Comparative Ventricular Electrophysiologic Effect of Racemic Bupivacaine, Levobupivacaine, and Ropivacaine on the Isolated Rabbit Heart

Jean Xavier Mazoit, M.D., Ph.D., * Anne Decaux, M.D., * Hervé Bouaziz, M.D., Ph.D., * Alain Edouard, M.D., Ph.D.*

**Background:** Numerous local anesthetics have an asymmetric tetrahedron carbon, which confers stereoselective differences between the isomers. The authors attempted to quantify the depressant effect of racemic bupivacaine, levobupivacaine, and ropivacaine on myocardial ventricular conduction and on myocardial contractility.

**Methods:** The authors studied the pharmacokinetics (outflow concentration) and pharmacodynamics (QRS widening) of the three drugs infused in an isolated rabbit heart preparation. All data were fitted simultaneously with use of mixed-effect modeling, thus allowing precise statistical comparison between the three drug parameters. The rate dependence of QRS widening was fitted separately.

**Results:** Racemic bupivacaine, levobupivacaine, and ropivacaine induced a calculated maximum increase in QRS duration in the ratio 1:0.4:0.3. CsS_{50}, the dose which caused half the maximum increase in QRS duration at steady state, was similar for all three drugs (22 μM free concentration). A rate dependence of QRS widening was observed, which was in the ratio 1:0.5:0.25 for racemic bupivacaine, levobupivacaine, and ropivacaine, respectively.

**Conclusions:** In the isolated rabbit heart, racemic bupivacaine, levobupivacaine, and ropivacaine induce an increase in QRS duration in the respective ratio of 1:0.4:0.3, which was rate dependent in approximately the same ratio. (Key words: Langendorff; NONMEM; pharmacometrics; PK-PD.)

NUNEROUS local anesthetics, including bupivacaine, have an asymmetrically substituted carbon, which confers stereoselective differences between the enantiomers. Bupivacaine binding to sodium channels and to serum proteins is stereoselective, and the levo-(S-)bupivacaine enantiomer is less cardiotoxic than the dextro-(R+)-enantiomer. However, new experiments strongly suggest that this stereospecific binding to the sodium channel is less important at the nerve site than at the heart site, thus explaining that levobupivacaine may cause nerve block of similar or greater intensity and duration than the racemic mixture. Similar observations have been made about R(−) and S(+)-mepivacaine. These findings indicate that, among local anesthetic stereoisomers, some are safer than their mirror enantiomer and than the usual racemic mixture. Ropivacaine (S[−]-1-propyl-2,6′-piperidoxylidide) is the only local anesthetic available as a pure enantiomer. Ropivacaine is believed to be safer than bupivacaine, which has one carbon less and is slightly less lipophilic than bupivacaine, is also slightly less potent than bupivacaine. QRS widening, observed with lidocaine, is related to ventricular conduction velocity slowing. Long-acting local anesthetics, such as ropivacaine, also impair ventricular conduction, primarily by blocking voltage-sensitive sodium channels, and this effect is more pronounced with bupivacaine than with lidocaine because of the rate dependence of the block. Moreover, stereosepecificity has been observed and this effect may vary depending on the drug and the channel studied.

To compare racemic bupivacaine, levobupivacaine, and ropivacaine...
ropivacaine, we attempted to quantify the depressant effect of these agents on myocardial ventricular conduction. Because bupivacaine toxicity has been shown to be rate dependent,3,22 we also studied the effect of heart rate on QRS duration changes induced by the three drugs.

Materials and Methods

We studied the effects of local anesthetics on an isolated rabbit heart model with use of a modification of our previously described procedure.5,15 Twenty-one male New Zealand rabbits, weighing 1,550–2,040 g, were studied in a random block design of three groups of seven animals each. This study was approved by our institutional animal care committee. Care of the animals conformed to the recommendation of the Helsinki Declaration and to the guidelines of the European Communities and French laws for animal experiments (accreditation No. 1989/2559 to Dr. Mazoit). Group 1 animals were infused with racemic bupivacaine, group 2 animals were infused with levobupivacaine, and group 3 animals were infused with ropivacaine. The experimenters were blind to the drug used until study completion. Nine control animals also were studied at random to ensure the stability of the preparation. Finally, we incorporated a pilot group of five previously studied rabbit hearts that had been infused with racemic bupivacaine. The results of this group were incorporated in the present study. The effect of heart rate was assessed by pacing the heart with a programmed interval between atrial stimuli. In order to verify that pacing of the atria induced a constant ventricular response rate, the heart rate was recorded at the end of each pacing interval.

