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The Critical Role of Concentration for Lidocaine Block of Peripheral Nerve In Vivo

Studies of Function and Drug Uptake in the Rat

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Background: **The adjustment of local anesthetic dosage for peripheral nerve block must meet two basic requirements: a drug concentration sufficient to inhibit Na^+ channels to the point of impulse failure and a volume of drug sufficient to expose a length of nerve longer than the "critical length" for propagation failure. This study examines the lidocaine dosage requirement, in milligrams, for functionally assayed sciatic nerve block in the rat using a fourfold range of volume corresponding to concentrations from 2 to 7 mg/ml and compares these blocks with the intraneural lidocaine content after injection of equipotent doses.**

Methods: **Lidocaine was injected percutaneously at the sciatic nerve in volumes of 0.05 ml, 0.1 ml, and 0.2 ml (all at pH 6.8), and quantitative neurobehavioral assays were conducted on male Sprague-Dawley rats weighing from 200 to 250 g. The dose requirements for 50% maximum possible effect (ED_{50}) and for just achieving complete block (*i.e.*, minimal blocking dose for 90% effect), the fraction of completely blocked animals, and the duration of complete block at all doses were assessed for the inhibition of three different functions: proprioception, motor, and nocifensive activities. Radiolabeled (^{14}C) lidocaine was injected in separate experiments, and the total drug content and its longitudinal distribution were determined in nerves dissected from animals (sevoflurane anesthetized) at 10 min, the time of peak block, after injection of the E_{50} and minimal blocking dose for 100% effect for the three different volumes.**

Results: **For all functions, the smaller the volume, the lower was the E_{50}, resulting in a nearly constant concentration to achieve an equivalent degree of block. Durations of block were longer, and the dose to full block was lower for the smaller injected volumes. Intraneural lidocaine, at the equipotent doses for analgesia, was not related to concentration but rather increased with increasing volume, being almost proportional to the given dose. The longitudinal spread of lidocaine was also greater with increasing volume of lidocaine solution.**

Conclusion: **Blocks of greater depth and longer duration result from injection of smaller volumes and, correspondingly, higher lidocaine concentrations containing the same dose. The corollary is that lower lidocaine doses are required to achieve the same effect when smaller volumes are injected. Curiously, when the equivalent E_{50} is injected, total drug taken into the nerve is less from the smaller volumes than from the larger volumes, even though the peak functional effects are equal. Total intraneural local anesthetic may not represent the effective drug in the compartment that contains nerve axons, the actual location of neural blockade.**

IN clinical use, a desirable dose of local anesthetic is one that produces an effective block of sufficient duration and minimum toxicity. When volume and concentration are adjusted to achieve a particular dose of local anesthetic for peripheral nerve block, one should consider both the blocking pharmacology (minimum impulse blocking concentration)[1,2] and the nerve anatomy (dependence on length of nerve exposed to drug).[3] A study of sciatic block in humans showed clearly that more concentrated prilocaine (3% *vs.* 1%) delivered in a smaller volume (with a vasoconstrictor) produced a block of shorter onset latency, longer duration, and greater motor deficit.[4] In almost all cases, however, the sciatic block was combined with other local nerve blocks; in addition, the vasoconstrictor (vasopressin) differed threefold in concentration between the two prilocaine concentrations. To investigate the influence of volume and concentration on functional blockade, where drug distribution in nerve could be examined directly and the effects of vasoconstrictors *per se* are not confounding, we examined various neurobehavioral deficits during sciatic nerve block by lidocaine alone in the rat and compared these with differences in radiolabeled lidocaine uptake into the nerve under different dosing conditions.

Materials and Methods

Animals

All procedures were approved by the Harvard Committee on Animals. Male Sprague-Dawley rats (250–300 g) were handled and trained for 7–10 days to familiarize them with the experimental environment and procedure.[5] All rats were housed in the Brigham and Women's Hospital animal facilities with controlled room temperature (21° ± 0.5°C) and a 12-h light–dark cycle. The animals were allowed access to food and water *ad libitum*.

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Lidocaine Injection

A unilateral sciatic nerve block was performed under brief sevoflurane anesthesia (Abbott Laboratories, North Chicago, IL).[6] Lidocaine was injected with a 27-gauge needle between the greater trochanter and the ischial tuberosity, with the bevel of the needle turned to the femoral head. When the needle encountered the body of the ischium, the lidocaine was injected over a period of 3 s.

Lidocaine Solutions

Lidocaine solutions were prepared by dissolving crystalline lidocaine hydrochloride (Sigma Chemical, St. Louis, MO) in 154 mM NaCl buffered with 5 mM piperazine-N,N'-bis (2-ethane) sulfonic acid (PIPES buffer; Sigma Chemical). The pH of each lidocaine solution was adjusted to 6.8 with NaOH to avoid possible variations of pH with different drug concentrations that could alter local pharmacokinetics.[7–9] Concentrations of lidocaine (as percentage of weight/volume) ranged from 0.2 to 2, 0.4 to 1.0, and 0.31 to 0.68 in the respective injected volumes of 0.05 ml, 0.10 ml, and 0.20 ml (n = 4–16 in each group). Total doses of 0.1–1.4 mg were injected as the product of these concentration and volume factors.

Assessment of Sciatic Nerve Functions

Proprioceptive, motor, and nociceptive functions mediated by impulses through the sciatic nerve were assessed by a blinded investigator using the method of Thalhammer *et al.*[5] The order of quantitative neurobehavioral testing was always proprioception followed by motor function and then nocifensive responses. The animals were observed and tested just before and 3, 7, and 10 min after lidocaine injection and every 5 min after these first four tests. All rats had fully recovered sensory and motor function by 1 min if sevoflurane general anesthesia alone was administered.

