) at the perineural site of injection.[9] Assuming complete absorption (fraction absorbed [*F*] = 1), a parameterization with F_{fast} and F_{slow} where $F_{slow} = 1 - F_{fast}$ was used. The interindividual variability (IIV) was characterized by assuming that the individual parameters were log-normally distributed around the population typical value:

$$P_{ij} = \theta_j \cdot \exp\left(\eta_{ij}\right) \quad (1)$$

where P_{ij} is the *j*-th parameter value for individual *i*, θ_j is the *j*-th typical parameter value of the population, and $\eta_{ij} \sim N\left(0, \omega_j^2\right)$. The structure of the variance–covariance matrix for IIV was refined after finalizing the covariate model. The improvement of model fit by inclusion of the covariates age, sex, and body weight was tested using the likelihood ratio criterion (see Statistical Analysis, third paragraph).

Pharmacodynamic Analysis. The two sensory thresholds (CPT and PPT) were modeled by assuming that the inhibition of nerve conduction at the femoral area would cause an increase in the current intensity needed for the perception of the stimulus. To collapse the hysteresis observed between the pharmacodynamic response and the amount in the depot compartment (derived from concentration–time data), a hypothetical effect compartment was added with an equilibrium half-life, $T_{1/2}\,k_{e0}$ (fig. 1). A sigmoid E_{max} model was then used to describe the time course of the effect:

$$E(t) = E_0 + \frac{E_{max} \cdot AE(t)^{\gamma}}{AE_{50}{}^{\gamma} + AE(t)^{\gamma}} \quad (2)$$

where E_0 is the baseline current intensity (*i.e.*, before the administration of the local anesthetic [CPT] or after recovery [PPT]), E_{max} is the current intensity at maximum ropivacaine-induced effect, AE_{50} is the effect-site amount corresponding to 50% of E_{max}, $AE(t)$ is the effect-site amount at time t, and γ is a shape parameter.

The binary response to ice-cold testing was analyzed using a time-to-event model,[10] with a time-varying hazard described as follows:

$$h(t) = \lambda\alpha(\lambda t)^{\alpha-1} \quad (3)$$

$$S(t) = e^{-\int_{t_j}^{t_{j+1}} h(t)\mathrm{d}t} \quad (4)$$

where the hazard $h(t)$ is a function of a rate constant λ and a shape parameter α (hazard increases with time when $\alpha > 1$). The survival curve $S(t)$, which describes the probability of not having an event (loss and recovery of cold sensation) within a certain time interval (t_j to t_{j+1}), is a function of the cumulative hazard. Hence, the likelihood for having an event at time t is the probability density function, that is, $S(t) \cdot h(t)$.

Statistical Analysis

Data analysis was performed with NONMEM®, version VII, level 1.1, ADVAN6 (ICON, USA).[11] The first-order conditional estimation method with interaction was used throughout the analysis except for binary data (ice-cold responses) where the Laplacian option was used. Observations (PPT) above the cutoff of the device were excluded from data analysis. The PK/PD analysis was performed using a sequential approach. First, empirical Bayesian estimates were obtained from the pharmacokinetic model and then used to predict ropivacaine-induced changes in log-transformed responses to neurostimulation (CPT and PPT). Model parameters were assumed to be log-normally distributed across the population (equation 1). Residual error was assumed to be proportional both for concentrations and effect parameters.

The method used for the quantitative assessment of nerve blockade, that is, CPT or PTT, was included as a covariate on E_0 and E_{max}. Additionally, the influence of patient demographic characteristics (age, body weight, and sex) was tested on key pharmacodynamic parameters. Using the objective function value (OFV), the likelihood ratio test was applied between nested models to test for any significant (ΔOFV > 6.64; $P < 0.01$; $df = 1$) improvement in model fit.

Model Evaluation

Visual predictive checks were used to evaluate the performance of the final models by comparing the 5th and 95th percentiles of the simulated (N = 1,000) anesthetic effects with the observed data. For ease of interindividual comparison, estimated sensory thresholds (in μA) were normalized by converting them to percent of maximum possible effect:

$$\%\mathrm{MPE} = \left(\frac{\mathrm{ER}_{pred} - \mathrm{ER}_{baseline}}{\mathrm{ER}_{max} - \mathrm{ER}_{baseline}}\right) \times 100 \quad (5)$$

where $\mathrm{ER}_{baseline}$, ER_{pred}, and ER_{max} are the estimated responses (CPT or PPT) at baseline, time *t*, and maximum ropivacaine-induced effect, respectively.