Drugs and Reagents

The drugs used were the commercial solutions for racemic bupivacaine and ropivacaine (ASTRA France, Paris, France). The solutions were tested for concentration accuracy with use of hydrochloride salts (ASTRA Pain Control, Södertalje, Sweden). Levobupivacaine hydrochloride was a gift from Chiroscience (Cambridge, United Kingdom). Racemic bupivacaine was tested with use of another hydrochloride monohydrate salt, from Sigma (St. Quentin Fallavier, France). After a concentration check, blind stock solutions of the drugs were prepared.

The same buffer, with the following composition, was used throughout the study: 118 mM NaCl, 4.7 mM KCl, 2.5 mM CaCl₂, 1.2 mM MgSO₄, 1.2 mM KH₂PO₄, 25 mM NaHCO₃, 5.5 mM glucose, and 2.0 mM Na pyruvate. The pH of the perfusate at heart inflow was maintained between 7.37 and 7.42. Reagents for chromatography and salts for buffer were purchased from Prolabo (Paris, France).

Study Procedure

The rabbits were anesthetized with 6 mg/kg pentobarbital intraperitoneally. Tracheotomy was performed, and the animals were ventilated manually. The chest was opened, and, after intravenous heparin injection, the heart was removed and mounted quickly on a nonrecirculating Langendorff apparatus, and the coronary arteries were perfused via the aorta at a constant flow of 30 ml/min with use of a modified Krebs-Henseleit buffer bubbled with a mixture of 95% oxygen and 5% carbon dioxide at 37°C. The hearts were paced atrially throughout the study with a bipolar electrode at 210 beats/min using a Chronocor IV stimulator (Telecronics, SOREM Presles en Brie, France), which delivered a square pulse of 3.5 mA. We used the following exclusion criteria for the preparation: (1) the presence of aortic valve regurgitation, (2) a rhythm (before pacing) less than 120 beats/min or greater than 170 beats/min, (3) the presence of arrhythmias, and (4) a dP/dt maximum lower than 1,000 mmHg/s. After an 8- to 12-min stabilization period, the drug (racemic bupivacaine, levobupivacaine, or ropivacaine) was infused into the inflow perfusate at 20 µM for 5 min (from T0 to T5) and at 5 µM during 15 min (from T5 to T20) with use of a model 33 Harvard pump (Harvard, Les Ulis, France). The concentrations infused correspond to amounts of 0.6 µM/min and 0.15 µM/min, respectively (at 30 ml/min buffer infusion). The hearts were studied during a total period of 60 min. The outflow perfusate was sampled with use of a fraction collector at frequent intervals up to 60 min. Pharmacodynamic variables (electrocardiography and left ventricular pressure) were recorded at the end of each effluent sampling time. Racemic bupivacaine, levobupivacaine, and ropivacaine were measured with use of gas chromatography. Electrocardiography was measured with use of surface electrodes. Data were recorded on a Gould 8000S chart recorder (Gould, Les Ulis, France). QRS duration of three consecutive beats, recorded at a paper speed of 200 mm/s, were averaged. The rate of pacing was modified between 17 and 19 min and between 50 and 52 min, with use of steps every 10 s from 170 to 350 beats/min, in increments of 20 beats/min (the starting point of the sequence [initial heart rate] and the order of change [increase or decrease in stimulation rate] were chosen at random). This additional procedure was performed to quantify the rate dependence of QRS duration. A preliminary study performed on five rabbit hearts with use of a step increase of racemic bupivacaine at 0, 1.535, 3.07, and 6.14 µM showed that, when the pacing rate was changed, ap-
proximate steady state QRS duration was attained after 4 or 5 s. A 10-min stabilization period was observed between changes in dose amount. The results of this preliminary group have been incorporated into the study (see after).

