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Sciatic Nerve Blockade in Infant, Adolescent, and Adult Rats

A Comparison of Ropivacaine with Bupivacaine

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Background: **Ropivacaine is a newly introduced local anesthetic. No data are available regarding its safety, efficacy, or sensory-selectivity in children. The sciatic block duration and systemic toxicity of bupivacaine and ropivacaine were compared among infant, adolescent, and adult rats.**

Methods: **Infant, adolescent, and adult rats received blocks with ropivacaine or bupivacaine. Nociceptive, proprioceptive, and motor blockade were assessed. Systemic effects (contralateral leg analgesia, seizures, respiratory distress, apnea) were quantified. Plasma local anesthetic concentrations were measured at terminal apnea.**

Results: **Nerve blockade for a given absolute dose lasted longer in infants than in older rats for both drugs. Block duration from ropivacaine generally was the same as or slightly shorter than bupivacaine. There was no difference in sensory-selectivity between the drugs. Doses required to induce all systemic toxicity indices were inversely related to age (*e.g.*, the lethal dose in 50% of animals [LD_{50}] of ropivacaine in infants is 155 mg/kg; in adults it is 54 mg/kg). All indices of toxicity occurred at higher doses per kilogram for ropivacaine than bupivacaine, at all ages (*e.g.*, the LD_{50} of bupivacaine in infants is 92 mg/kg; in adults it is 30 mg/kg). Plasma concentrations at terminal apnea were higher for ropivacaine than for bupivacaine at all ages, and were higher in infants than in older rats.**

Conclusions: **Ropivacaine resembles bupivacaine in its local anesthetic effects but has a greater margin of safety. For a given absolute dose, sciatic blockade in infant rats lasts longer than in adolescents or adults. Although the doses (in milligrams per kilogram) causing toxicity were much higher in infants than in adults, this probably does not correspond to a wider therapeutic index. (Key words: Effective dose in 50% of animals [ED_{50}]; lethality; modality specificity.)**

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LOCAL anesthetics are used widely in children for topical and infiltration analgesia and for peripheral and central nerve blockade. Despite the excellent record of safety for these techniques, seizures and cardiovascular depression may occur with excessive doses or with inadvertent intravascular injection.[1–6]

Ropivacaine is an amino-amide local anesthetic recently released for clinical use in the United States and many other countries. Studies in adult animals and in adult humans suggest that ropivacaine may have two advantages over bupivacaine: (1) It may have greater sensory-to-motor selectivity, and (2) it may be less cardiotoxic at equianesthetic doses and consequently have a wider margin of safety. No data in infant animals or children are available on the safety or efficacy of ropivacaine.

In adult humans, the relative potency of local anesthetics in producing mild systemic toxicity has been studied in volunteers receiving intravenous infusions until they report central nervous system symptoms or show electrocardiographic changes.[7] Such studies are unlikely to

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be performed in infants and younger children both because of ethical considerations and because of their more limited ability to report symptoms. Most of our information regarding systemic toxicity of local anesthetics in human infants and children is derived from case reports or clinical series reporting adverse events with particular doses or infusion rates. Studies in pigs[8] and sheep[9] have reported that infant animals are less susceptible than adult animals to the toxic effects of intravenously administered local anesthetics. However, there have been studies in dogs[10] that found the opposite trend with age, and there have been claims of increased susceptibility to cardiovascular and respiratory depression in human neonates.[11]

We recently reported the development of an infant rat model to study the developmental aspects of local anesthetic action using percutaneous sciatic nerve blockade.[12] In the current study, we modified our previous model to compare the efficacy and toxicity of ropivacaine with those of bupivacaine. Specifically, we addressed the following questions: (1) How does the duration of sciatic nerve block from each drug compare in infant, adolescent, and adult rats? (2) Does one drug appear more sensory selective than the other in young or older rats? (3) How toxic is each drug in infant rats compared with adolescent or adult rats?

Materials and Methods

Stock Bupivacaine and Ropivacaine Solutions

Bupivacaine and ropivacaine hydrochloride (Astra USA, Westborough, MA) were obtained in 0.5% solutions and were diluted to the desired concentration in normal saline.

Animal Care

Animals were cared for in compliance with protocols approved by the Children's Hospital Animal Care and Use Committee. Sprague-Dawley rats were obtained from Charles River Laboratories (Wilmington, MA). Rats are referred to as infants at 5 days of age, adolescents at 15 days, and adults at 70 days. Infant rats weighed 14 ± 3 g (mean and standard deviation; n = 114), adolescents weighed 37 ± 5 g (n = 96), and adults weighed 300 ± 61 g (n = 104). They were housed in groups and kept in a 6 A.M. to 6 P.M. light-dark cycle. Rats were handled repeatedly by the investigators to diminish any effects of stress-induced analgesia. Infant and adolescent rats were separated from their mothers during testing but were promptly returned for warmth and food thereafter.