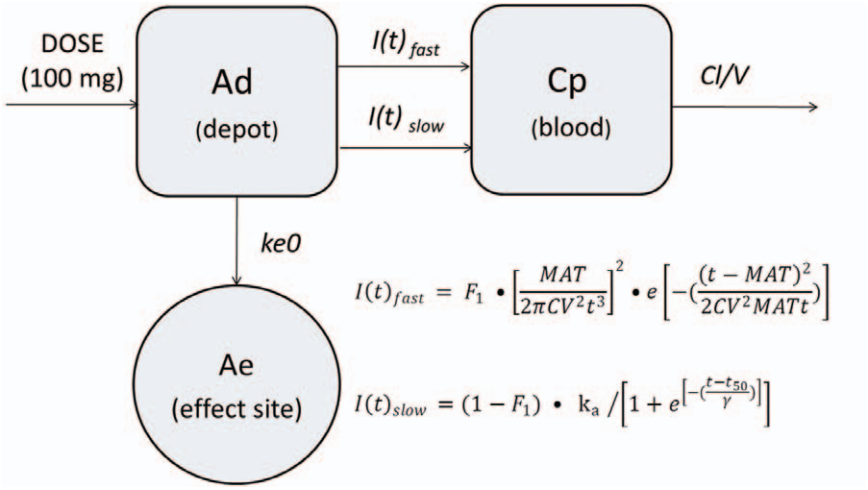

Fig. 1. Schematic representation of the pharmacokinetic–pharmacodynamic model used to describe the effect of ropivacaine on current perception and pain thresholds after a femoral nerve block in orthopedic patients. A_d = amount in the depot compartment; A_e = amount in the effect-site compartment; Cl = clearance; C_p = ropivacaine plasma concentrations; CV^2 = variance of the input time distribution; F_1 = fraction estimated for the fast input ($I(t)_{fast}$); γ = shape factor; k_a = first-order absorption rate constant; k_{e0} = first-order depot-effect site equilibrium rate constant; MAT = mean absorption time for the fast input rate; t = time after dosing; t_{50} = time to achieve 50% of the maximum input rate; V = volume of distribution.

Stability of the final PK/PD model parameters was evaluated by parametric bootstrapping using 1,000 random samples. The estimated parameters were examined for bias and precision *via* descriptive statistics.

External validation was conducted by assessing the ability of our population model to predict ropivacaine plasma concentrations previously obtained from a separate group of patients in our institution.[12] Briefly, data were retrospectively collected from 12 orthopedic patients after a femoral nerve block using a single injection (30 ml) of 0.5% ropivacaine hydrochloride plus epinephrine 1:200,000, followed by a 48 h infusion of 0.2% ropivacaine hydrochloride at 12 ml/h. Linearity between the dose and the area under the plasma concentration–time curve was assumed. Nine blood samples were collected during the infusion. Ropivacaine plasma concentrations were measured using an analytical assay similar to that used for the model-building group. The demographic characteristics of the patients used for model development were similar to those used for validation. Ropivacaine plasma concentrations were predicted by fixing the parameters in the structural and variance model to the parameter estimates in the final model. The predicted values were compared with the corresponding observed values, given the dosage history. Bias and precision were calculated with 95% CIs, using equations 6 and 7:

$$\text{Biais} = \sum \frac{\left(C_{\text{pred}} - C_{\text{obs}}\right)}{N} \quad (6)$$

$$\text{Precision} = \sum \frac{\left|C_{\text{pred}} - C_{\text{obs}}\right|}{N} \quad (7)$$

where C_{obs} and C_{pred} are the observed and predicted concentration, respectively, and N denotes number of observations.

Results

Table 1 presents the demographic characteristics of the participants. One patient was excluded from data analysis for major protocol violation (wrong solution used for nerve blockade). Femoral nerve block was unsuccessful in three patients out of 19, as measured by ice-cold testing. In these patients, CPT values (78.3 ± 36.2 μA) were also not significantly different from baseline values (65.9 ± 18.9 μA) and were therefore excluded from pharmacodynamic analysis. In the remaining 16 patients who experienced loss of cold sensation, three of them had to be evaluated using PPT measurements during the recovery phase. IV sedation (fentanyl, 0.75 μg/kg) was given to all patients except one. No adverse effect occurred throughout the study.

Pharmacokinetic Data Analysis

Mean observed plasma concentrations of ropivacaine are given in figure 2. A biphasic release of the agent from the femoral space was observed, with a rapid initial phase (mean absorption time [MAT] of 27.2 min; 95% CI, 21–37 min) and a slower phase (first-order absorption rate constant $[k_a]t_{1/2}$ of 2.6 h; 95% CI, 1.9–4.9 h). To further illustrate this, a deconvolution analysis[13] was performed on the measured plasma concentrations using IV data from the literature.[14] As shown in figure 3, the resulting cumulative fraction of ropivacaine absorbed *versus* time exhibit a biexponential function, representing two parallel absorption processes. Modeling of covariate effects resulted in a significant relationship ($P < 0.01$; ΔOFV = 8.91) between

Table 1. Characteristics of the Study Population

	Pharmacokinetics	Pharmacodynamics
n	19	16
Sex (M/F)	5/14	4/12
Age, yr	62.4 ± 6.6	62.6 ± 7.1
Weight, kg	87.7 ± 16.8	84.9 ± 16.5
Height, cm	166.6 ± 10.7	166.3 ± 11.3
BMI, kg/m^2	31.7 ± 5.8	30.6 ± 5.0
Surgical site (L/R)	11/8	9/7

Values are mean ± SD.
BMI = body mass index.

