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Effect of Ropivacaine on Cutaneous Capillary Blood Flow in Pigs

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The effect of subcutaneous infiltration of ropivacaine and bupivacaine on local cutaneous blood flow was assessed by the laser Doppler method. One milliliter of each of ten test solutions (ropivacaine 0.25% and 0.75%, bupivacaine 0.25% and 0.75%, and saline, each with and without added epinephrine 5 μg/ml) was injected subcutaneously at separate sites on the side of each pig (n = 6). Skin blood flow was measured by laser Doppler at all sites before and 5, 10, 15, and 30 min after injection. Subcutaneous injection of ropivacaine 0.25% or 0.75% decreased cutaneous blood flow by a maximum of 52% ± 11% and 54% ± 14% (mean ± SE), respectively. In contrast, bupivacaine 0.25% or 0.75% increased flow by 90% ± 32% and 82% ± 48%, and injection of saline increased blood flow by 32% ± 17%. Cutaneous blood flow after the injection of ropivacaine was significantly lower than after injection of bupivacaine or saline, and was also lower than at the uninjected control site ($P = 0.0009$). All of the solutions with epinephrine decreased blood flow to a similar extent (48–73%, $P = 0.3$). The ability of ropivacaine to produce cutaneous vasoconstriction offers several advantages over the other local anesthetics presently available for infiltration anesthesia. (Key words: Anesthetics, local: bupivacaine; ropivacaine. Measurement techniques, blood flow: laser Doppler. Sympathetic nervous system, vasoconstrictors: epinephrine.)

ALL LOCAL ANESTHETICS, except cocaine, are considered to produce vasodilation when injected subcutaneously at clinically useful concentrations.[1] In contrast, ropivacaine, a new long-acting aminoamide local anesthetic, produces skin blanching when injected subcutaneously in humans, suggesting a vasoconstrictive action on the cutaneous microvasculature.[2] The purpose of this study is: 1) to quantify the effects of ropivacaine on cutaneous blood flow; 2) to compare these effects with those produced by bupivacaine; and 3) to assess the ability of epinephrine to produce vasoconstriction when added to either of these drugs.

Methods

We chose to study the effects of local anesthetics in pigs because pig skin is considered to be the closest to that of humans of any experimental animal.[3] Six piglets (13.3 ± 0.2 kg, mean ± SE) were anesthetized using intraperitoneal thiamylal (25–40 mg/kg). A stable depth of sedation was maintained with continuous iv methohexital, titrated to a minimal lid reflex and a regular respiratory rate. Throughout the experiment, the animals spontaneously breathed through a "snout-cone" connected to a standard anesthesia machine delivering 100% oxygen. Although blood gases were not monitored, no periods of apnea or irregular respiration occurred. The physiologic well-being of the animals was maintained throughout the experiments without need for mechanical or pharmacologic intervention. Rectal temperature was maintained by warming the ambient room temperature and placing a heated water blanket beneath the animal. All animals quickly recovered after completion of the experiment and discontinuation of the methohexital.

One side of each animal was carefully shaved from front leg to rump (but not on the legs). Eleven experimental skin sites, 2.0 cm in diameter (the diameter of the laser Doppler probe), were marked on the side of the animal. These 11 sites were at least 7.5 cm apart and at least 10 cm from skin that was in contact with the water blanket. Skin blood flow was allowed to equilibrate for 15 min after the stimulus of shaving and marking before blood flow measurements were made. Baseline blood flow was sequentially measured at the 11 skin sites using a laser Doppler capillary perfusion monitor (Medpacific LD® 5000). The laser Doppler probe rests lightly on the skin and is secured in place with double-sided tape (double-stick discs, 3M®). The probe takes approximately 3 s to produce a stable reading. We left the probe in place for 20 s before moving it to the next site. A complete sequence of blood flow measurements at the 11 sites takes approximately 4 min.