Sciatic Blockade Technique

Before nerve block injections were given, rats were anesthetized briefly with halothane by face mask.[12,13] General anesthesia lasted < 2 min. The block was conducted by introducing a 30-gauge needle posteromedially to the greater trochanter, pointing in an anteromedial direction.[13,14] Once bone was contacted, the needle was withdrawn 1 mm and drug was injected. The left leg was always used for blocks; the right leg served as control. Investigators assessing neurobehavioral and toxic effects were blinded to the drugs and doses that each rat received.

Assessment of Nerve Blockade

The effectiveness of block was measured every 15 min in all rats, applying the methods of Thalhammer *et al.*[14] and Hu *et al.*[12], with some modifications[13] noted here. The sample size (n) for all experiments was 8–10 rats. The following modalities and functions were measured.

Nociceptive Block. Nociceptive block was tested in two ways. Mechanical nociception was assessed by pinching the lateral aspect of the plantar surface of the hindpaw for one second. All rats were treated with the same specified tool (medium pointed curved forceps, Fisher Scientific, Pittsburgh, PA) by the same investigator. Rats were scored as to whether they withdrew to pinch (score = 1) or did not withdraw (score = 0).

Thermal nociception was measured by a modified hotplate test.[15] The time that a rat would leave its hindpaw on a hot plate (model 39D Hot Plate Analgesia Meter; IITC Inc., Woodland Hills, CA) at 56°C was measured using a stopwatch (this time is called thermal latency). The paw was removed from the hotplate after 12 s by the investigator to avoid harming the rat. This test was repeated three times on each hindpaw for each rat at every time point.

Positional Placing Response. The positional placing response is a test of proprioception. The hindpaw of each rat was pulled back with the dorsum touching the table surface, and its response was scored as follows: 1 = the foot was returned to a position alongside its flank, with the claws splayed (normal); 2 = the foot was returned forward, but with the toes clubbed; 4 = the foot could not be returned (complete motor block). Any intermediate outcome was a score of 3. In infant rats, the score was 4 even in the unblocked state (consequently

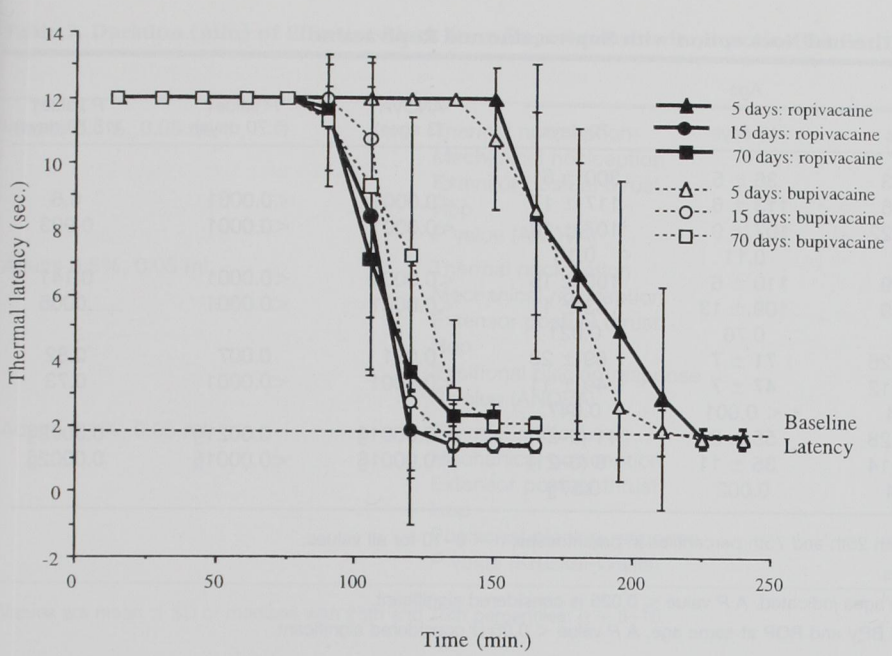

Fig. 1. The time course of thermal latency from sciatic nerve block with 0.1 ml 0.5% bupivacaine and ropivacaine in infant (5 days), adolescent (15 days), and adult (70 days) rats. Data points are mean latency ± SD. n = 8 for each group.

this test was not used as a measure of block efficacy in infants).