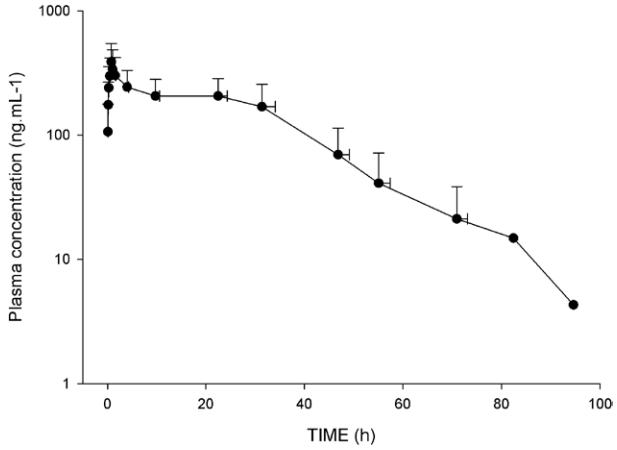

Fig. 2. Observed total ropivacaine plasma concentration *versus* time profiles obtained after a femoral nerve block (dose = 100 mg) in orthopedic patients (n = 19). Values are mean ± SD.

age and k_a. The model predicted k_a to change by approximately 3.0% for each 1-yr difference from the median (62 yr; range, 45–74 yr). Likewise, apparent volume of distribution (*V/F*) was significantly ($P < 0.01$; ΔOFV = 11.4) affected by body weight, which accounted for approximately 1.4% changes for each kilogram difference from the median weight (86.6 kg; range, 56.2–117.4 kg). Parameter estimates for the final population pharmacokinetic model are presented in table 2.

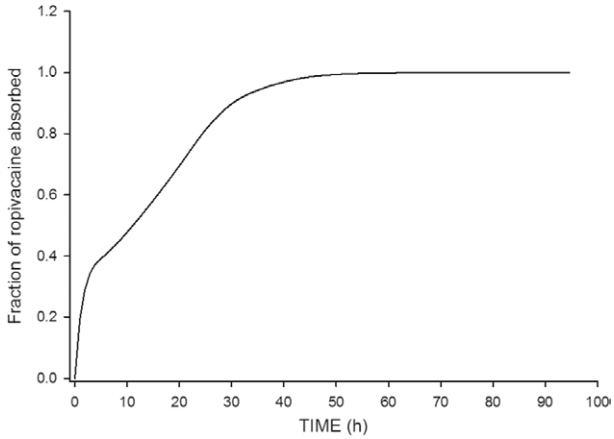

Fig. 3. Cumulative fractions of ropivacaine absorbed *versus* time in the population typical profile. Absorption–time data were obtained by deconvolution of the ropivacaine plasma concentrations–time data against the intravenous (IV) unit impulse–response curve, derived from IV data reported in the literature.[14]

Pharmacodynamic Data Analysis

The effect of ropivacaine on ice-cold sensation and sensory thresholds after a femoral nerve block in orthopedic patients is presented in figure 4. There was a wide range in the observed maximal intensity for CPT (680 ± 630 μA; n = 13) and PPT (8.35 ± 0.09 mA; censored in two out of

Table 2. Population Pharmacokinetic Model Parameters

Parameters*	Population Estimates (SE %)†	95% CI‡ of Population Estimate	IIV§ (CV%)‖ (SE %)†	95% CI‡ of IIV§ (CV%)‖
Cl/*F*, l/h	9.71 (7.75)	8.32–10.9	30.8 (14.1)	21.2–36.2
k_a, h^{-1}	0.264 (28.8)	0.142–0.686	24.0 (32.1)	5.6–33.9
Age on k_a#	1.87 (31.1)	0.41–4.20		
V/F, l	74.6 (9.06)	39.1–83.2	23.4 (20.4)	11.7–32.7
BW on *V/F***	1.23 (22.1)	0.72–1.91	—	—
t_{50}, h	24.0 (11.5)	19.2–33.0	—	—
MAT, h	0.471 (17.9)	0.352–0.623	58.2 (17.5)	35.7–73.0
VAR, %	1.15 (6.21)	0.981–1.29	—	—
F_{fast}	0.425 (12.7)	0.246–0.524	—	—
Proportional residual variability (CV%)§	20.9 (9.27)	18.5–24.5	—	—

* Dose in equivalent base (88.3 mg). † Standard error estimated by the covariance step in NONMEM expressed as percent. ‡ 95% CI. The lower and upper limits for 95% were calculated using the bootstrap. § Interindividual variability, calculated as (variance)$^{1/2}$ × 100%. ‖ CV%: coefficient of variation expressed as percent. # $k_a = \left(\frac{age}{62}\right)^{1.57}$. ** $V/F = \left(\frac{BW}{91}\right)^{1.36}$.

BW = total body weight; Cl / *F* = apparent clearance; F_{fast} = fraction of the dose absorbed; k_a = first-order absorption rate constant; MAT = mean absorption time; t_{50} = time required to achieve 50% of the maximum input rate; *V/F* = apparent volume of distribution; VAR = normalized variance of the Gaussian distribution used to characterize the input rate.

