

Effect of Epinephrine on Lidocaine Clearance In Vivo

A Microdialysis Study in Humans

Christopher M. Bernards, M.D.,* Dan J. Kopacz, M.D.†

Background: Local anesthetic nerve block prolonged by epinephrine is thought to result from local vasoconstriction and consequent decreased local anesthetic clearance from the injection site. However, no study has yet confirmed this directly in humans by measuring tissue concentrations of local anesthetic over time. In addition, recent studies have shown that the α_2 -adrenergic receptor agonist, clonidine, also prolongs nerve block without altering local anesthetic clearance. Because epinephrine is also an α_2 -adrenergic receptor agonist, it is possible that epinephrine prolongs local anesthetic block by a pharmacodynamic mechanism and not a pharmacokinetic one. This study was designed to address this issue.

Methods: Microdialysis probes were placed adjacent to the superficial peroneal nerve in both feet of eight volunteers. Plain lidocaine (1%) was injected along one peroneal nerve and lidocaine with epinephrine (2.5 $\mu\text{g}/\text{ml}$) was injected along the other nerve in a double-blinded, randomized manner. The concentration of lidocaine in tissue was measured at 5-min intervals, and sensory block and cutaneous blood flow were assessed by laser Doppler at 10-min intervals for 5 h. The resulting data for lidocaine concentration *versus* time were fit to a two-compartment model using modeling software.

Results: Epinephrine prolonged sensory block by decreasing local blood flow and slowing clearance. There was no evidence of a pharmacodynamic effect of epinephrine.

Conclusion: Although epinephrine activates α_2 -adrenergic receptors, its mechanism for prolonging the duration of local anesthetic block rests on its ability to decrease local anes-

thetic clearance and not on a pharmacodynamically mediated potentiation of local anesthetic effect. (Key words: Elimination; local anesthetics; modeling; pharmacokinetics.)

TO prolong the duration of peripheral and central neuraxial blocks, epinephrine is often added to the local anesthetic.^{1,2} It has been presumed that the block-prolonging effect of epinephrine results from an epinephrine-mediated decrease in local blood flow, resulting in slower local anesthetic clearance from the injection site. Evidence cited to support this pharmacokinetic mechanism derives from the fact that peak plasma concentrations of local anesthetics are decreased when epinephrine is added.^{1,2} In addition, epinephrine lacks any local anesthetic activity in its own right, which indicates that the effect of epinephrine is not pharmacodynamically mediated.

However, data from multiple studies give cause to question this conventional wisdom. For example, clonidine, an α_2 -adrenergic receptor agonist, prolongs the duration of both central and peripheral local anesthetic blocks without altering local anesthetic plasma concentrations.^{3,4} These findings suggest that the prolonged block is a pharmacodynamic effect of clonidine and not a pharmacokinetic one. Consistent with this, Butterworth and Strichartz⁵ found that the α_2 -adrenergic receptor agonists clonidine and guanfacine dose-dependently inhibit the compound action potentials in A-alpha and C fibers. Gaumann *et al.*⁶ have reported similar results. Because epinephrine also has α_2 -adrenergic receptor agonist activity, it is possible that the block-prolonging effect of epinephrine is also an α_2 -adrenergic receptor-mediated pharmacodynamic effect and not a pharmacokinetic effect resulting from decreased local anesthetic clearance.

There is also reason to question the conventional wisdom that epinephrine prolongs local anesthetic block by decreasing local blood flow. Again, this postulate is based on the observation that local anesthetic plasma concentrations are generally lower when epinephrine is

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* Associate Professor of Anesthesiology, University of Washington.

† Staff Anesthesiologist, Virginia Mason Medical Center; Clinical Associate Professor, Department of Anesthesiology, University of Washington.