Extensor Postural Thrust. The extensor postural thrust is a measure of motor strength. The rat was held above a digital balance and allowed to bear weight on one hindpaw at a time. The maximum weight that the rat could bear without its ankle touching the balance was measured. In the 5-day-old rats, extensor postural thrust was scored as 0 or 1, depending on whether the rat could bear weight.

Hopping. Hopping tested several integrated functions. Each rat was suspended above a horizontal surface and was slowly moved laterally, with one foot touching the table surface. The rat was scored (1 or 0) according to whether it could hop on that foot.

Analysis of Neurobehavioral Data

The duration of effective block for mechanical nociception for each rat was calculated as the mid-point between the last time when there was no response to pinch and the first time when there was a response to pinch. The duration of block of thermal nociception was the time required for latency to return to a value of 7 s (baseline latency is approximately 2 s; thus, 7 s represents the mid-point between maximal latency, which is set at a cutoff of 12 s, and baseline). Nociceptive data are also represented graphically (fig. 1) by averaging the latencies in a treatment group at different times after injection. The duration of block for the positional placing response was defined as the time that it took for the score to recover to a value of 2. The duration of block for hopping was the mid-point of the last time when the rat could not hop and the first time when it could. The duration of block for extensor postural thrust was defined as the time until 50% recovery of weight bearing.

In all animals in which injection did not result in loss of pinch sensation, a thermal withdrawal latency of at least 7 s, a positional placing response score of 2 or more, a hopping score of 0, or at least a 50% reduction in weight-bearing in the extensor postural thrust test, the duration of effective block for the appropriate modality was considered 0 (zero) for computational purposes.

Toxicologic Indices and Determination of Plasma Concentration of Bupivacaine and Ropivacaine

Thermal latency was measured in the contralateral (uninjected) limb in all rats, as a measure of systemic toxicity.[13] Animals were scored as to whether they developed a latency of 12 s (score = 1) or not (score = 0). Seizures and respiratory distress were assessed as being either present (score = 1) or absent (score = 0) at any time. These clinical determinations were always made by the same observer. Seizures were diagnosed in rats displaying rapid, jerking, chaotic movements. These were not subtle and could not be confused with volitional movement of agitated rats. Respiratory distress was di-

Table 1. Duration (min) of Effective Block of Thermal Nociception with Bupivacaine and Ropivacaine

		Age			ANOVA* (3 ages)	*P* value† (5:70 days)	*P* value† (15:70 days)
		5 days	15 days	70 days			
Weight (g)		14 ± 3	36 ± 5	300 ± 61			
0.5%, 0.1 ml	Bupivacaine	172 ± 5	113 ± 6	117 ± 17	<0.0001	<0.0001	0.6
	Ropivacaine	179 ± 22	107 ± 9	107 ± 10	<0.0001	<0.0001	0.993
	P value‡	0.48	0.11	0.18			
0.5%, 0.05 ml	Bupivacaine	147 ± 9	110 ± 6	100 ± 15	<0.0001	<0.0001	0.141
	Ropivacaine	141 ± 9	109 ± 13	83 ± 11	<0.0001	<0.0001	.0005
	P value‡	0.27	0.76	0.021			
0.1%, 0.1 ml	Bupivacaine	109 ± 26	71 ± 7	69 ± 23	0.001	0.007	0.82
	Ropivacaine	88 ± 12	47 ± 7	49 ± 11	<0.0001	<0.0001	0.73
	P value‡	0.064	< 0.001	0.047			
0.1%, 0.05 ml	Bupivacaine	67 ± 28	55 ± 9	11 (0–24)	<0.0001§	0.0021§	0.0002§
	Ropivacaine	52 ± 14	35 ± 11	8 (0–21)	<0.0001§	<0.0001§	0.0002§
	P value‡	0.144	0.002	0.57§			

Values are means ± standard deviation, or medians with 25th and 75th percentiles in parentheses; n = 8–10 for all values.

* *P* value of ANOVA (or Kruskal-Wallis) for all three ages.

† *P* value of *t* test (or Mann-Whitney U test) comparing ages indicated. A *P* value < 0.025 is considered significant.

‡ *P* value of *t* test (or Mann-Whitney U test) comparing BPV and ROP at same age. A *P* value < 0.05 is considered significant.

§*P* value of Mann-Whitney U test or Kruskal-Wallis test.

agnosed in rats in which a pattern of slow deep breathing, gasping, or stertorous breathing developed.

Toxicity is expressed both graphically (milligrams of drug per kilogram shown on the x-axis; percentage of rats affected on the y-axis) and in terms of the dose per kilogram that affected 50% of rats (*i.e.*, the ED_{50}). The $ED_{50(sz)}$, $ED_{50(resp)}$, $ED_{50(lat)}$, and the lethal dose that affected 50% of rats (LD_{50}) are used for seizures, respiratory distress, the development of maximal latency (*i.e.*, at 12 s) in the contralateral leg, and terminal apnea, respectively.