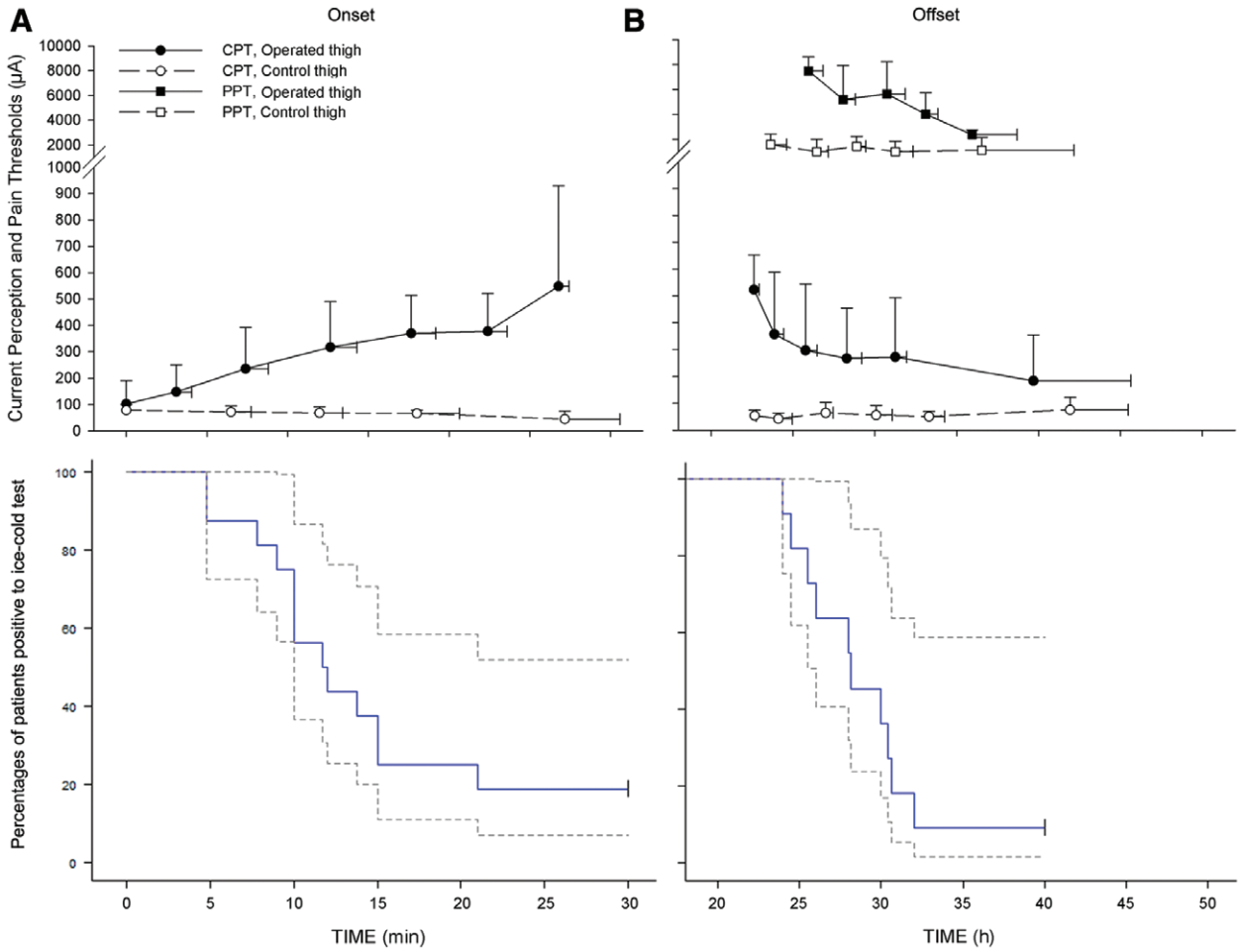

Fig. 4. Pharmacodynamic and clinical endpoints during the onset (*A*) and offset (*B*) of sensory nerve blockade after a single-bolus dose (100 mg). Current perception (CPT; *circles*, n = 13) and pain perception (PPT; *squares*, n = 3) thresholds over the middle anteromedial aspect of the operated (*thick lines*) and control (*broken lines*) thighs (*top*). Values are mean ± SD. Ice-cold testing (*bottom*). Kaplan–Meier plots describing the probability of not having an event (loss or recovery of cold sensation) ± 95% CIs (*broken lines*).

three patients) measurements, with an approximate six-fold increase from mean CPT baseline value (102 ± 88 μA). Ropivacaine maximal response on sensory threshold was observed within 22 ± 13 min of dosing, with a subsequent return to baseline at 29.6 ± 4.3 h. The increase and decrease in electrical stimulus threshold closely paralleled the time course of loss and recovery of ice-cold sensation, respectively.

The results of the pharmacodynamic analysis are summarized in table 3. Ropivacaine-induced effect on sensory thresholds was characterized by a temporal delay relative to its amount in the depot compartment (fig. 5A). As shown in (fig. 5B), the counterclockwise hysteresis was successfully minimized by the link model. For the binary response to ice-cold testing, a time-increasing hazard ($\alpha > 1$) was fitted to the time course of loss ($\alpha = 1.55$) and recovery ($\alpha = 3.77$) of ice-cold sensation. Attempts were made to link this response to effect-site without any improvement in the model fit. None of the pharmacodynamic model parameters showed age, body weight, or sex dependency.

Model Evaluation

Best, median, and worst individual fits of the final pharmacodynamic model are given in figure 6. The final PD model adequately described the overall time course of ropivacaine-effect data. A visual predictive check of the maximum possible effect *versus* the amount in the effect-site compartment is represented in figure 7. As shown in this figure, the effect-site amount producing a maximal possible effect varied from approximately 5 to 30 mg.

Predicted and observed ropivacaine plasma concentrations obtained from the external validation are plotted *versus* time in figure 8. The population pharmacokinetic model adequately described ropivacaine plasma concentrations in the validation patients, with an overall mean bias of −0.080 μg/mL (95% CI, −0.209 to 0.048) that was not statistically different from zero ($P = 0.221$). The overall precision was 0.440 μg/mL (95% CI, 0.341 to 0.539).