Pharmacokinetics and Pharmacodynamics. We used the model previously described. Briefly, linear pharmacokinetics were assumed, and the heart was described by a two-compartment open model (with the assumption of venous equilibrium). If $C_0$ is drug concentration in the inflow perfusate, the outflow perfusate concentration ($C$) can be expressed as a function of time ($t$) by the following relation:

$$C = k_{10} A_1 / Q$$

where $k_{10}$ is the exit rate constant from the central compartment, $A_1$ is the amount of drug in the central compartment at time $t$, and $Q$ is the perfusate flow. Fitting was performed with use of standard equations with the procedure ADVAN 3 from the program NONMEM (version V, level 1). The volume of the central compartment was not measurable with data from outside the heart. Therefore, we set all volumes to unity. We calculated the three rate constants, $k_{12}$, $k_{21}$, and $k_{10}$, from the central to the peripheral compartment, from the peripheral to the central compartment, and from the central compartment to outflow, respectively.

The increase in QRS duration ($E$) was fitted simultaneously to the $E_{\text{max}}$:

$$E = E_0 + \frac{E_{\text{max}} A_i}{A_{i50} + A_i}$$

where $E_0$ is the basal QRS duration, $E_{\text{max}}$ is the maximum increase in QRS duration, and $A_{i50}$ is the drug amount in compartment $i$ that produces half $E_{\text{max}}$ at steady state.

A special-effect compartment model, as described by Sheiner et al., was also tried. The steady state perfusate concentration that produced half $E_{\text{max}}$ ($C_{\text{ss}50}$) was calculated as $C_{\text{ss}50} = A_{i50} / k_{10}$, in case of an effect occurring in the central compartment.

Statistics

Between-group comparison of QRS duration measured before and at the end of each infusion was performed using the Student $t$ test with the Bonferroni correction. Results are expressed as the arithmetic mean and SD, except for figure 3, in which the standard error of the mean was used for clarity of the figure.

The data were fitted using the program NONMEM. Its use permits the fitting of mixed-effects models by using two levels of random errors (intraindividual and interin...
individual variability). By using nested models, it allows testing of the statistical difference between drugs for a specified parameter in a wide range of experiments.27

Extended least squares were used as measure of goodness-of-fit28 (see appendix in Web enhancement).

The concentration–time data first were fitted with use of the first-order method. The parameter estimates obtained at this step were used then (fixed at the value obtained at this step) for the calculation of the effect parameter estimates using the whole data set. The choice between the different pharmacokinetic (PK) models (one or two compartments) and pharmacodynamic (PD) models (effect in the central, peripheral, or special-effect compartment) was made with use of the Akaike criterion.29 Thus, a full model, with all interindividual variability parameters considered to be relevant, was defined (see appendix in Web enhancement). After this full model was defined, the choice between the full model and successive reduced models was made with use of the log-likelihood ratio test.30 To avoid overparametrization, we only considered parameters with an estimated coefficient of variation (CV) of the estimates that was less than 60%.31,32 Intraindividual variability (assay error, model mispecification, and so forth) was modeled using a combined constant CV and additive error model without interaction for pharmacokinetic and an additive error model for pharmacodynamic. Interindivdual variability was modeled as \( \exp(\eta) \) (assuming a log-normal distribution), in which \( \theta \) is the vector of the fixed-effect parameter and \( \eta \) is the vector of interindividual variability, with variance \( \sigma^2 \). We used the hybrid method, with the mean \( \bar{\eta} \) corresponding to pharmacokinetic parameters set to 0. We assumed no covariance either between the elements of \( \epsilon \), the vector of residual error resulting from intraindividual and measurement variability, or between the elements of \( \eta \) and the elements of \( \epsilon \).