Rats that became apneic for 20 s received intraperitoneal pentobarbital before cardiac puncture and the aspiration of blood for determination of plasma drug levels. The whole blood was placed on ice immediately, and the plasma was separated by centrifugation within 30 min and stored at −20°C. Plasma concentrations of ropivacaine and bupivacaine were subsequently determined by gas chromatography as described.[16]

Statistical Analysis

Durations of block and latencies in groups of rats are expressed as mean ± SD. Most statistical inferences are made with the Student's *t* test (paired in comparisons between injected and contralateral legs, unpaired in all other cases), or with analysis of variance. In two instances (where adult rats were injected with 0.05 ml 0.1% bupivacaine or ropivacaine) the data were not normally distributed because of the presence of many zero-duration blocks. Here the results were reported as medians (25th to 75th percentiles). For comparisons involving these two data sets, we performed nonparametric tests (Kruskall-Wallis, Mann-Whitney U test, or both, or Wilcoxon matched-pairs signed-rank test). When multiple statistical comparisons were made between groups, Bonferroni correction was used; if n comparisons were made, a *P* value of 0.05/n was considered significant.

The LD_{50} and effective concentration that affected 50% of rats values were calculated and compared using logit (logistic regression) analyses, using Stata statistical software (Stata Corporation, College Station, TX).

Results

Effect of Age on the Duration of Thermal Nociceptive Block from Bupivacaine and Ropivacaine

Rats at 5 days (infants, 14 ± 3 g), 15 days (adolescents, 37 ± 5 g), and 70 days (adults, 300 ± 61 g) were injected with bupivacaine or ropivacaine at a fixed dose (*i.e.*, not scaled to body weight). Figure 1 shows the time course of thermal latency for ropivacaine in all three ages (n = 8–10 in all neurobehavioral experiments). Analysis of the durations of thermal nociceptive block (table 1) showed that the block lasted longer in infant rats than in adolescent or adult rats for both drugs at all dosages. At

Table 2. Duration (min) of Effective Block from Bupivacaine or Ropivacaine for Each of the Functions Tested

		Bupivacaine	Ropivacaine
Infants 0.5%, 0.05 ml	Thermal nociception	147 ± 9	141 ± 9
	Mechanical nociception	146 ± 11	141 ± 10
	Extensor postual thrust	150 ± 8	144 ± 10
	Hop	150 ± 8	144 ± 5
	P value (ANOVA)	0.76	0.74
Adults 0.5%, 0.05 ml	Thermal nociception	100 ± 14	83 ± 11
	Mechanical nociception	92 ± 18	79 ± 11
	Extensor postual thrust	108 ± 12	84 ± 11
	Hop	105 ± 14	81 ± 13
	Positional placing response	101 ± 14	84 ± 12
	P value (ANOVA)	0.21	0.83
Adults 0.1%, 0.05 ml	Thermal nociception	11 (0–24)	8 (0–21)
	Mechanical nociception	0 (0–9)	0 (0–0)
	Extensor postual thrust	39 (25–50)	9 (0–18)
	Hop	45 (34–56)	23 (0–23)
	Positional placing response	46 (34–53)	24 (15–25)
	P value (Kruskal-Wallis)	0.04	0.007

Values are mean ± SD or medians with 25th and 75th percentiles; n = 8–10.

the higher volume of injectate (0.1 ml), there was no difference in the duration of block between adolescent and adult rats. However, when the volume was reduced to 0.05 ml, the duration of thermal nociceptive block was slightly longer in adolescents than in adult rats. At the lowest dosage (0.05 ml of 0.1% drug), where the difference between adolescents and adults was most striking, there were many (four of eight) zero-duration blocks in each of the adult groups.

At most doses, there was little difference between the duration of block in adult and adolescent rats, despite a more than eightfold difference in weight. For example, the duration of thermal nociceptive block for 0.1 ml 0.5% ropivacaine was 107 ± 10 min (mean ± SD) for adult rats and 107 ± 9 min for adolescent rats ($P = 0.993$). The duration of thermal nociceptive block in infants (179 ± 22 min) was increased compared with that of adolescents ($P < 0.0001$) by approximately 70%. The average weight of infant rats was approximately 2.3 times less than adolescent rats.