Discussion

A population PK/PD model was developed to characterize the anesthetic effect of ropivacaine after a femoral nerve

Table 3. Population Pharmacodynamic Model Parameters

Parameters*	Population Estimates (SE %)†	95% CI‡ of Population Estimate	IIV§ (CV%)‖ (SE %)†	95% CI‡ of IIV§ (CV%)‖
Biomarker (CPT and PPT measurements)				
E_0 , μA	77.0 (15.1)	54.7–111	59.0 (18.3)	31.8–76.2
Method# on E_0	18.5 (30.8)	9.69–34.1	—	—
E_{max} , μA	460 (18.8)	329–772	57.9 (34.8)	17.6–89.9
Method** on E_{max}	26.3 (20.8)	18.2–42.4	—	—
AE_{50} , mg	13.4 (11.8)	10.9–20.4	49.1 (24.1)	24.3–75.0
γ	8.68 (18.3)	4.11–15.1	48.3 (19.5)	23.5–64.8
k_{e0} , h^{-1}	1.20 (14.3)	0.838–2.25	51.6 (21.1)	19.3–78.4
σ^2 (CV%)‖	28.1 (12.8)	20.5–35.5	—	—
Clinical endpoint (loss and recovery of ice-cold sensation)				
λ_{loss} , h^{-1}	3.30 (20.6)	—	—	—
α_{loss}	1.55 (17.1)	—	—	—
$\lambda_{recovery}$, h^{-1}	0.04 (9.85)	—	—	—
$\alpha_{recovery}$	3.77 (56.9)	—	—	—

* Dose in equivalent base (88.3 mg). † Standard error estimated by the covariance step in NONMEM expressed as percent. ‡ 95% CI (using bootstrap). § Interindividual variability, calculated as $(\text{variance})^{1/2} \times 100\%$. ‖ Coefficient of variation expressed as percent (in the log-domain). # E_0 = population estimate × 18.5 (when PPT measurements are used). ** E_{max} = population estimate × 26.3 (when PPT measurements are used).

α = shape parameter for the hazard; γ = shape parameter; λ = first-order rate constant; σ^2 = residual variability (constant in the log-domain); AE_{50} = effect-site amount corresponding to 50% of E_{max} ; CPT = current perception threshold; E_0 = current intensity before the administration of ropivacaine; E_{max} = current intensity at maximum ropivacaine-induced effect; k_{e0} = first-order equilibrium rate constant; PPT = pain perception threshold.

block in orthopedic patients. Taking into account the effect of age and body weight on the absorption and distribution of the local anesthetic, the proposed model adequately describes the time course of sensory blockade after a single-dose injection.

We previously established the pharmacokinetic model describing the complex systemic absorption of ropivacaine after a femoral nerve block in 15 orthopedic patients.[6] With the use of extended rich pharmacokinetic samplings and IV data from the literature,[14] the biphasic release of the local anesthetic from its injection site was revealed by deconvolution.[13] A combination of inverse Gaussian and time-dependent inputs, roughly representing respectively the absorption from the interstitial fluid and surrounding fatty tissues, was used to describe the fast and slow release of the agent from its perineural site of injection. This approach provided empirical Bayesian estimates of the individual rates of systemic absorption that were subsequently used in the current PK/PD analysis.

A significant relationship between age and k_a has been identified in this study. The increased permeability caused

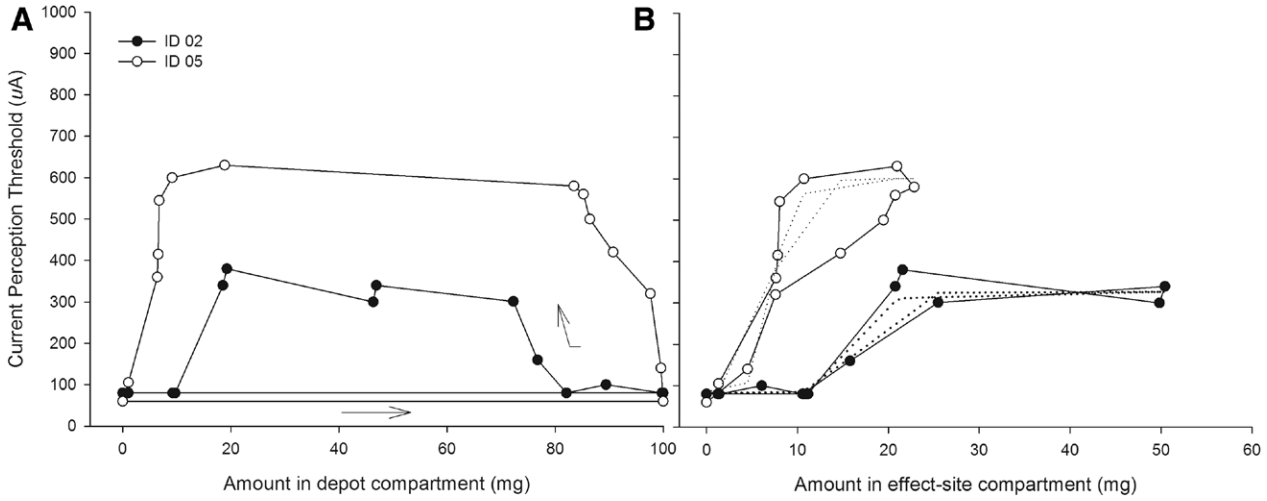

Fig. 5. Temporal delay of the current perception threshold (CPT) in two representative patients having received a single injection (20 ml) of 0.5% ropivacaine for femoral nerve block. Counterclockwise hysteresis loop of the estimated amount in the depot compartment *versus* CPTs (*full lines*; *A*). The *arrows* indicate the time course. Corresponding CPT *versus* estimated effect-site ropivacaine amount and model fit (*broken lines*; *B*).