The rate dependence of QRS duration was tested with use of the following linear model:

\[
\text{QRS} = \text{Intercept} + \text{Slope}_i \times C_i \times (HR - HR_0)
\]

where \( HR \) is heart rate and \( C_i \) is the concentration of drug \( i \) in perfusate. The slope was considered linearly dependent on drug concentration and, therefore, was set as the product of an intrinsic parameter for drug \( i \) (Slope\(_{\text{e}}\)) times the concentration of that drug (\( C_i \)). Both parameters (Intercept and Slope\(_{\text{e}}\)) had a fixed effect and a random effect (modeled as \( \exp(\eta) \)) component. A constant CV was used to model the residual intraindividual error. Data from a pilot study were incorporated in the fitting procedure, considering interoccasion variability with a different \( \eta \) and \( \epsilon \).

### Results

QRS duration was constant throughout the study period in all control hearts. Local anesthetic infusion was followed by rapid QRS widening. Arrhythmias occurred during the rapid infusion phase (3–6 min after infusion initiation) and at the time of discontinuation of drug

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**Table 1. Summary of Data‡**

<table>
<thead>
<tr>
<th></th>
<th>Racemic Bupivacaine (n = 7)</th>
<th>Levobupivacaine (n = 7)</th>
<th>Ropivacaine (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal QRS duration (ms)</td>
<td>30 ± 4</td>
<td>29 ± 3</td>
<td>32 ± 5</td>
</tr>
<tr>
<td>( \Delta \text{QRS} ) (ms)</td>
<td>86 ± 14†</td>
<td>41 ± 15†</td>
<td>29 ± 8†</td>
</tr>
<tr>
<td>( \Delta \text{QRS20} ) (ms)</td>
<td>35 ± 11†</td>
<td>15 ± 7‡</td>
<td>9 ± 7§</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PVC</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>VT</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PVC at discontinuation¶</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Number of hearts without arrhythmias</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

* \( P < 0.001 \) versus levobupivacaine and versus ropivacaine.
† \( P < 0.001 \) versus baseline.
‡ \( P < 0.005 \) versus baseline.
§ \( P < 0.05 \) versus baseline.
¶ Two hearts in the bupivacaine group had episodes of bigeminy.

\( E_0 = \) basal QRS duration; \( \Delta \text{QRS} \) and \( \Delta \text{QRS20} \) = observed absolute increase in QRS duration, respectively, at the end of the first infusion (5 min) and at the end of the second infusion (20 min); Block = intraventricular block, i.e., lack of ventricular electric activity during at least one cardiac cycle despite pacing; PVC = premature ventricular contraction; VT = ventricular tachycardia lasting more than six consecutive beats.

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Anesthesiology, V 93, No 3, Sep 2000
Because of the small number of hearts used, it was impossible to compare the number of arrhythmias that occurred with each drug. In fact, only one heart in the racemic bupivacaine group, four hearts in the levobupivacaine group, and four hearts in the ropivacaine group had no arrhythmias (table 1). Four hearts experienced arrhythmias at infusion discontinuation. The maximum observed increase in QRS was significantly greater with racemic bupivacaine than with the two other drugs at the end of the two infusion phases (i.e., at T5 and T20) (table 1).

Fitting was adequate with use of the two-compartment open model and the QRS widening effect located in the central compartment, i.e., with no delay between outflow concentration and effect (table 2 and fig. 1). Table 2 shows the statistical difference between models. Racemic bupivacaine and levobupivacaine had a similar k21 and k10. E\textsuperscript{max} was significantly different among the three drugs, whereas Css50 was similar for the three drugs (tables 2 and 3). E\textsuperscript{max} was more than twice as much for racemic bupivacaine than for levobupivacaine and approximately 4 times as much for racemic bupivacaine than for ropivacaine (table 3 and fig. 2). The approximate E\textsuperscript{max} ratio was 1:0.4:0.25 for racemic bupivacaine, levobupivacaine, and ropivacaine, respectively. QRS widening showed a marked rate dependence, which was linearly related to dose amount, at least for racemic bupivacaine (table 3 and fig. 3). The rate dependence of QRS widening (slope of the QRS duration–heart rate relation) was significantly different between the three drugs, with an approximate ratio of 1:0.5:0.2 for racemic bupivacaine, levobupivacaine, and ropivacaine, respectively.