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Address reprint requests to Dr. Bernards: Department of Anesthesiology, University of Washington, Box 356540, Seattle, Washington 98195. Address electronic mail to: chrisb@u.washington.edu

included. However, data exist to suggest that this may be a systemic effect of epinephrine rather than a local tissue effect. Specifically, Sharrock *et al.*⁷ have shown that intravenous administration of low-dose epinephrine significantly reduces bupivacaine plasma concentrations after epidural bupivacaine injection. They hypothesized that the decreased plasma concentration was the result of an epinephrine-mediated increase in cardiac output and in bupivacaine's volume of distribution and was not the result of diminished bupivacaine clearance from the epidural injection site. Consistent with this hypothesis, intravenous phenylephrine infusion resulted in significantly greater bupivacaine plasma concentrations than occurred when low-dose epinephrine was infused.

Although this hypothesis is unproved, it does point out the problems inherent in trying to infer what happens to local anesthetic concentrations in tissue by measuring drug concentration in plasma. Therefore, this study was designed to determine whether epinephrine alters the local clearance of lidocaine after peripheral nerve block in humans. To address this issue, microdialysis probes were placed along the superficial peroneal nerve and lidocaine concentrations were measured continuously after injection of lidocaine with and without epinephrine.

Methods

The Institutional Review Board of the Virginia Mason Medical Center approved our study. We enrolled eight paid volunteers (six men, two women; ages 31–55 yr) after they gave written informed consent.

Experimental Preparation

The right and left superficial peroneal nerves were identified over the dorsum of the foot by direct visualization, palpation, or both. A single 2-inch, 18-gauge intravenous catheter and needle (Insyte; Becton Dickinson, Sandy, UT) was used for microdialysis probe placement and lidocaine injection in each foot. The catheter and needle combination was inserted through the skin immediately adjacent to the superficial peroneal nerve, threaded through the subcutaneous tissue parallel to the nerve for a distance of approximately 3 cm, and then made to exit through the skin of the dorsum of the foot. The needle was removed, leaving the intravenous catheter tip protruding approximately 3–5 mm through the skin. A loop microdialysis probe was inserted through this distal tip of the intravenous catheter, and the cath-

eter was then withdrawn 5–10 mm so that its tip rested entirely in the subcutaneous tissue. Microdialysis fluid (normal saline) was infused through the dialysis probe at 10 μ l/min using a syringe pump (model PHD 2000; Harvard Instruments, Natick, MA).

Approximately 20 min after the dialysis probe was placed, 2 ml 1% lidocaine with or without 2.5 μ g epinephrine (1:400,000) was injected over 1 min through the intravenous catheter as it was slowly withdrawn from the subcutaneous tissue. This process ensured that the local anesthetic was deposited immediately adjacent to the superficial peroneal nerve and that the microdialysis probe rested in the center of the local anesthetic "depot." When the drug injection was complete, dialysate samples were collected continuously at 5-min intervals (*i.e.*, 50 μ l volumes) until the block had resolved or 5 h had elapsed.

Each volunteer received lidocaine injections in the right and left foot 5 min apart. One solution contained plain lidocaine in normal saline and the other contained lidocaine plus epinephrine. The solutions were administered in a double-blinded, randomized manner from coded vials freshly prepared by the Virginia Mason Medical Center pharmacy.

After drug injection, pinprick, light touch, and cold sensitivity (iced test tube) were tested sequentially every 10 min in the area over the third and fourth metatarsal-phalangeal joints. The volunteers' reaction to pinprick was assessed using a 27-gauge dental needle. Light touch was assessed using a 3.84 N von Frey hair (when tested in this area before sensory blockade, this was the lowest pressure that was perceptible). All tests of sensation were performed without the volunteer observing the test, and volunteers were asked to describe what, if anything, they felt. Sensations were scored as present or absent; no attempt was made to quantify these sensations.

Hot and warm thermal perception thresholds were determined in the same anatomic area using a custom-built thermode-thermocouple starting at a temperature of 30°C and increasing at a rate of 1.5°C/s to a cutoff of 50°C (to prevent thermal injury). The volunteers were asked to tell the investigator when the probe felt noticeably warm and then uncomfortably hot. Thermal thresholds were tested every 10 min.