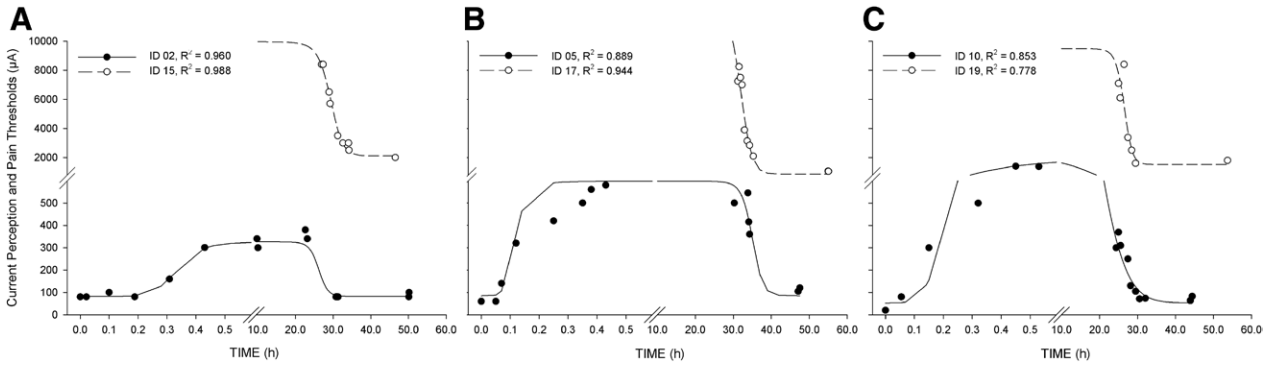

Fig. 6. Best (*A*), median (*B*), and worst (*C*) model fits according to the coefficient of determination (R^2) for the time course of current perception (*filled circles*) and pain (*open circles*) thresholds. The *dots* represent the measured sensory thresholds (in μA). The *lines* are the data fits.

by the age-related deterioration of the myelin sheaths and surrounding tissues at the site of injection[15] may have accelerated the slow component of the local anesthetic release into the systemic circulation. In addition, a significant relationship between body weight and V/F was observed. The relatively high lipid solubility of ropivacaine and the presence of fatty tissues nearby the femoral nerve may have contributed to the observed increase in V/F in our overweight patients.

A one-compartment model has been used to characterize the disposition kinetics of ropivacaine in our patients. In the absence of concomitant IV data, it was not possible to describe the initial rapid distribution phase characterized previously using a multicompartment model. Using a stable-isotope method, Simon *et al.*[14] provided a thorough description of the systemic absorption and disposition of ropivacaine after epidural administration and observed a significantly lower clearance in elderly patients compared to younger subjects. It may be that the age-related changes in absorption observed in our study was caused by the disposition itself, which would be consistent with the literature. Further clinical studies will be needed to validate the clinical relevance of this finding.

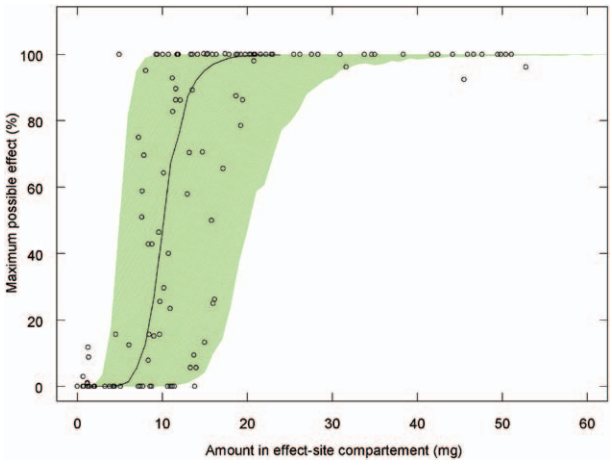

Fig. 7. Visual predictive check of the maximum possible effect (%) *versus* amount in the effect-site compartment. The *circles* represent the observations normalized by the estimated values for maximal response and baseline, the *shaded areas* represent the 95% CIs of the model simulations (N = 1,000), and the *solid black line* depicts the median profile.

The population pharmacokinetic model was externally validated using retrospective data[12] that were not used for model building, which is considered to be the most rigorous validation method.[16] In these patients, 30 ml of 0.5% ropivacaine hydrochloride plus epinephrine 1:200,000 followed by an infusion of 0.2% ropivacaine hydrochloride at 12 ml/h for 48 h was administered by a three-in-one femoral technique. Predicted ropivacaine plasma concentrations obtained from the final model agreed with levels observed in that study without significant bias, suggesting that the population pharmacokinetic model can be used to simulate different dosing regimens.

We have previously shown that CPT measurements can be applied to characterize, in a quantitative manner, the sensory onset of a peripheral nerve block in orthopedic patients.[5] Results obtained herein further support our findings where a mean four-fold increase over baseline values (102 ± 88 μA; n = 13) was observed for CPTs during recovery. This is approximately 30 times the variability observed in the control leg (SEM_{CV} ~13.5%), allowing a good discrimination between the sensory response to ropivacaine and baseline noise.