**Discussion**

The current study confirms that levobupivacaine and ropivacaine induce a much lower impairment of intraventricular conduction than does racemic bupivacaine. The number of hearts used in each group does not allow statistical comparison of the number and type of arrhythmias. However, either block (defined as the absence of electrical activity during at least one cardiac cycle, despite pacing) or premature ventricular contraction was more frequent in the racemic bupivacaine group (table 1). These arrhythmias are usually described with use of bupivacaine and are associated with decreased intraventricular conduction velocity and reentry phenomenon.22 This result is in accordance with the fact that racemic bupivacaine significantly leads to a greater impairment

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**Table 2. Model Building: Statistical Significance**

<table>
<thead>
<tr>
<th>PK model</th>
<th>Objective Function</th>
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<tbody>
<tr>
<td>Full model</td>
<td>k12, k21 and k10 relevant for all three drugs</td>
</tr>
<tr>
<td>Reduced models</td>
<td>k10 equal for rac- and levobupivacaine</td>
</tr>
<tr>
<td></td>
<td>k21 and k10 equals for rac- and levobupivacaine</td>
</tr>
<tr>
<td></td>
<td>k12, k21 and k10 equals for rac- and levobupivacaine</td>
</tr>
<tr>
<td>* P &lt; 0.05 OF\textsubscript{4} vs. OF\textsubscript{3}</td>
<td></td>
</tr>
<tr>
<td>All other models led to OFs &gt;&gt; OF\textsubscript{4}</td>
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<table>
<thead>
<tr>
<th>PK–PD model (QRS)</th>
<th>Objective Function</th>
</tr>
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<tbody>
<tr>
<td>Full model</td>
<td>E\textsubscript{max} and Css50 relevant for all three drugs</td>
</tr>
<tr>
<td>Reduced models</td>
<td>Css50 equal for all three drugs</td>
</tr>
<tr>
<td>All other models led to OFs &gt;&gt; OF\textsubscript{2}</td>
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<table>
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<tr>
<th>Rate dependence model (QRS)</th>
<th>Objective Function</th>
</tr>
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<tbody>
<tr>
<td>Full model</td>
<td>Slope relevant for all three drugs</td>
</tr>
<tr>
<td>Reduced models</td>
<td>Slope equal for rac and levobupivacaine</td>
</tr>
<tr>
<td></td>
<td>Slope equal for levobupivacaine and ropivacaine</td>
</tr>
<tr>
<td>* P &lt; 0.001 OF\textsubscript{1} vs. OF\textsubscript{2} and vs. OF\textsubscript{3}</td>
<td></td>
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</table>

The best model for PK was the two compartment model. The best model for PD was the model with effect in the central compartment and Css50 equal for the three drugs. The best model for rate dependence was the full model. Goodness of fit is represented by the objective function (OF).
of intraventricular conduction and to a higher rate dependence. The use of nonlinear mixed-effect modeling allowed us to show that the theoretical maximum effect on QRS duration was significantly greater with levobupivacaine than with ropivacaine, whereas Css50 was similar for all three drugs. Therefore, at similar free concentrations in blood, the three drugs are expected to induce ventricular conduction impairment in the approximate ratio (intrinsic activity) of 1:0.4:0.25 for racemic bupivacaine, levobupivacaine, and ropivacaine, respectively.

We used the global mixed-effect modeling technique, rather than the classic two-stage method because the former approach permits more accurate calculation of confidence intervals for parameter estimates than does the latter.31,32 Two assumptions were made for interindividual variability estimation. First, we assumed a log-normal distribution for pharmacokinetic and pharmacodynamic parameters, and, therefore, we modeled interindividual variability as \(\exp(\eta)\). Second, we assumed a nonlinear behavior for pharmacodynamic data. Therefore, we used the hybrid method in NONMEM.

Fitting of pharmacokinetic data was adequate with use of the well-stirred, two-compartment model.6,15,33 The three drugs showed significantly different kinetic parameters. However, these differences are relatively minor, as shown in figure 2. At the time of discontinuation of drug administration, myocardial washout was rapid, even in the racemic bupivacaine group. These results are in accordance

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Fig. 2. Chronologic evolution of drug concentration (left) and QRS duration (right) during and after racemic bupivacaine (RAC-BUPI) (A), levobupivacaine (LEVO) (B), and ropivacaine (ROPI) (C) infusions. Kinetics are almost similar for all three drugs, with a rapid washout after discontinuation of drug infusion. Racemic bupivacaine induced a much higher QRS widening than did the two other drugs.
with our previous studies, which showed that bupivacaine did not accumulate in the myocardium and that the toxic effect of long-lasting local anesthetics was not the consequence of drug accumulation in tissue.