We chose to use the laser Doppler monitor because it is noninvasive and permits rapid and repeated measurements without altering cutaneous blood flow. The laser Doppler capillary perfusion monitor functions by directing a laser light beam upon the skin and then evaluating the reflected light. Laser light is reflected from static tissue without change in frequency. However, light reflected from moving red blood cells undergoes a frequency shift as a result of the Doppler effect. The magnitude of this frequency shift, or Doppler shift, is directly proportional to the velocity and mass of erythrocytes in the capillary bed, and linearly correlates ($R = 0.8–0.98$) with blood flow as measured by other techniques (plethysmography, radiolabeled microsphere uptake, ^{133}Xe washout, elec-

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tromagnetic flow probe).[4–7] Finally, laser Doppler measurements of capillary flow correlate with blood loss from skin incisions in pigs.[8]

Ten test solutions were injected subcutaneously in each animal: normal saline; ropivacaine 0.25% and 0.75%; and bupivacaine 0.25% and 0.75% (each administered with and without epinephrine 5 μg/ml). The 11th site was not injected and served as a control. The drugs were randomized to the various sites and observers were blinded to the identity of the solutions injected. We chose 5 μg/ml because this concentration of epinephrine was found to be optimal for reducing blood flow in a similar model.[9] One milliliter of solution was injected through a 30-G needle held at a 45° angle to the skin, with the needle point directly below the center of each experimental site. Subcutaneous injections are easy to standardize in the pig because intradermal injection is almost impossible to perform due to nondistensibility of the skin. Injection of 1 ml of solution routinely raises a wheal approximately 2 cm in diameter. Injections were made in the same order and over the same time span as the baseline blood flow measurements. Blood flow was measured at all ten injected sites 5, 10, 15, and 30 min after injection. These measurements were made in the same order and over the same time frame as previous measurements and injections. Blood flow at the uninjected, control site was measured immediately prior to and immediately after the measurements at the injected sites. These two measurements were averaged to obtain the control blood flow for each interval. Serum levels of local anesthetic were not measured. No attempt was made to measure the duration of anesthesia because pin prick or other painful stimulation of the skin alters cutaneous blood flow.[10]

Regional differences in blood flow were accounted for by normalizing the measurements of flow made after injection of a test solution to the baseline flow at the site prior to injection. Changes in blood flow are expressed as a percent change from control blood flow. Variations in skin blood flow over the course of the experiment were accounted for by normalizing the changes in blood flow at a given site to the changes in blood flow at an uninjected control site. Thus, the change in cutaneous blood flow at an injected site is determined by the formula:

$$\%\ \text{change in blood flow} = \frac{S_x - S_0}{S_0} - \frac{C_x - C_0}{C_0} \times 100$$

where S_x is the blood flow at an injected site X min after injection, S_0 is the baseline flow at that site prior to injection, C_x is the flow at the control site X min after the injections were made at the injected sites, and C_0 is the blood flow at the control site at the same time that the baseline flow measurements were made at the injected sites.

Although the maximum increase or decrease in cutaneous blood flow usually occurred 5–10 min after the anesthetic solution was injected, there was some variability in the time to maximum effect between piglets. To define the maximum changes in blood flow, we averaged the maximum changes in blood flow produced by each drug.

Differences in baseline capillary flows at individual sites were assessed by ANOVA. Changes in capillary flow produced by the solutions were compared using ANOVA with repeated measures models.[11] Differences were assessed between the two concentrations of each drug, each concentration of the two different drugs, each solution with and without epinephrine, each drug solution and saline, and each solution and the uninjected control site. Although we report all P values less than 0.05, the Bonferroni correction for multiple comparisons indicates that a P value less than 0.003 is required for statistical significance. Normalized blood flows were analyzed by repeated measures ANOVA with two grouping factors (by drug and concentration) and one within factor (blood flow over time). Differences in the maximum changes in blood flow produced by injection of the plain solutions were assessed by ANOVA. Similarly, differences in the maximum changes produced by the epinephrine-containing solutions were compared by ANOVA. When significant differences were found, 95% confidence intervals were used to identify the groups that differed. Differences in the maximum changes produced by each plain solution and the corresponding epinephrine-containing solution were assessed by paired t test.