Comparison of the Duration of Block from Bupivacaine and Ropivacaine

There was no significant difference in the duration of block between bupivacaine and ropivacaine at the higher dosage (0.1 ml 0.5% drug) at any age (table 1). In the infant, there was no significant difference between the durations of thermal nociceptive block with bupivacaine and ropivacaine at any volume or concentration. With blocks performed using either lower volumes or more dilute concentrations in adolescents and adults, some comparisons showed a shorter duration of thermal nociceptive block with ropivacaine compared with bupivacaine (table 1).

Functional Selectivity of Bupivacaine and Ropivacaine

We also evaluated the degree to which bupivacaine and ropivacaine affected the duration of block of various functional modalities (table 2). There were no significant differences between hotplate latency and any of the other four modalities (mechanical nociception, extensor postional thrust, hopping response, and positional placing response) when the higher doses (0.05 ml of 0.5% drug) were used in any of the age groups (top two sections of table 2; data for adolescent rats not shown). The results were similar for rats injected with 0.1 ml 0.5% drug and 0.1 ml 0.1% drug (data not shown).

It was possible that the lack of modality specificity was a result of the use of doses of local anesthetic high enough to fully block all fiber types regardless of their individual susceptibilities. To test this hypothesis, we compared the durations of block of the functional modalities at the lowest dose. In adult rats only that received 0.05 ml of 0.1% solution (bottom section of table 2), the mean durations of the various modalities were different (Kruskall-Wallis test). Nevertheless, because of the low probability values required for statistical significance with multiple comparisons, we could not demonstrate differences in the duration of block for individ-

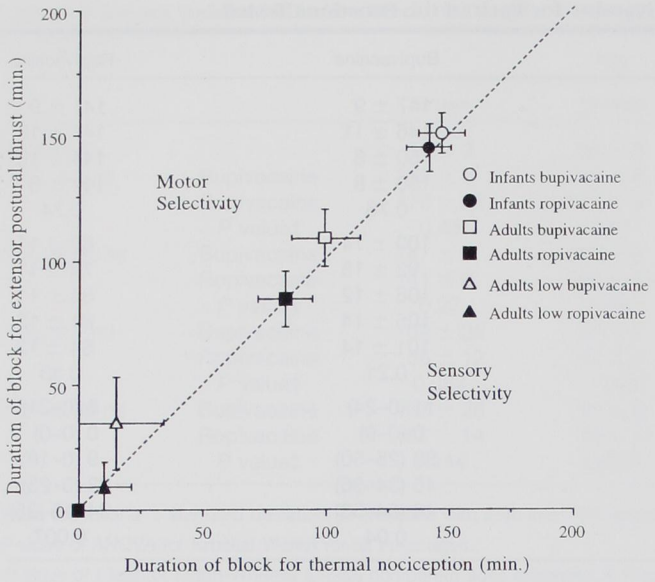

Fig. 2. A comparison of the durations of motor (extensor postural thrust) and sensory (thermal nociception) block for infant and adult rats receiving 0.05 ml 0.5% ropivacaine or bupivacaine, or 0.05 ml 0.1% drug ("low" dose in the figure). Data points are mean latency ± SD, except for the low doses, which are median with 25th and 75th percentiles. The dotted line is a line of identity between nociceptive and motor blockade. n = 8–10 for each group.

ual functions. Therefore, to the limits of detection by these measures, ropivacaine and bupivacaine were equally nonselective in their pattern of blockade.

Figure 2 focuses on the clinically important comparison of the durations of motor block (extensor postural thrust; y-axis) and sensory block (thermal nociception; x-axis). There was no clear sensory selectivity (which would result in points below the diagonal line) for either drug at any dose.

Toxicity of Bupivacaine and Ropivacaine

Groups of rats were injected at the sciatic nerve with increasing doses of bupivacaine or ropivacaine (scaled to body weight) and were observed for the development of (1) increased thermal latency in the contralateral (*i.e.*, uninjected) extremity, (2) clinical seizures, (3) clinical respiratory distress, and (4) terminal apnea. Table 3 tabulates the doses per kilogram at which 50% of rats were affected by each of these (ED_{50} or LD_{50}). All comparative statements made in the following description of those data assume that $P < 0.01$ is required for statistical significance.

There was a consistent pattern of toxicity in all groups. The ED_{50}s for the various indices generally occurred in the order $ED_{50(resp)} \leq ED_{50(lat)} \leq ED_{50(sz)} \leq LD_{50}$ (except in infants in which overt seizure activity was not seen in infant rats, possibly because respiratory arrest occurred first). This was true at all ages, and for both drugs.