We used the simple E_max model for QRS widening fitting because the addition of a sigmoid parameter resulted in overparametrization. Fitting was adequate, but a small bias that caused underestimation of the highest QRS values was observed (fig. 2). The Css_{50} (the inflow or outflow steady state concentration that produced half the maximum effect) was similar for all three drugs. We have already shown that the Css_{50} was similar between racemic bupivacaine and lidocaine and between racemic bupivacaine, levobupivacaine, and \textit{R}(1)-bupivacaine.

The Css_{50} for the three drugs was similar to the value previously reported (43 μM vs. 29–39 μM in the current study and previous studies, respectively). The calculated Css_{50} (43 μM, i.e., approximately 14 to 15 μg/ml) needs to be interpreted carefully because we used a protein-free perfusate solution. We may estimate that the approximate free concentration that is necessary to double the basal QRS duration at 210 beats/min was 2.4, 7.2, and 14.4 μg/ml for racemic bupivacaine, levobupivacaine, and ropivacaine. These concentrations are in the range of the free concentrations expected to occur during accidental massive intravenous injection for racemic bupivacaine, but they are likely more than those expected during the same complication for levobupivacaine and ropivacaine.

All three drugs showed a marked rate dependence of QRS widening (table 3 and fig. 3). This rate dependence was statistically different between the three drugs (table 2). With racemic bupivacaine, the slope of the relation between heart rate and QRS duration was related linearly to the dose within the range of frequencies used (fig. 3, top), and nothing indicated that this phenomenon is different with the other two local anesthetics. Therefore, for the comparison between racemic bupivacaine, levobupivacaine, and ropivacaine, we modeled QRS duration as a linear function of inflow concentration with use of equation 3. Fitting was adequate (fig. 3, bottom).

The rate dependence of QRS widening was in the range of 1:0.5:0.2 for racemic bupivacaine, levobupivacaine, and ropivacaine, respectively, which approximates the ratio of E_{max} calculated for these drugs. The dose–effect curve parameters (E_{max} and Css_{50}) were calculated at a fixed frequency of 210 beats/min. Because QRS duration was related linearly to drug concentration and heart rate, changes in heart rate might change E_{max}, with a fixed ratio between drugs. However, it may be reasonably speculated that even drugs that rapidly dissociate from the receptor may increase intrinsic activity at extreme heart rates. In contrast,Css_{50} is not expected to vary with changes in heart rate.

In conclusion, using mixed-effect modeling, we showed that racemic bupivacaine, levobupivacaine, and ropivacaine block intraventricular conduction in the rab-

### Table 3. QRS Widening

<table>
<thead>
<tr>
<th></th>
<th>k12 (min(^{-1}))</th>
<th>k21 (min(^{-1}))</th>
<th>k10 (min(^{-1}))</th>
<th>E_{max} (ms)</th>
<th>Css_{50} (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rac-Bupivacaine</td>
<td>0.079 (10%)</td>
<td>0.11 (8%)</td>
<td>0.55 (10%)</td>
<td>330 (50%)</td>
<td>43 (44%)</td>
</tr>
<tr>
<td>Levo-Bupivacaine</td>
<td>0.12 (12%)</td>
<td>—</td>
<td>—</td>
<td>132 (31%)</td>
<td>—</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>0.15 (27%)</td>
<td>0.21 (18%)</td>
<td>0.86 (21%)</td>
<td>81 (29%)</td>
<td>—</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rate dependence of QRS</th>
<th>HR (_0) (beats/min)</th>
<th>Intercept (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rac-Bupiv</td>
<td>0.083 (12%)</td>
<td>0.041 (38%)</td>
</tr>
<tr>
<td>Levo-Bupiv</td>
<td>0.083 (12%)</td>
<td>0.041 (38%)</td>
</tr>
<tr>
<td>Ropivac</td>
<td>0.083 (12%)</td>
<td>0.041 (38%)</td>
</tr>
</tbody>
</table>