Testing of all sensory modes was discontinued 10 min after (*i.e.*, one testing interval) the volunteers could feel pinprick, light touch, and cold sensation.

Cutaneous blood flow velocity at the injection site was tested at baseline before drug injection and then every

10 min after drug injection using a laser Doppler flow probe (MedPacific LD 5000, Seattle, WA). Flow velocity was also measured at an unblocked control site on the anterior leg to verify that there were no spontaneous changes in flow unrelated to local anesthetic administration. Flow velocity was calculated as previously described⁸ using the equation:

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

Where S_x is the blood flow velocity at the injection site x minutes after injection, S_0 is the baseline blood flow velocity at the injection site, C_x is the blood flow velocity at the control site x minutes after the injection and C_0 is the baseline blood flow velocity at the control site.

Manufacture of Microdialysis Probes

Custom loop microdialysis probes were made by one of the authors (C.M.B.) from cellulose dialysis fibers (Spectrum Medical Industries, Houston, TX) with a 215- μm inside diameter, a 235- μm outside diameter, and a molecular weight cutoff of 6,000 d. Epoxy cement was used to coat all but the center 20 mm of the dialysis fiber, thus creating a 20-mm "dialysis window." The epoxy was spread evenly by running a 2-cm length of PE-10 tubing over the fiber while the epoxy was still wet. After the epoxy had cured, a 90- μm -diameter wire was placed in the lumen of the dialysis probe and the probe was bent in half. The wire allowed the probe to be bent without occluding the lumen. The inflow end of the dialysis probe was connected to an approximately 1-m-long length of PE-10 tubing that was fitted with tubing connectors to allow for connection to a syringe pump. The outflow end of the dialysis probe was connected to a 40-cm length of PE-10 tubing. The probes were allowed to "cure" for 24 h, after which they were sterilized by exposure to ethylene oxide in the University of Washington gas sterilization facility. All probes were used within 72 h of being created.

Assessment of Dialysis Probe Performance

In an effort to correct lidocaine concentrations in the dialysate for differences in the recovery efficiency of each probe, the probes were placed in a vial containing a 1% lidocaine solution after being removed from the test volunteers and the solution was dialyzed for 10 min at a

dialysate flow rate of 10 $\mu\text{l}/\text{min}$. However, two probes were irreparably damaged during removal (the inflow or outflow tubing connection was severed), so their recovery efficiency could not be calculated. Consequently, no attempt was made to correct the measured lidocaine concentrations for differences in individual probe efficiency.

To show that the probe efficiency did not deteriorate over time, four identically manufactured probes were placed in a vial containing a 2% solution of lidocaine and this solution was dialyzed at a dialysate flow rate of 10 $\mu\text{l}/\text{min}$. After three 10-min samples of 100 μl were obtained, the four probes were placed subcutaneously in the flank of an anesthetized pig for 5 h. At the end of 5 h, the probes were removed and used to again dialyze the 2% lidocaine solution *in vitro*. The concentration of lidocaine recovered by each probe before and after implantation in the pig were compared to determine if the probe's recovery characteristics changed over time.

Lidocaine Analysis

Lidocaine concentration was measured using a modification of a previously described gas chromatography-mass spectrometry method⁹ with bupivacaine (250 ng) as the internal standard. The samples were alkalized with 0.1 M potassium hydroxide and extracted once into 2-ml ethyl acetate-heptane (1:1, vol/vol).

The gas chromatograph, a Hewlett-Packard model 5890 II, was equipped with a model 5972A mass selective detector, a model 7673 liquid automatic sampler, a split splitless capillary inlet system, and an electronic pressure control system (Hewlett Packard Corp., Mountain View, CA). The capillary column was a J&W Scientific model DB 5 (Folsom, CA).