Toxicity from both local anesthetics occurred at lower doses (scaled to body weight) in adults than in adolescents or infants. The LD_{50} for bupivacaine was 30 ± 5 mg/kg in adult rats, and 92 ± 6 mg/kg in infant rats. Similarly, the LD_{50} for ropivacaine was 56 ± 6 mg/kg in adult rats, and 145 ± 6 mg/kg in infants. For both drugs the onset of toxicity in infant rats was seen only at doses per kilogram exceeding doses per kilogram that would be universally toxic in adults (as evidenced by the fact that the $ED_{50(resp)}$ in infants was more than double the LD_{50} in adults). The LD_{50}s in adolescent rats were between the infant and adult values. For both drugs, the ED_{50}s for the three other indices of toxicity, $ED_{50(resp)}$, $ED_{50(lat)}$, and $ED_{50(sz)}$, were also lowest in adults, were intermediate in adolescents, and were highest in infants. (It bears noting, however, that the absolute doses required to induce toxic end points were higher in adult than in infant rats. For example, the LD_{50}s for ropivacaine in infant and adult rats were 145 mg/kg and 56 mg/kg, respectively, which corresponded to 2 mg and 16.8 mg, respectively.)

Ropivacaine was consistently less toxic than bupivacaine. The LD_{50}s and all three ED_{50}s were significantly higher for ropivacaine than for bupivacaine at all ages. In infant rats (fig. 3), the onset of overtly toxic effects occurred at a higher dose per kilogram of ropivacaine than the uniformly fatal dose per kilogram of bupivacaine: The $ED_{5(resp)}$ for ropivacaine was 116 ± 6 mg/kg, whereas the LD_{95} for bupivacaine was 103 ± 11 mg/kg ($P = 0.025$). This impressive disparity between the toxic ranges of the two drugs was not seen to the same degree in the adult and adolescent rats.

Plasma Concentrations of Ropivacaine or Bupivacaine at the Time of Terminal Apnea

Plasma was obtained from all rats that developed terminal apnea during the experiments, and the concentration of bupivacaine or ropivacaine was measured as described in Materials and Methods. The data were grouped by age and by drug (table 4). The lethal concentration of ropivacaine was twice that of bupivacaine in adult rats, 2.5 times bupivacaine in adolescents, and 3.3 times bupivacaine in infant rats. The lethal serum concentrations of both drugs were significantly higher (table 4) in infant rats than in adults (by a factor of approximately 1.5 for bupivacaine and 2 for ropiva-

Table 3. Doses (mg · kg^{-1}) of Bupivacaine and Ropivacaine Required to Induce Respiratory Distress, Increased Contralateral Latency, Seizures, or Terminal Apnea in 50% of Rats (ED_{50} or LD_{50})

		Age of Rats				
		5 days		15 days		70 days
Weight (g) of rats		14 ± 3		37 ± 5		300 ± 61
Bupivacaine	$ED_{50\ (resp)}$	74 ± 6	*	35 ± 5	*	21 ± 3
		†		†		
	$ED_{50\ (lat)}$	84 ± 6	*	47 ± 5	*	22 ± 4
	$ED_{50\ (sz)}$	†		51 ± 6	*	27 ± 4
	LD_{50}	92± 6	*	49 ± 6	*	30 ± 5
Ropivacaine	$ED_{50\ (resp)}$	124 ± 3	*	51 ± 5	*	35 ± 3
		†		†		
	$ED_{50\ (lat)}$	131 ± 2	*	60 ± 5	*	37 ± 3
						†
	$ED_{50\ (sz)}$	†		67 ± 7	*	46 ± 5
						†
	LD_{50}	145 ± 6	*	67 ± 7	*	56 ± 6

Values are ED_{50} with 95% confidence intervals for respiratory distress, contralateral latency, seizures, and terminal apnea.

* Statistical difference ($P < 0.01$) between adjacent values.

† Statistical difference ($P < 0.01$) between values above and below the symbol (there is no $ED_{50\ (sz)}$ for infant rats).

The following statistically significant differences also occurred: (1) each value for bupivacaine was less than the corresponding value of ropivacaine, (2) each value for infants was greater than the corresponding adult value, and (3) each LD_{50} was higher than the corresponding $ED_{50\ (resp)}$ and, in the case of infants and adults injected with ropivacaine, the $ED_{50\ (lat)}$.

caine), but they were not higher in adolescent compared with adult rats.

Discussion

Ropivacaine produced sciatic nerve blockade in infant, adolescent, and adult rats that appeared quite similar in duration and modality-selectivity to that seen with bupivacaine.

The duration of thermal nociceptive blockade from ropivacaine was not markedly different from bupivacaine at the higher dosages used, at any age. This is consistent with the findings of many investigators[17–25] in adult humans. Other investigators have found that the duration of blockade of ropivacaine is shorter than that of bupivacaine,[26–31] a pattern that also occurred in our study in adult and adolescent rats at the lower dosages.