The best model was the model with k12 and E_{max} significantly different for all drugs, k21 and k10 identical for rac- and levobupivacaine and Css_{50} similar for all three drugs (see table 2). Data are estimates of PK, PD, and rate dependence parameters (% coefficient of variation of parameter estimate). \(\omega^2\) is the variance of interindividual variability parameter (\(\psi\)). Data are given with two significant digits. The rate dependence of QRS widening was tested in the range 170–350 beats/min. k12, k21, and k10 are rate constants from central compartment to peripheral compartment, from peripheral to central compartment and elimination from central compartment, respectively. E_{max} and Css_{50} are the calculated maximum QRS duration and perfusate steady state concentration leading to half E_{max}, respectively.
Data obtained in the three groups during infusion of 5

The choice between levobupivacaine and ropivacaine neces-

sitates further investigation, particularly to compare tox-

icity with nerve-blocking potency.

The authors thank Mrs. Régine le Guen (Kremlin-Bicêtre College of
Medicine, Paris-Sud University, France) for her technical assistance and
Dr. Genery from ChiroScience (Cambridge, United Kingdom) for the
gift of levobupivacaine.

References

1. Clarkson CW: Stereoselective block of cardiac sodium channels
65:1306–23

2. Lee-Son S, Wang GK, Concus A, Crill E, Strichartz GR: Stero-
dlective inhibition of neuronal sodium channels by local anesthetics:
Evidence for two sites of action? ANESTHESIOLOGY 1992; 77:324–35

3. Mazoit JX, Cao LS, Samii K: Binding of bupivacaine to serum
proteins, isolated albumin and isolated alphal-acid glycoprotein:
Differences between the two enantiomers are partly due to cooperativity.
J Pharmacol Exp Ther 1996; 256:109–15

effects of the enantiomers of bupivacaine on the electrophysiological
properties of the guinea-pig papillary muscle. Br J Pharmacol 1991;
103:1275–81

5. Denson DD, Bebbehani MM, Gregg RV: Enantiomer-specific effect
of an intravenously administered arrhythmogenic dose of bupiva-
caine on neurons of nucleus tractus solitarius and the cardiovascular

6. Mazoit JX, Boico O, Samii K: Myocardial uptake of bupivacaine, I:
Pharmacokinetics and pharmacodynamics of bupivacaine enantiomers
in the isolated perfused rabbit heart. Anesth Analg 1993; 77:477–82

comparison of the cardiovascular effects of levobupivacaine and rac-
ivacaine following intravenous administration to healthy volun-

bupivacaine in local anesthetic-sensitive ion channels of peripheral
nerve. ANESTHESIOLOGY 1999; 91:786–95

9. Aberg G: Toxicological and local anesthetic effects of optically
active isomers of two local anesthetic compounds. Acta Pharmacol
Toxicol (Copenh) 1972; 31:737–86

10. Akerman B: Uptake and retention of the enantiomers of a local
anesthetic in isolated nerve in relation to different degrees of blocking
of nervous conduction. Acta Pharmacol Toxicol (Copenh) 1973; 32:
225–36

11. Dyhre H, Lang M, Wallin R, Renck H: The duration of action of
bupivacaine, levobupivacaine, ropivacaine and pethidine in peripheral

12. Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield P, Lundh R:
Acute toxicity of ropivacaine compared with that of bupivacaine.
Anesthesiol Analg 1989; 69:565–9

13. Pitkanen M, Feldman HS, Arthur GR, Covino BG: Chronotropic
and inotropic effects of ropivacaine, bupivacaine, and lidocaine in the
spontaneously beating and electrically paced isolated perfused rabbit

14. Polley LS, Columb MO, Naughton NN, Wagner DS, van de Ven
CJ: Relative analgesic potencies of ropivacaine and bupivacaine for
epidural analgesia in labor: Implications for therapeutic indexes.
ANESTHESIOLOGY 1999; 90:944–50