Injections of 1 μl were made in the splitless mode with a helium carrier gas pulse pressure of 40 psi. After 1 min, the head pressure was decreased to 10 psi and the inlet purged. The oven temperature was held at 40°C for 1 min, increased to 220°C at 40°C/min, and then increased again to 300°C at 30°C/min. The injector and transfer line temperatures were 250 and 300°C, respectively. The mass analyzer was set to detect selected ion masses generated by an ionizing current of 70 eV. The intensities of characteristic ions in two groups were monitored for 100 ms dwell times each. Group 1 ions were 86 m/z for lidocaine and 140 m/z for bupivacaine. Lidocaine and bupivacaine eluted at 8.9 and 10.5 min, respectively. Lidocaine concentrations were not corrected for *in vivo* recovery.

The standard curves of peak area ratios (analyte/std)

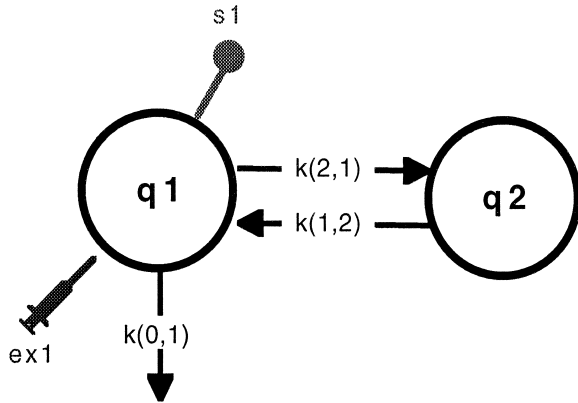


Fig. 1. The two-compartment model (q1 and q2) used to fit the lidocaine concentration data. Lidocaine was injected into (ex1) and sampled from (s1) the central compartment (q1).

versus analyte concentration were linear ($r^2 > 0.99$) from 0.1 to 50 $\mu\text{g/ml}$ for lidocaine. The interday coefficient of variation was 8% ($\leq 2\%$ bias) for six quality control samples containing 2.5 μg lidocaine.

Pharmacokinetic Modeling

The data for lidocaine concentration versus time were fitted to a two-compartment model in which lidocaine was injected into, sampled from, and eliminated from the central compartment (fig. 1). Because of the inevitable time delay in sampling the central compartment using microdialysis, data before the peak lidocaine concentration were not included in the modeling. All compartmental modeling was done using SAAM II modeling software (SAAM Institute, Seattle, WA), which calculated the distribution constants $k_{0,1}$, $K_{1,2}$, $k_{2,1}$, and the volume of the central compartment, v .

Clearance from the central compartment (Cl) was calculated as the product of the distribution rate constant (k) and the volume of the central compartment (v). Alpha and beta elimination half-lives were calculated from these equations:

$$t_{1/2 \alpha} = \frac{1}{2}[(k_{0,1} + K_{1,2} + k_{2,1}) + ((k_{0,1} + K_{1,2} + k_{2,1})^2 - 4k_{1,2}k_{0,1})^{1/2}]$$

$$t_{1/2 \beta} = \frac{1}{2}[(k_{0,1} + K_{1,2} + k_{2,1}) - ((k_{0,1} + K_{1,2} + k_{2,1})^2 - 4k_{1,2}k_{0,1})^{1/2}]$$

Statistical Analyses

Differences in elimination rate constants, clearances, and half-lives between the plain and epinephrine injec-

tions were assessed for statistical significance using the Student paired t test. Differences between the groups in lidocaine concentration over time and cutaneous blood flow over time were assessed by repeated measures analysis of variance. Differences in the duration of sensory block for each of the sensory modes tested were assessed for statistical significance by survival analysis and the Wilcoxon statistic using SPSS/PC+ software (SPSS, Chicago, IL). This nonparametric analysis was used because not all blocks in the epinephrine group had resolved when the studies were concluded at 5 hours, which made it impossible to calculate a mean block duration. Differences in lidocaine recovery by dialysis probes before and after implantation in the pig were assessed by the Student paired t test. All data are reported as the average \pm SD.