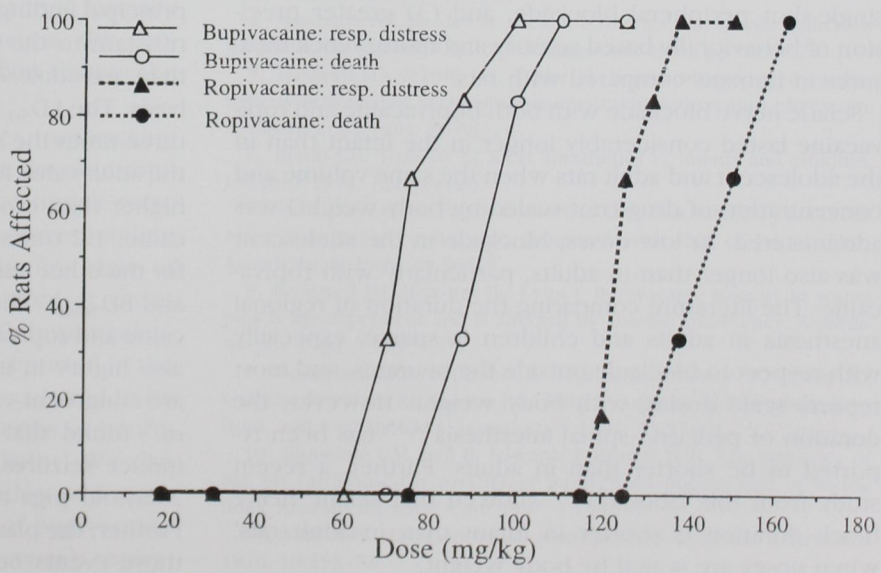

Fig. 3. The percentage of infant rats in which respiratory distress (the earliest sign of toxicity in our study) and terminal apnea developed with increasing doses of bupivacaine or ropivacaine.

Table 4. Plasma Concentrations (μg/ml) of Ropivacaine and Bupivacaine at Time of Terminal Apnea

Age of rats (days)	Bupivacaine	n	Ropivacaine	n	*P* Value between Drugs
5	11.3 ± 5.3	17	37.6 ± 17.5	12	0.0003
15	7.1 ± 1.9	12	18 ± 12.3	18	0.002
70	7.9 ± 1.9	15	15.8 ± 7.3	28	<0.0001
ANOVA *P* value (all ages)	0.007		<0.0001		
P value 5 *versus* 70 days	0.023		0.001		
P value 15 *versus* 70 days	0.30		0.48		

Values are mean plasma concentration (in μg) ± SD. The *P* values are the results of *t* tests, unless stated otherwise. $P < 0.025$ is considered statistically significant.

We did not find significant differences in sensory versus motor block duration between the two drugs administered over a range of volumes and concentrations. Specifically, ropivacaine did not have a prolonged duration of sensory (thermal nociceptive) block compared with motor (extensor postural thrust) block. These data are consistent with the findings of some adult human studies, usually involving epidural anesthesia,[18,20,23,29,31,32] although other investigators have suggested that ropivacaine has a longer duration, frequency of sensory block, or both relative to motor block compared with bupivacaine.[17,19,21,22,24,26,28,30,33] Studies of ropivacaine and bupivacaine in brachial plexus block[23] and intercostal nerve block[29] did not show a relatively longer sensory block. Brachial plexus blockade in the guinea pig also did not show a relative prolongation of sensory over motor blockade.[25] The lack of sensory selectivity, in contrast to some human studies, may reflect at least three factors: (1) true species differences, (2) pharmacokinetic and pharmacodynamic differences between steady state prolonged epidural infusion *versus* single-shot peripheral blockade, and (3) greater precision of behaviorally based sensory and motor block measures in humans compared with rats.

Sciatic nerve blockade with both bupivacaine and ropivacaine lasted considerably longer in the infant than in the adolescent and adult rats when the same volume and concentration of drug (not scaled by body weight) was administered. At low doses, blockade in the adolescent was also longer than in adults, particularly with ropivacaine. The literature comparing the duration of regional anesthesia in adults and children is sparse, especially with respect to blockade outside the neuraxis, and most reports scale dosing with body weight. However, the duration of pediatric spinal anesthesia[34,35] has been reported to be shorter than in adults. Further, a recent study from this laboratory[12] showed that sciatic nerve block duration is shorter in infant than in adult rats, when doses are scaled by body weight.