Of interest, an overall good agreement was found between the responses to transcutaneous electrical stimulation and ice-cold testing. The mean time from injection to maximal ropivacaine-induced effect on CPTs was within 22 min, with a subsequent return to baseline 30 h thereafter. These results are in accordance with Beaulieu *et al.*[17] who reported similar time course of loss and recovery of ice-cold sensation (onset: ~16 min, duration: ~26 h) after a combined sciatic (15 ml) and femoral (25 ml) nerve block using 0.5% ropivacaine hydrochloride in orthopedic patients (n = 25).

Examination of CPT measurements obtained on the untreated leg showed almost unchanged CPTs, thereby confirming that the sedative effect of opioids does not appear to interfere at 5 Hz. This finding is in agreement

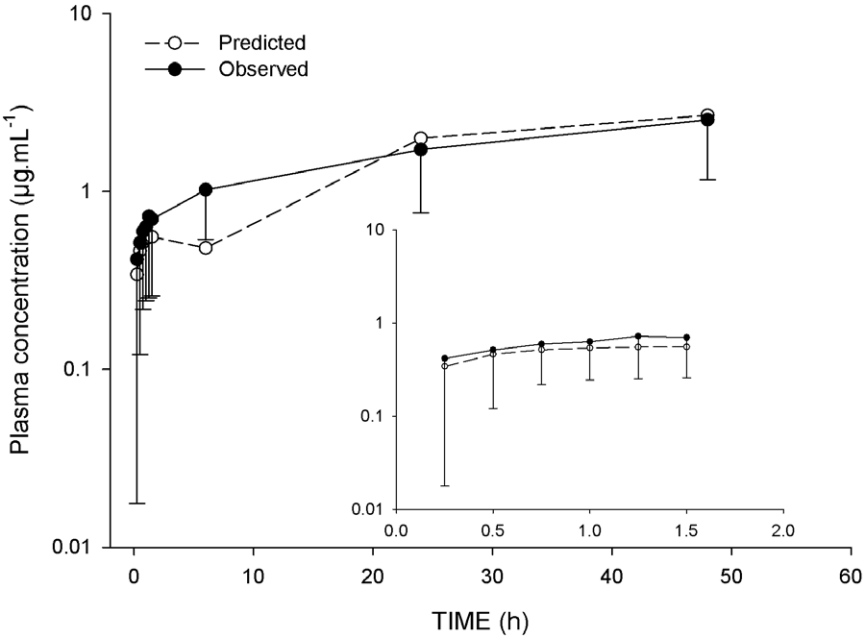

Fig. 8. Mean predicted (*open circles*) and observed (*filled circles*, mean ± SD) plasma ropivacaine concentrations *versus* time profiles using our population model parameters and the data used for external validation (Kaloul *et al.*[12]).

with Liu *et al.*[18] who reported that perception threshold to 5 Hz was not changed at dermatome L2 by either epidural or IV fentanyl administration in eight healthy volunteers.

PPT measurements had to be used as a rescue pharmacodynamic endpoint to quantitatively assess femoral nerve block in some patients (3 out of 13) who experienced a successful sensory block (as confirmed by loss of cold sensation) without any concomitant change in CPT response. This discrepancy between the biomarker and the clinical endpoint may result from differences in anatomic distribution of the femoral nerve.[19] Indeed, standardized positioning of electrodes may have prevented us from capturing the full magnitude of the anesthetic effect in those patients, also contributing to the observed variability in maximal CPT response. Furthermore, the ice-cold test produces a weak stimulus that is blocked more easily than stronger stimuli.[20] This may explain why the estimated λ_{loss} ($3.30\,h^{-1}$) was significantly faster than k_{e0} ($1.20\,h^{-1}$). Therefore, the perception of weak stimuli may be blocked regardless of strength of ropivacaine exposure.

CPTs were chosen instead of PPTs mostly because of the relatively fast onset of sensory blockade expected to occur after a femoral nerve block. The intensity at which the stimulus begins to evoke pain will not only take a longer time but is also expected to be censored at ropivacaine maximal effect, resulting in the loss of clinically important information. A likelihood-based approach[21] was tried to handle data above the security threshold obtained in two patients. This method, however, was not retained as it did not further improve the model fit, most likely because of the small proportion of censored data.

The PK/PD relationship of the quantitative biomarker was modeled according to a sigmoid E_{max} model, thereby providing a meaningful pharmacodynamic estimate of AE_{50}. The amount in the depot compartment was indirectly derived from the biphasic rate of systemic absorption of ropivacaine and the equilibrium rate constant (k_{e0}) between the depot and hypothetical effect site. Assuming a complete absorption ($F = 1$) and a fixed volume of 1, one could hypothetically derive the kinetic at the site of injection using the concentration–time data. Typical population estimate for AE_{50} was 13.4 mg, which is pharmacologically reasonable given the mean ED_{50} reported for epidural ropivacaine analgesia in laboring women (15.3: 13.7–17.1 mg).[22] For k_{e0}, we found a longer mean half-life than that reported for epidural anesthesia (34 *vs.* 9 min, respectively).[23] In view of the high density of tissues in the femoral area, a lower rate of lateral diffusion of the local anesthetic is expected compared to epidural administration. In addition, nonspecific uptake of the local anesthetic in fatty tissues adjacent to the femoral nerve may have lowered perineural concentrations, thereby decreasing the concentration gradient and, in turn, the passive diffusion of the agent through the nerve sheath. Finally, the heterogeneous nature of the tissues surrounding the femoral nerve may also have contributed to the relatively high IIV observed for k_{e0} (approximately 52%; table 2).