This study was approved by the Research Advisory Committee and the Animal Care and Use Committee of the Virginia Mason Research Center. The guidelines of the American Association for the Accreditation of Laboratory Animal Care were followed for animals in this study.

Results

Subcutaneous injection of ropivacaine reduced cutaneous blood flow to a similar degree at both concentrations (0.25% *vs.* 0.75% $P = 0.4$, tables 1 and 2). Bupivacaine increased cutaneous blood flow equally at the two concentrations studied (0.25% *vs.* 0.75% $P = 0.2$). When the data for the two concentrations of each drug are combined and compared, ropivacaine decreased whereas bupivacaine increased absolute capillary blood flow ($P = 0.03$). When the effects of the drugs are normalized (percent change from control), the magnitude and direction of change in blood flow produced by ropivacaine was significantly different from that produced by bupivacaine ($P = 0.01$) (fig. 1).

When the maximum changes in blood flow produced by injection of these drugs are compared, blood flow was

TABLE 1. Blood Flow at Each Site before (baseline) and 5, 10, 15, and 30 min after Injection of the Local Anesthetic or Saline and at an Uninjected Control Site

Drug	Concentration (%)	Baseline	Flow (MV) Time after Injection (min) 5	10	15	30
Ropivacaine	0.25	93 ± 9	81 ± 17	90 ± 13	84 ± 10	78 ± 10
Ropivacaine*	0.75	101 ± 14	81 ± 21	60 ± 8	67 ± 9	61 ± 11
Bupivacaine	0.25	75 ± 8	112 ± 12	123 ± 35	93 ± 13	96 ± 10
Bupivacaine	0.75	108 ± 15	171 ± 55	161 ± 40	160 ± 43	185 ± 69
Saline	—	85 ± 6	82 ± 14	77 ± 12	94 ± 8	101 ± 8
Control (uninjected)	—	92 ± 12	86 ± 10	95 ± 10	90 ± 9	88 ± 10

Values are mean ± SE, n = 6 for all measurements.
* $P = 0.03$, *versus* the uninjected control site by ANOVA with repeated measures. No other significant differences between drugs, concentrations, or any drug and saline or control when blood flows after injection of each solution are individually compared by ANOVA with repeated measures.

significantly lower after the injection of ropivacaine than after injection of bupivacaine, saline, or at the uninjected control site (table 2, $P = 0.0009$). The addition of epinephrine to ropivacaine did not alter the maximum decrease in blood flow observed; however, epinephrine significantly decreased blood flow when added to bupivacaine or saline (table 2).

Epinephrine increased the vasoconstriction produced by ropivacaine 0.25% but not 0.75% (table 3). However, the P value for 0.25% (0.03) would not be considered statistically significant if the Bonferroni correction is applied. The addition of epinephrine to bupivacaine reduced skin blood flow, counteracting the vasodilatory effects of this drug ($P = 0.004$, table 4).

There was no difference in capillary blood flow prior to injection (baseline flows) among the test sites ($P > 0.4$) (table 1). Blood flow at the uninjected control site did not change significantly during the course of the experiments. The mean coefficient of variation for repeated measurements at uninjected control sites over the 30-min test period was 11.8% (with a range of 0–30%).