Results

The *in vitro* lidocaine recovery efficiency of the 14 probes that were assessed after removal from the volunteers was $30 \pm 6.2\%$. Therefore, fractional recovery was good and the variability between the probes was modest. The average lidocaine concentration in the dialysate of the four test probes implanted subcutaneously in a pig averaged $6,399 \pm 924 \mu\text{g/ml}$ before implantation and $6,590 \pm 494 \mu\text{g/ml}$ after 5 h of implantation ($P = 0.44$). This represents an average recovery efficiency of $32 \pm 5\%$ and $33 \pm 2\%$, respectively.

Pain, touch (fig. 2), and cold sensation were blocked completely in both groups, but for all three sensory modes the duration of blockade was significantly longer in the epinephrine group compared with the plain lidocaine group. All blocks resolved in the plain lidocaine group before the end of the 5-h data collection period. In contrast, in the epinephrine group, touch, cold sensation, and pinprick were still blocked in 6, 5, and 4 of the volunteers, respectively, at the end of 5 h.

Similarly, the threshold temperature for sensing warm and hot stimuli (fig. 3) were elevated in both groups, but again the thresholds were elevated longer in the epinephrine group compared with the plain lidocaine group.

For those four volunteers in whom the block of pinprick sensation resolved within 5 h with the plain lidocaine and lidocaine plus epinephrine solutions, the lidocaine concentration in the tissue dialysate when the block resolved was significantly greater in the epinephrine group ($78 \pm 27 \mu\text{g/ml}$) compared with the plain lidocaine group ($9.8 \pm 3.95 \mu\text{g/ml}$; $P = 0.0001$). Simi-

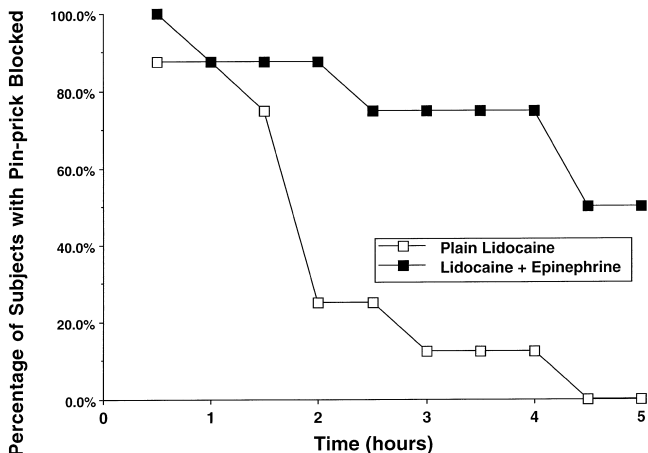


Fig. 2. The percentage of volunteers who still had sensory block to pinprick at various times after injection of plain lidocaine or lidocaine plus epinephrine. Sensory block persisted significantly longer in the epinephrine group for all sensory modalities tested: pinprick, touch, and cold.

larly, in the three volunteers in whom cold sensation resolved with both solutions, the lidocaine concentrations were epinephrine, $39 \pm 8.25 \mu\text{g/ml}$, and plain lidocaine, $9.3 \pm 7.2 \mu\text{g/ml}$ ($P = 0.0003$).

In an effort to define the relation between lidocaine dialysate concentration and effect, we plotted dialysate concentration *versus* the fraction of volunteers with pinprick sensation blocked for both groups (fig. 4). As can be seen, a rightward shift emerged in the concentration-*versus*-effect curve for lidocaine plus epinephrine compared with the plain lidocaine group.

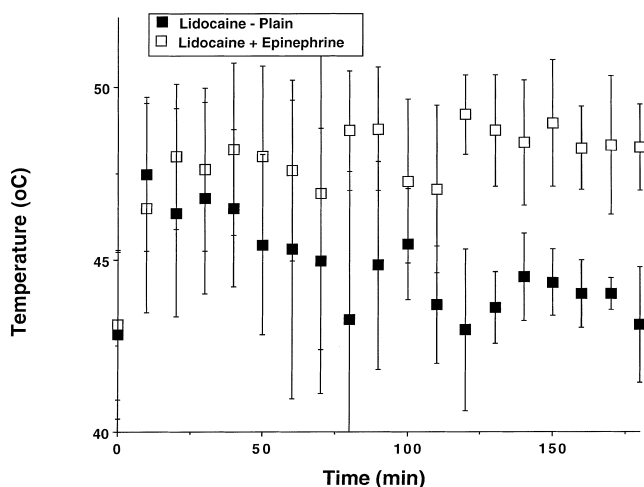


Fig. 3. The threshold for perceiving the temperature of a thermode as uncomfortably hot. The threshold remained elevated significantly longer in the lidocaine + epinephrine group. Data are the mean \pm SD.