In contrast to previous findings where a significant correlation between onset time and weight was found after neural blockade,[24] none of the pharmacodynamic parameters showed age, body weight, or sex dependency. It cannot be excluded that, in a larger sample size, the effect of these demographic factors on various component of neural blockade could be reproduced. The relatively homogenous group of patients used in our study may have also

contributed to this apparent discrepancy. Given that, the model should be used within the context of the data and any extrapolation should be done with caution. Another potential limitation of the current analysis is the underlying assumption of a complete bioavailability of the injected solution. As the concentration at the injection site was not measured, the time course of the amount of local anesthetic in the depot relies entirely on our model. All these factors have to be taken into account during the interpretation of the estimated AE_{50}.

Results obtained from the current PK/PD analysis suggest that the effect-site amount required for producing 90% of the maximum possible effect is approximately 20 mg (fig. 7). Considering that dose is the primary determinant of the analgesic effect during a perineural infusion,[25] one can use the model developed herein to simulate the minimal infusion rate required to maintain an amount of ropivacaine at the effect-site corresponding to 2 × AE_{90}. Results from the simulation study (appendix) suggest that following a bolus dose of 100 mg, the infusion rate of 0.2% ropivacaine hydrochloride should be of at least 3 ml/h during 48 h to maintain a complete sensory block. This estimate is similar to that reported by Zaric *et al.*,[26] who used 0.2% ropivacaine hydrochloride at a rate of 5 ml/h to reach an effective sciatic nerve block in 60 orthopedic patients.

Conclusions

In conclusion, a population PK/PD model that quantitatively describes the sensory component of a femoral nerve block in orthopedic patients was developed. Further clinical studies will be needed to validate the clinical relevance of this finding.

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Competing Interests

The authors declare no competing interests.

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Appendix: Simulation Study—Identification of the Minimal Effective Infusion Rate

Although 0.2% ropivacaine hydrochloride is frequently used for postoperative analgesia, the optimal dosing regimen *via* a femoral nerve catheter has never been determined empirically.[27] Current reports on ropivacaine infusion

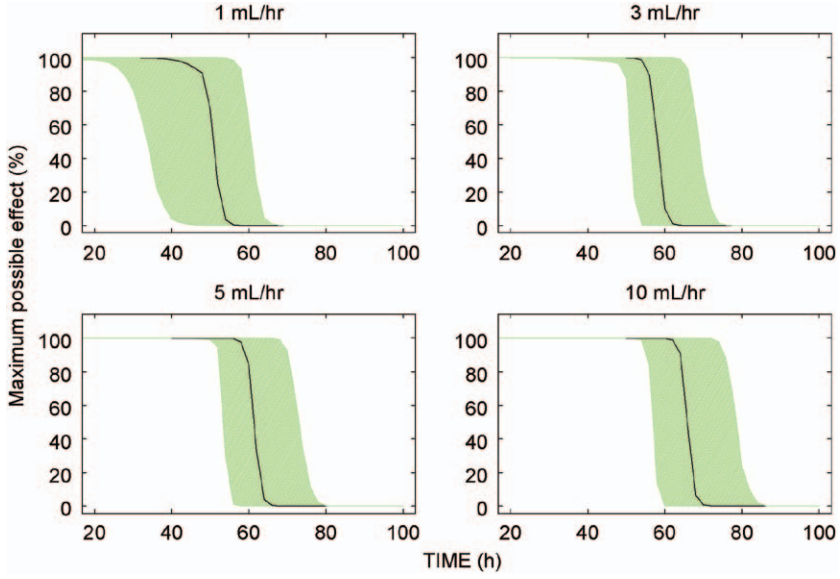

Fig. 9. Simulation analysis using the final pharmacokinetic–pharmacodynamic model at different dosing regimens (1, 3, 5, and 10 ml/h of 0.2% ropivacaine for 48 h after a single-bolus dose of 100 mg). The *shaded areas* represent the 95% CIs of the model simulations (N = 1,000), and the *solid black line* depicts the median profile.

regimens propose ranges varying from 5 to 12 ml/h, with a loading dose varying between 100 and 225 mg.[12,26,28] To further evaluate the minimal effective dose, we performed a simulation study in which we generated 1,000 replicates using the final population pharmacokinetics–pharmacodynamic model at different dosing strategies (combination of 100 mg bolus dose and 48 h basal infusion rate varying from of 1 to 10 ml/h). These datasets were then analyzed and compared by calculating the 5th, 50th, and 95th percentile of the maximum possible effect *versus* time profiles. Results obtained are depicted in figure 9, suggesting that 0.2% ropivacaine hydrochloride infusion rate should be of at least 3 ml/h for 48 h when following a single-bolus dose of 100 mg. This result is in agreement with Zaric *et al.*,[26] who reported a similar infusion rate (5 ml/h) for 0.2% ropivacaine hydrochloride during a sciatic nerve block in orthopedic patients.

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