TABLE 2. Maximum Percent Change in Capillary Blood Flow at Each Site after Subcutaneous Injection of a Test Solution with or without Added Epinephrine

Solution	Plain	With Epinephrine (5 μg/ml)
Ropivacaine 0.25%	−52 ± 11*	−48 ± 8
Ropivacaine 0.75%	−54 ± 14*	−52 ± 13
Bupivacaine 0.25%	+90 ± 32	−73 ± 9†
Bupivacaine 0.75%	+82 ± 48	−70 ± 11‡
Saline 0.90%	+32 ± 17	−60 ± 7†
Control (uninjected)	+5 ± 11	—

Values are mean ± SE, n = 6 for all measurements.
* $P = 0.0009$, ropivacaine *versus* bupivacaine, saline, or control.
† $P = 0.001$, test solution + epinephrine *versus* plain solution.
‡ $P = 0.03$, test solution + epinephrine *versus* plain solution.

Discussion

Ropivacaine (S-(−)-1-propyl-2′,6′-pipecoloxylidide hydrochloride monohydrate) is a promising new local anesthetic. A cogener of bupivacaine and mepivacaine (bupivacaine has a butyl, mepivacaine a methyl, side chain), ropivacaine also differs in that it is prepared purely as the (S)-enantiomer. Initial studies indicate that ropivacaine's duration and potency are similar to bupivacaine.[2] Ropiv-

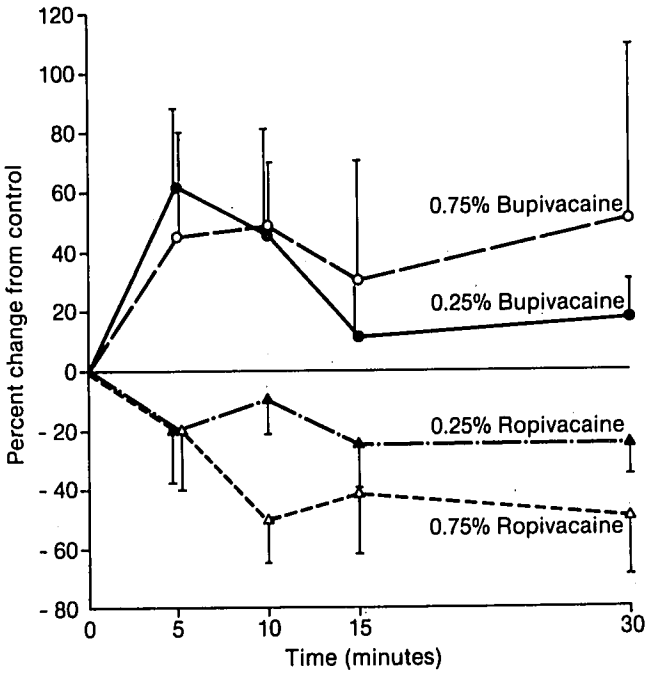

FIG. 1. Change in capillary blood flow (%) produced by ropivacaine and bupivacaine *versus* time (mean ± SEM). The direction and magnitude of change produced by ropivacaine was significantly different from that produced by bupivacaine ($P = 0.01$). There were no significant differences between 0.25% and 0.75% ropivacaine, or between 0.25% and 0.75% bupivacaine.

TABLE 3. Blood Flow at Each Site before (baseline) and 5, 10, 15, and 30min after Injection of Ropivacaine (R) with or without 5 μg/ml Epinephrine (E) and at an Uninjected Control Site

Drug	Concentration (%)	Baseline	Flow (MV) Time after Injection (min) 5	10	15	30	P* *versus* Control
R	0.25	93 ± 9	81 ± 17	90 ± 13	84 ± 10	78 ± 10	0.6
R	0.75	101 ± 14	81 ± 21	60 ± 8	67 ± 9	61 ± 11	0.03
R + E†	0.25	84 ± 16	51 ± 10	47 ± 10	43 ± 9	43 ± 10	0.01
R + E‡	0.75	89 ± 11	54 ± 10	62 ± 14	81 ± 22	88 ± 28	0.4
Saline + E	—	85 ± 11	45 ± 5	46 ± 7	46 ± 5	58 ± 15	0.002
Control (uninjected)	—	92 ± 12	86 ± 10	95 ± 10	90 ± 9	88 ± 10	—

