Disposition Kinetics of Ropivacaine in Humans

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The pharmacokinetic characteristics of a new local anesthetic drug, ropivacaine, were determined after intravenous infusion of 50 mg of the hydrochloride salt into six healthy male volunteers. Results showed that the disposition of ropivacaine can be described by a biexponential function. Its blood clearance (0.72 ± 0.16 L/min) is intermediate between that of mepivacaine and bupivacaine. Plasma binding averaged 94% ± 1% and the volume of distribution at steady state based on blood drug concentration was 59 ± 7 L. The terminal elimination half-life was 111 ± 62 min.

Key Words: ANESTHETICS, LOCAL—ropivacaine. PHARMACOKINETICS—ropivacaine.

Ropivacaine (*S*-(-)-1-propyl-2′,6′-pipecoloxylidide hydrochloride monohydrate), an amide-type local anesthetic, is the *N*-propyl homologue of bupivacaine and mepivacaine (Figure 1). It is used in water-soluble form as the hydrochloride monohydrate salt. In contrast to bupivacaine and mepivacaine, which are used as racemates, ropivacaine has been developed as the levoisomer. Animal experiments have shown ropivacaine to be less toxic than bupivacaine after intravenous (IV) administration (1). In particular, the ratio between lethal and convulsive doses is higher with ropivacaine than it is with bupivacaine, and ropivacaine is less potent than bupivacaine at inducing cardiac arrhythmias (Astra Pharmaceuticals AB, Södertälje, Sweden; personal communication). As a prelude to comparing the toxicity of ropivacaine and bupivacaine in humans, a low-dose pharmacokinetic study was carried out to elucidate its disposition kinetics.

Methods

Six healthy male volunteers, aged 19–34 yr, took part in the study, which was approved by the local ethics committee. Written informed consent was obtained. The height of the subjects ranged from 172 to 187 cm and their weights were between 65 and 87 kg. All subjects were in the normal weight range for their height. Alcohol, caffeine-containing drinks, and cigarettes were not allowed during the study or for 24 h before it began.

A control blood sample and an initial 12-lead electrocardiogram were obtained before 50 mg (10 mL) of ropivacaine hydrochloride monohydrate as a 0.5% wt/vol solution was infused intravenously at a constant rate, using a Harvard infusion pump, over 15 min (0.67 mL/min). Venous blood (10 mL) was withdrawn from the opposite arm 5, 10, 15, 16, 20, 25, 30, 35, 40, 50, 60, 90, and 120 min and 4, 6, 12, 24, and 25 h after the start of the infusion. The plasma was separated immediately by centrifugation and stored in glass tubes at −20°C until assay. Additional 5-mL blood samples were taken at 16 and 30 min to measure the whole-blood drug concentrations and the extent of plasma protein binding. Heart rate, blood pressure, and 12-lead electrocardiograms were recorded at 5-min intervals for 30 min. In addition, the subjects were monitored continuously using a Roche 125 electrocardiograph. Symptoms or signs of toxicity were recorded.

Plasma and whole blood concentrations of ropivacaine were measured by a gas chromatographic method using a nitrogen-sensitive detector with a precision of 8% at 1 μg/mL. The minimum assayable concentration was 10 ng/mL. Plasma protein binding

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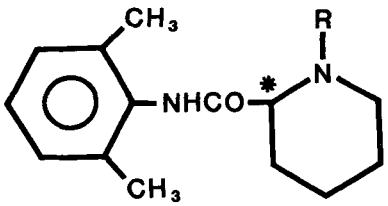

Figure 1. Chemical structure of ropivacaine compared with mepivacaine and bupivacaine. An *asterisk* denotes an asymmetric carbon atom. Ropivacaine, R = n-C_3H_7; mepivacaine, R = n-CH_3; bupivacaine, R = n-C_4H_9. Ropivacaine has been developed as a single enantiomer (levoisomer), whereas mepivacaine and bupivacaine are used as racemates.

was measured using an ultrafiltration technique (Amicon Micropartition System) at 37°C, with mean plasma ropivacaine concentrations of 1.43 ± 0.40 and 0.92 ± 0.17 μg/mL at 16 and 30 min, respectively. Ultrafiltration was preferred to equilibrium dialysis as less than 0.1% of radiolabeled ropivacaine binds to the membrane at the concentrations involved.

Drug concentration-time ($C_{(t)}$) profiles during and after infusion were fitted by Equation (1) using the NONLIN program (2). Concentrations were weighted by the reciprocal of their squared values.

Equation (1) is as follows:

$$C_{(t)} = \frac{R_0}{V_1}\left[\frac{(1 - e^{\lambda_1\tau}) \cdot C_1 e^{-\lambda_1 t}}{-\lambda_1} + \frac{(1 - e^{\lambda_2\tau}) \cdot C_2 e^{-\lambda_2 t}}{-\lambda_2}\right], \quad (1)$$

where τ = infusion time, R_0 = infusion rate, and V_1 = initial volume of distribution.

Values of various pharmacokinetic parameters were calculated from the coefficients (C_1, C_2) and exponents (λ_1, λ_2), which are terms of Equation (1) using standard equations (3). All results were expressed as mean ± SD.