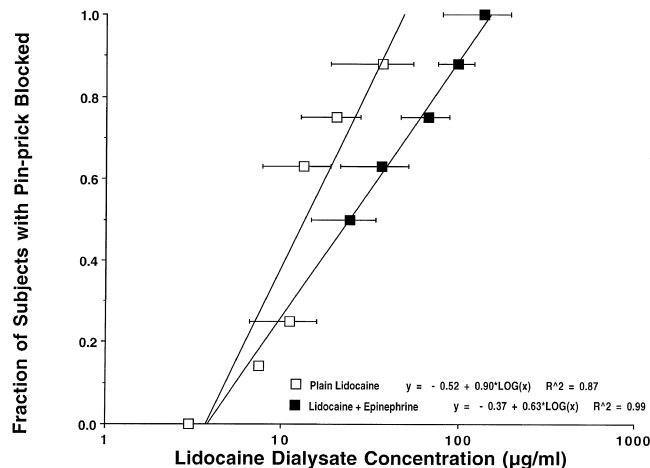


Fig. 4. The relationship between lidocaine dialysate concentration and the fraction of subjects with pin-prick blocked. Note that addition of epinephrine results in a rightward shift in the concentration-response relationship.

Interestingly, blood flow velocity was increased above baseline values in both groups, but the increase was markedly greater in the plain lidocaine group compared with the epinephrine group (fig. 5).

Figure 6 shows the data for mean lidocaine concentration *versus* time for both groups and the curve fit by SAAM II. However, all modeling and the calculation of pharmacokinetic parameters (*e.g.*, Cl, K, $t_{1/2}$) was performed on the data from individual volunteers rather than on averaged group data. The average coefficient of

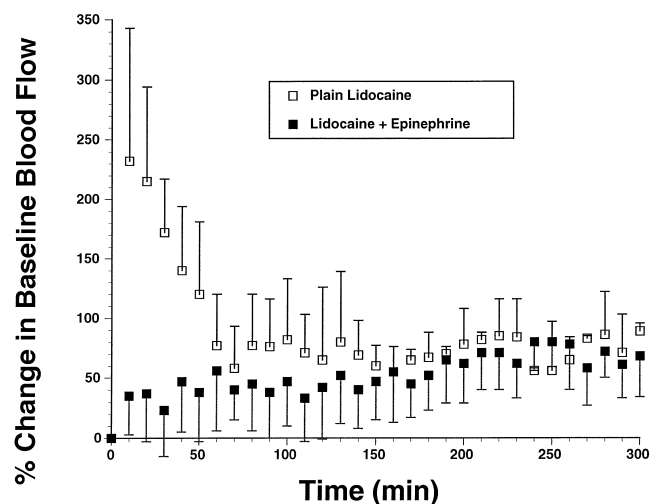


Fig. 5. The change in cutaneous blood flow after injection of plain lidocaine or lidocaine + epinephrine. Flow increased above baseline in both groups, but the increase was significantly greater in the plain lidocaine group. Data are the mean \pm SD.