Values are mean ± SE; n = 6 for all measurements.
* *P* values are for the changes produced by injection of each solution compared with the changes that occurred at the uninjected control site over the 30 min after injection of the drug.
† $P = 0.03$, R *versus* R + E.
‡ $P = 0.9$, R *versus* R + E.

acaine's chemical properties are similar to bupivacaine ($pK_a = 8.1$ and protein binding > 90% for both) except that lipid solubility is lower for ropivacaine (intermediate between lidocaine and bupivacaine).[2,12] Additionally, ropivacaine appears to be less cardiotoxic than bupivacaine.[13,14] Preliminary clinical trials of ropivacaine in humans are currently in progress.

Despite these similarities, ropivacaine appears to have different effects on the cutaneous microvasculature. We have shown in this study that ropivacaine is an effective vasoconstrictor, whereas bupivacaine is a vasodilator. This vasoconstrictive effect should make ropivacaine an ideal agent for infiltration anesthesia prior to operations on the skin. In this situation, ropivacaine would simultaneously provide anesthesia and help reduce bleeding.

Theoretically, a local anesthetic that produces vasoconstriction would be expected to have a prolonged duration of action. Vasoconstriction should reduce local blood flow, decrease vascular uptake of local anesthetic, and prolong the time that the local anesthetic concentration is sufficiently high to produce anesthesia. Thus, ropivacaine's vasoconstrictive effect should decrease vascular uptake and prolong its duration of anesthetic action. Indeed, subcutaneous infiltration of ropivacaine has been shown to produce sensory anesthesia that lasts two to four times longer than that following bupivacaine.[15] Furthermore, the vasoconstrictive effect of ropivacaine could eliminate the need for epinephrine, thereby abolishing the potential side effects resulting from systemic absorption of epinephrine.

Epinephrine can be added to bupivacaine to produce vasoconstriction,[9] prolong the duration of anesthesia,[15] increase the intensity of neural blockade,[16] and/or lower the peak blood level that results from systemic absorption.[17] Although epinephrine may produce the same effects when added to ropivacaine, it does not appear to be as effective in reducing capillary blood flow over the first 30 min. Yet the addition of epinephrine to ropivacaine increases the duration of infiltration anesthesia.[15] This result could be explained if epinephrine decreases blood flow beyond the time we measured (30 min), or perhaps epinephrine prolongs duration by some other mechanism.

Our finding that bupivacaine produces vasodilation is in agreement with some previous reports but not others.[18,19] The discrepancy in results may in part be explained by differences in methodology. First, local anes-

TABLE 4. Blood Flow at Each Site before (baseline) and 5, 10, 15, and 30 min after Injection of Bupivacaine (B) with or without 5 μg/ml Epinephrine (E) and at an Uninjected Control Site

Drug	Concentration (%)	Baseline	Flow (MV) Time after Injection (min) 5	10	15	30	P* *versus* Control
B	0.25	75 ± 8	112 ± 12	123 ± 35	93 ± 13	96 ± 10	0.5
B	0.75	108 ± 15	171 ± 55	161 ± 40	160 ± 43	185 ± 69	0.2
B + E†	0.25	80 ± 9	28 ± 5	43 ± 8	50 ± 12	44 ± 11	.001
B + E‡	0.75	90 ± 11	49 ± 13	42 ± 10	52 ± 13	49 ± 14	<.0001
Saline + E	—	85 ± 11	45 ± 5	46 ± 7	46 ± 5	58 ± 15	.002
Control (uninjected)	—	92 ± 12	86 ± 10	95 ± 10	90 ± 9	88 ± 10	

Values are mean ± SE; n = 6 for all measurements.
* *P* values are for the changes produced by injection of each solution compared with the changes that occurred at the uninjected control site over the 30 min after injection of the drug.
† $P = 0.01$, B *versus* B + E.
‡ $P = 0.03$, B *versus* B + E.