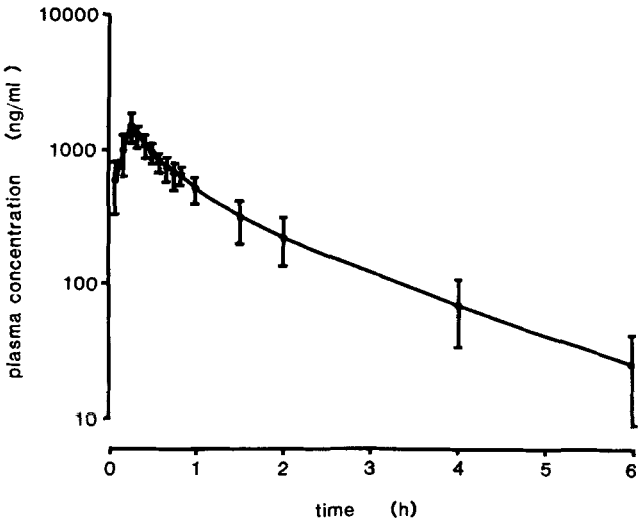

Figure 2. Mean (±SD) venous plasma concentrations of ropivacaine (base) over 6 h after starting a constant-rate IV infusion in six subjects (50 mg of ropivacaine hydrochloride given over 15 min).

Derived pharmacokinetic parameters are shown in Table 1 together with the mean blood/plasma drug concentration ratio and the mean free fraction of drug in plasma. The volume of distribution of unbound drug (Vu_{ss}) was calculated by dividing plasma V_{ss} values by the free fraction of drug in plasma for each individual subject and is also given in Table 1. The mean terminal elimination half-life ($t_{½}$) was 111 ± 68 min and the mean plasma and blood clearances were 0.50 ± 0.12 and 0.72 ± 0.16 L/min, respectively. The volume of distribution at steady state based on blood drug concentration (V_{ss}) was 59 ± 7 L. The mean extent of plasma protein binding was high, 94% ± 1%, with a blood/plasma concentration ratio of 0.690 ± 0.059.

Results

None of the subjects had any symptoms or signs of systemic toxicity, and there were no significant alterations in heart rate, blood pressure, or electrocardiograms during the study.

Concentrations of ropivacaine in plasma samples collected more than 6 h after the start of infusion of 50 mg of ropivacaine could only be detected in one subject. The peak plasma concentration ranged between 1073 and 2048 ng/mL, with a mean of 1503 ± 362 ng/mL. The mean parainfusion and postinfusion plasma concentration–time profile of ropivacaine (Figure 2) was well described by Equation (1) as assessed by the "goodness-of-fit" criteria of Boxenbaum et al. (4).

Discussion

Ropivacaine is less lipid-soluble than bupivacaine (5), but would be expected to be more lipid-soluble than its *N*-methyl homologue mepivacaine. Predictably, therefore, as compared with bupivacaine and mepivacaine, it has intermediate values of unbound volume of distribution at steady state (Vu_{ss}) and blood clearance (Table 2). The former parameter is a better index of tissue binding than the volume of distribution based on the total drug concentration (V_{ss}) in blood, which is more influenced by offsetting differences in plasma binding (5). The major part of ropivacaine in whole blood is associated with the plasma proteins. The extent of protein binding in plasma was very similar to that of bupivacaine (Table 2), and most of

Table 1. Pharmacokinetic Parameters for Ropivacaine in Humans

Variable		Mean	SD
Exponents of equation describing plasma drug concentration–time profile	λ_1 (L/min)	0.057	0.047
	λ_2 (L/min)	0.0079	0.0035
Coefficients of equation describing plasma drug concentration–time profile	C_1 (ng/mL)	1354	510
	C_2 (ng/mL)	482	350
Terminal half-life	$t_{1/2,z}$ (min)	111	62
Plasma clearance	Cl (L/min)	0.50	0.12
Blood clearance	Cl_b (L/min)	0.72	0.16
Volume of distribution at steady state (based on total plasma drug concentration)	V_{ss} (L)	42	5
Volume of distribution at steady state (based on unbound drug concentration)	Vu_{ss} (L)	742	94
Free fraction in plasma	fu	0.06	0.01
Blood/plasma concentration ratio	$K_{b/p}$	0.690	0.059
Volume of distribution at steady state based on blood drug concentration	$V_{ss,b}$	59	7

Table 2. Pharmacokinetic Parameters Describing the Disposition of Mepivacaine, Bupivacaine, and Ropivacaine in Humans

Variable	Mepivacaine	Bupivacaine	Ropivacaine
$t_{1/2,z}$ (min)	114	162	111
Cl_b (L/min)	0.78	0.58	0.73
$V_{ss,b}$ (L)	84	73	59
Vu_{ss} (L)	382	1028	678
Protein binding (%)	78	96	94
$K_{b/p}$	0.92	0.73	0.69

Data for mepivacaine and bupivacaine are from Tucker (6).
Clearance values refer to whole blood clearance. Volumes of distribution are specified with respect to arterial sampling for mepivacaine and bupivacaine and peripheral venous sampling for ropivacaine.

this binding is accounted for by association with α_1-acid glycoprotein. The present data show that clearance of ropivacaine appears to be closer to that of mepivacaine than to that of bupivacaine, suggesting an intermediate hepatic extraction ratio and, therefore, a dependence of its elimination on both liver blood flow and enzyme activity (6). Similarly, the terminal $t_{1/2}$ of the two lower homologues appears to be less than that of bupivacaine (Table 2), reflecting differences in the balance between clearance and distribution, but also, possibly, differences in the ability to calculate the terminal elimination phase accurately as a result of analytical insensitivity.

All of the above observations on the relative pharmacokinetics of the agents must also be qualified by the fact that a single isomer (ropivacaine) is being compared with racemates (mepivacaine, bupivacaine), and there may be appreciable stereoselectivity in disposition processes.

Knowledge of the disposition kinetics of ropivacaine will assist in the design of safe IV infusion regimens to assess the threshold toxicity of the drug in humans, to evaluate its systemic uptake from various perineural sites after single, multiple, or continuous dosage, and to estimate its therapeutic index.

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