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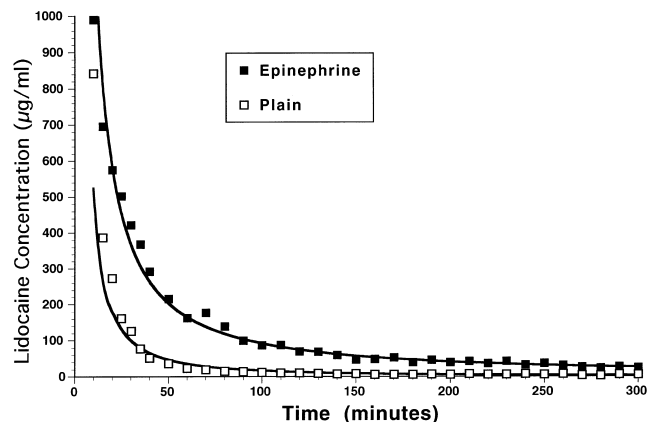


Fig. 6. The lidocaine concentration over time in the plain lidocaine group (*open squares*) and the lidocaine plus epinephrine group (*closed squares*). Data points represent the mean concentration at each time point. The curve represents the best fit calculated for each set of data points using SAAM II. Importantly, pharmacokinetic values were determined from the curves fit for each volunteer and not from these mean data.

variation for the rate constants $k_{(0,1)}$, $K_{(1,2)}$, $k_{(2,1)}$ and central compartment volume, V , were 15 ± 7 , 26 ± 27 , 20 ± 10 , and 17 ± 10 , respectively, in the epinephrine group and 14 ± 8 , 23 ± 20 , 18 ± 13 , and 26 ± 13 , respectively, in the plain lidocaine group.

The elimination rate constant, $k_{(0,1)}$, and clearance, $Cl_{(0,1)}$, were significantly greater in the plain lidocaine group compared with the epinephrine group, whereas $t_{1/2}$ was significantly shorter in the plain lidocaine group (table 1). There was no significant difference between the groups for the elimination rate constants, $k_{(1,2)}$, $k_{(2,1)}$; the volume of the central compartment, V ; or for $t_{1/2\beta}$ (table 1).

Discussion

The purpose of this study was to determine whether epinephrine altered the clearance of lidocaine from tissue. Consistent with expectations, the addition of epinephrine significantly prolonged all measures of block duration. In addition, as indicated by the slower elimination rate constant, $k_{(0,1)}$, the slower clearance, $Cl_{(0,1)}$, and the longer $t_{1/2\alpha}$, epinephrine also slowed lidocaine clearance from the injection site. Therefore, the data suggest that epinephrine prolongs local anesthetic block by slowing drug clearance. Although this has long been the conventional wisdom, this is the first study, to our knowledge, that has directly demonstrated this fact by measuring drug concentrations in tissue over time.

There is no evidence to suggest that the prolonged

sensory block results from a pharmacodynamic ability of epinephrine to potentiate the effect of lidocaine. In fact, the data suggest the possibility that epinephrine may actually increase the lidocaine concentration necessary to produce sensory block. For example, the dialysate concentrations of lidocaine were markedly higher with the epinephrine-containing solution when pinprick sensation and cold sensation recovered. In addition, the dose-concentration relation between dialysate concentration and pinprick appears to be shifted to the right (fig. 4). Two possible explanations for these findings seem reasonable. First, epinephrine may alter the relation between the lidocaine concentration at the injection-sampling site (tissue) and the adjacent effect site (nerve) such that the nerve concentration of lidocaine is actually the same in the two groups despite a markedly higher lidocaine tissue concentration in the epinephrine group. Second, epinephrine might have a pharmacodynamic effect that results in diminished lidocaine potency.

Unfortunately, we could not determine which (if either) of these potential explanations is correct, because the microdialysis technique used measures the lidocaine concentration in the subcutaneous injection-sampling site and not in the adjacent nerve. In fact, microdialysis, as used in this study, does not necessarily measure the "actual" lidocaine concentration in the tissue, because there is no assurance that equilibrium is reached between the extracellular fluid space and the dialysis fluid as the dialysate moves through the microdialysis probe.¹⁰ Therefore, although the large differences in lidocaine concentration between the two groups at the time that sensation returned is intriguing, theoretically it is possible that the actual tissue and nerve concentrations are the same. Additional studies in which the lidocaine concentration is measured within the nerve at the time when sensation returns are needed to provide a definitive answer to this question. Despite these limitations of microdialysis, it is an accurate measure of relative differences in drug concentration over time and is, therefore, ideally suited for pharmacokinetic modeling.¹¹