Although the common clinical practice of scaling local anesthetics doses by weight in children makes sense from a toxicologic perspective, it is not clear that weight-based dosing is relevant for efficacy in nerve blockade. Our data showed constancy of block duration (or a relatively small difference) when the same volume of drug was injected in adolescent and adult rats despite an eightfold difference in mass. (The only group in which there was a large difference between adults and adolescents was in the lowest dose group, in which the difference was largely accounted for by the larger number of unsuccessful blocks in the adults: Four of eight blocks were of zero duration for both bupivacaine and ropivacaine, whereas there were none in the adolescents. Our study could not distinguish between geometric, pharmacokinetic, and pharmacodynamic reasons for these unsuccessful blocks. Technical failure is an unlikely cause given the fact that these investigators consistently have success rates > 99% for obtaining block when larger doses are used.)

The toxicologic section of this study contains two principal findings. The first is that infants are much more resistant to the toxicity of bupivacaine and ropivacaine than are adolescents and adults on a dose-per-kilogram basis. The LD_{50} (in milligrams per kilogram) in infants is three times the adult value for bupivacaine and 2.7 times the adult value for ropivacaine. Adolescent LD_{50}s are also higher than in adults but less so (1.5 times for bupivacaine, 1.2 times for ropivacaine). The same is also true for the other manifestations of toxicity measured (ED_{50rd} and ED_{50lat}). The plasma concentrations of both bupivacaine and ropivacaine at the time of terminal apnea were also higher in infants than in older rats. These findings are congruent with some previous research. Badgwell *et al.*[8] found that the doses of bupivacaine required to induce seizures, dysrhythmias, or both were higher in 2-day-old pigs than in 2-week-old or 2-month-old pigs. Further, the plasma concentrations of bupivacaine when those events occurred was higher in 2-day-old than in

older pigs. However, unlike our findings, that study reported that the lethal dose (defined in mg/kg) was the same between the age groups. Morishima *et al.*[9] found that the dose that elicited convulsions from a lidocaine infusion was more than three times greater in newborn sheep than in adult animals, and they found similar differences in other measures of toxicity, such as hypotension and cardiovascular collapse. However, there is no universal agreement among laboratory investigations about the relative safety of ropivacaine *versus* bupivacaine. Riquelme *et al.*[10] found that 6-week-old dogs required a lower dose of bupivacaine than other ages to induce cardiovascular depression, and the plasma concentration that induced cardiovascular depression was lower in dogs younger than 13 weeks (inclusive) than in older dogs. (Interestingly, the mean toxic dose of bupivacaine in 2-week-old dogs was not lower than that of older dogs, and was possibly higher.) Our study provides further support of the view that infant animals are resistant to local anesthetic toxicity.

Although the LD_{50}s for both local anesthetics in the infant rat is approximately three times the adult value in milligrams per kilogram, this should not be construed as indicating that the therapeutic index (LD_{50}:ED_{50} ratio) of either drug is greater in infants. If equal doses (in milligrams) are delivered to an infant or to an adult rat, the infant will receive 21.3 times as many milligrams per kilogram. Thus the therapeutic index in the infant rat is likely to be lower than in the adult (the local anesthetics would have to be 21.3/3 = 7.1 times more potent in the infant than in the adult for their therapeutic indices to be equal). We did not determine the ED_{50}s of local anesthetics in this study, and therefore we cannot formally calculate the therapeutic index. Nonetheless, the conclusion that ropivacaine is safer in the infant than in the adult is probably not warranted.

The second finding was that at all ages, ropivacaine caused less toxicity than bupivacaine. The doses of ropivacaine required for toxicity or terminal apnea were typically approximately 1.5 times the corresponding doses of bupivacaine. In fact, in infants the first signs of toxicity from ropivacaine were encountered at doses that would have been uniformly lethal with bupivacaine. These findings are in accord with results reported in the current literature, in which ropivacaine was found to be safer than bupivacaine[17,25,26,28,36–38] in terms of neurologic and cardiovascular toxicity, and lethality. We also showed that the lethal plasma concentration of ropivacaine was significantly greater than that of bupivacaine at all ages. Thus the differences in LD_{50} between ropivacaine and bupivacaine, and between infants and adults, are not solely the result of differences in uptake, distribution, and clearance, but rather appear to reflect intrinsic pharmacodynamic differences in toxicity or susceptibility.

In conclusion, we found little difference in efficacy and no difference in modality specificity between ropivacaine and bupivacaine. We also found that the duration of both drugs is longer in infants than in adults when equal volumes of the same drug concentrations are administered. However, there appears to be a much greater margin of safety with ropivacaine than bupivacaine, especially in infants. The data that we report here are the first demonstration of the safety of ropivacaine in an animal model of pediatric regional anesthesia and of its superior safety compared with bupivacaine. We believe these findings warrant further investigation in clinical comparisons of the two drugs in children.

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