thetics can produce contrasting responses in different capillary beds in an animal such that vasodilation may occur in one capillary bed while vasoconstriction occurs in another.[13,20] Thus, the effect of local anesthetics on muscle arterioles may be different from the effects we observed in cutaneous blood vessels. Similarly, the surgical preparation required for previous studies may account for differences in results. Invasive techniques suffer from tissue manipulation, which may alter the response to local anesthetics. Furthermore, *in vitro* studies are flawed by vessel denervation, which eliminates neurally mediated changes in vascular tone. Finally, differences in anesthetic concentration or method of application (topical, intravenous, subcutaneous injection, or perfusion bath) may also have contributed to this variability. We chose to use the laser Doppler because it is noninvasive and it permits repeated measurements without altering cutaneous flow.[4–7] In addition, the anesthetic concentrations were in the clinical range (0.25–0.75%) and were administered subcutaneously for infiltration anesthesia. Thus, this study had many characteristics that make the results clinically relevant.

Our study could be criticized because we did not monitor and manipulate the respiratory and hemodynamic status of the pigs. Alterations in respiration or blood pressure may alter cutaneous blood flow. However, other factors that are difficult to quantify (*e.g.*, sympathetic tone) or are poorly understood (*e.g.*, anesthetic effects on hypothalamic temperature regulation) are also likely to have important effects on capillary blood flow.[21] Rather than try to measure and manipulate all "known" physiologic variables, we chose to perform sequential measurements of capillary blood flow at an uninjected (control) site, thus measuring the important end result of any physiologic perturbations. The stability of control blood flow measurements during the course of these experiments indicates that variations in the physiologic status of these animals were not sufficient to alter cutaneous flow (table 1).

Another concern is that systemically absorbed local anesthetic or epinephrine may have affected our measurements. Each animal received a total of 40 mg of local anesthetic subcutaneously, one-half of which was given in combination with epinephrine. However, systemic uptake of local anesthetic from subcutaneous tissue is slow and results in low serum levels.[22] Although some local anesthetic was absorbed into the systemic circulation, the amount was not sufficient to alter capillary blood flow because blood flow at the uninjected control site did not change in the 30 min after injection of these drugs. In addition, the low blood levels resulting from systemic absorption should have little effect compared with the high concentrations of local anesthetic at the site of injection.

The mechanism by which ropivacaine produces vasoconstriction was not addressed in this study. Possible mechanisms include direct smooth muscle activation of precapillary and/or postcapillary vessels or the indirect release of other vasosactive substances. When administered at extremely low concentrations, all local anesthetics will produce vasoconstriction.[1] In contrast, at concentrations commonly used for regional anesthesia, local anesthetics, except cocaine, produce vasodilation. Cocaine's mechanism of action is indirect, due to the blockage of reuptake of norepinephrine at sympathetic nerve endings. Although this mechanism is possible for ropivacaine, it seems unlikely based on the significant differences in chemical structure between ropivacaine and cocaine.

Our results for ropivacaine pertain only to its effect on cutaneous capillary vessels. Vascular beds are known to vary in their response to drugs and stimuli; thus, our results cannot be extrapolated to other organ systems or tissues.[16,18,23]

In conclusion, ropivacaine appears to be ideally suited for infiltration anesthesia due to its long duration of action and its ability to decrease cutaneous blood flow. Whereas other local anesthetics, such as bupivacaine, require the addition of epinephrine to provide vasoconstriction, ropivacaine produces vasoconstriction without the addition of epinephrine, thus eliminating the potential side effects of the absorbed epinephrine. Further study is necessary to determine whether ropivacaine produces vasoconstriction in epidural or spinal vessels or in the vasa vasora of peripheral nerves. The decrease in cutaneous blood flow with ropivacaine offers several advantages over presently available local anesthetics, especially for infiltration anesthesia, when the use of epinephrine is undesirable.

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