It is also important to note that the dialysis probes used do not appear to have been a potential source of error. Implantation of the probes in the subcutaneous tissue of a pig for 5 h did not alter their *in vitro* recovery efficiency, indicating that the measured rate of decrease in lidocaine concentration over time represents an actual change in lidocaine concentration and not probe efficiency. In addition, the fact that *in vitro* recovery was a robust 30% in both 1% and 2% lidocaine also suggests that the probes can respond "accurately" to changing lidocaine concentrations.

Table 1. Pharmacokinetic Constants

Variable	Lidocaine Alone	95% CI	Lidocaine plus Epinephrine	95% CI	P
$K_{0,1}$ (min)	0.124 ± 0.028	0.058–0.19	0.031 ± .003	0.023–0.039	0.0189
$K_{1,2}$ (min)	0.0125 ± 0.003	0.005–0.02	0.012 ± 0.003	0.004–0.02	0.9479
$K_{2,1}$ (min)	0.032 ± 0.015	–0.003–0.067	0.019 ± 0.004	0.009–0.02	0.4571
Volume (ml)	0.016 ± 0.002	0.011–0.021	0.025 ± 0.007	0.007–0.044	0.3371
$Cl_{0,1}$ (ml/min)	.0016 ± .0007	0.001–0.003	.00066 ± .0003	0.00048–0.001	0.0059
$Cl_{2,1}$ (ml/min)	0.0002 ± .00003	0.00011–0.0003	.0003 ± .00007	0.00009–0.00043	0.6009
$t_{1/2 \alpha}$ (min)	2.19 ± 0.95	1.4–2.98	6.01 ± 3.33	3.2–8.7	0.0361
$t_{1/2 \beta}$ (min)	21.38 ± 6.0	7.3–36	27.34 ± 5.6	14–41	0.556

CI = confidence interval; CL = clearance; $t_{1/2}$ = half life.

Although the mathematical compartments constructed for the purposes of modeling cannot generally be said to represent genuine physiologic compartments (e.g., muscle, brain), it is tempting to do so in this study. Because epinephrine decreased local cutaneous blood flow and the lidocaine rate elimination constant $K_{(0,1)}$ while increasing $t_{1/2 \alpha}$, it seems reasonable to hypothesize that $K_{(0,1)}$ represents elimination from the injection site *via* local blood flow. Compartment 2 presumably represents nonspecific, reversible binding to local tissues.

As earlier studies^{8,12} have shown, plain lidocaine caused a significant increase in local cutaneous blood flow, albeit with considerable interindividual variation (as previous studies have also shown). The addition of epinephrine significantly attenuated the lidocaine-mediated increase in cutaneous blood flow, although flow still increased above baseline values. This finding is also consistent with earlier studies in humans using the same methods.⁸

We chose the concentrations of epinephrine (2.5 µg/ml) and lidocaine (1%) in the hope that complete local anesthetic block would occur, that epinephrine would prolong the block, and that the block would resolve in a reasonable time. However, even at these concentrations, one half of the volunteers in the epinephrine group still had dense blocks at the end of the 5-h data collection period. For that reason, we could not calculate the average lidocaine tissue concentrations at which the block resolved in each group. Previous studies have shown dose-dependent effects of epinephrine⁸ on block duration, so we would expect that higher concentrations of lidocaine and epinephrine would produce results that are qualitatively similar to those we report here.

In conclusion, we believe we have reported the first simultaneous *in vivo* measurements of local anesthetic concentration and nerve function in humans. We found that epinephrine prolongs local anesthetic block by

slowing lidocaine elimination from the injection site, presumably by decreasing local blood flow. No evidence suggests that epinephrine prolongs block by binding to α_2 -adrenergic receptors, as some studies suggest may be the case for clonidine.

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