Proprioception. Proprioceptive performance is based on quantification of the "hopping" and "tactile placing" reactions. The functional status was graded with 0 (normal), 1 (slightly impaired), 2 (severely impaired), or 3 (absent). Hopping tests the rat's ability to move laterally when the rat's forelegs are lifted from the supporting surface and its body is shifted laterally; the normal response is to hop with the weight-bearing limb in the direction of the movement to prevent falling. With block of proprioception, initiation of lateral movement is delayed and animal's leg drags on the table. Tactile placing tests the rat's ability to reposition the knuckled toes when the dorsum of the foot is pressed. The rat is kept in a normal resting posture, but the hind paw toes are plantar flexed with their dorsi placed on the table. Control rats, without sciatic block, spontaneously straighten their toes and place the plantar surface down on the table, but with impaired proprioception, the rat could not fully correct this posture. Because this modality was evaluated on an ordinal scale, the degree of proprioceptive impairment was expressed as the median value ± range for maximum impairment. The duration of proprioceptive block was expressed as the mean time in minutes (± SD) until the response returned to a value of 3 (a normal response) after injection.

Motor Function. Motor function was evaluated by the maximum force generated during "extensor postural thrust." The rat is held upright with one hind limb extended so that the body's weight is supported by the distal metatarsus and toes, which are placed on an electronic digital balance for support. Extensor postural thrust is measured in grams as the active force that resists contact of the platform by the heel of that tested leg. Normal motor function is established before injection by measuring the applied force necessary to bring the heel to the platform (assigned "zero" motor block score). The reduction in this force is expressed as a percentage of the control force, with zero corresponding to the fully flaccid leg.

Nocifensive Response. Nociception was evaluated by the nocifensive responses of movement and vocalization to cutaneous pain (skin pinch) and deep bone pinch (DP) in the foot area innervated by the sciatic nerve. Forceps tips are squeezed across a skin fold over the lateral metatarsus for skin pinch or on the distal phalanx of the fifth toe for DP. The withdrawal responses are graded by comparison with predrug behavior and with the contralateral uninjected leg (unaffected by ipsilateral block), with a scale as follows: 4 (normal, rapid robust withdrawal + vocalization), 3 (withdrawal is weaker and slower than on the control side, some vocalization), 2 (slow and only partial withdrawal movement, no vocalization), 1 (only a weak attempt to withdraw, no vocalization), and 0 (no movement or vocalization response).[9]

Treatment of Behavioral Data

Changes of each function were quantitatively evaluated by four different criteria, as follows:

1. as percentage of maximal possible effect (%MPE) for motor function or as graded response score for proprioception and nociception at different times after lidocaine injection
2. as the fraction of animals that were completely blocked for any time at a particular dose
3. as the duration of complete block for analgesia
4. as the area under the curve for graded analgesia integrated over time

We defined the duration of full analgesia as the time after injection when the response to DP rose above 1 (recovery time) minus the time after injection when the response fell below 3 (onset time).

Comparison of the effects of the doses in three volumes used for injection was made: (1) by graphing the dose–response curves and comparing the interpolated dose for 50% effect (ED_{50}) and greater than 90% effect

(minimal blocking dose for 100% effect) for the peak inhibition; (2) by comparing the fraction of fully blocked animals; (3) by comparing the duration of full block (complete loss of nocifensive responses to pinch) after lidocaine injection; and (4) by comparing areas under the curve.

Lidocaine Uptake

Radiolabeled [^{14}C]lidocaine (purchased from Du Pont New England Nuclear Research Products; currently Perkin-Elmer, Boston, MA) was added to the lidocaine solution to be injected at a 1:100 volume dilution. This did not change the pH but did add 1% ethanol to the injectate. The animals were killed with an overdose of sevoflurane anesthesia 10 min after injection, a time around which the peak neurobehavioral effects occurred. Doses of lidocaine used for these uptake studies were the ED_{50}s and the minimal blocking doses for 100% effect determined according to the neurobehavioral results for each volume. The sciatic nerve was rapidly excised and frozen as previously described.[6] It was then cut into six segments, each 5 mm in length, along a total length of 3 cm. Each piece was weighed on an analytic balance ($\pm$ 0.2 mg) and then digested in a mixture of 500 μl tissue solubilizer (Solvable®; Packard, Meriden, CT) with 100 μl deionized water at 50°C for 120 min. After nerve digestion and cooling to room temperature, 5 ml liquid scintillation cocktail (Bio-Safe II; Research Products International, Mount Prospect, IL) was added to the digested nerve. Radioactivity was assayed for 10 min by liquid scintillation spectroscopy. The specific radioactivity of the soaking lidocaine solution was determined by addition of 100 μl radiolabeled lidocaine injectate at each concentration to a nerve-free digestion mixture. The total count was corrected by subtracting background activity ($\sim$ 18 cpm). Counting efficiency, determined by the addition of internal standard, was the same for samples of nerve and soaking solutions. Intraneural lidocaine was expressed as nanomoles of lidocaine per milligram wet weight of nerve. Total lidocaine, determined by summing the amount of lidocaine present in all six segments, and peak intraneural lidocaine (usually found in the third or fourth nerve segment) are reported.

Statistical Analysis

Effects of each of three doses (0.625 mg, 0.75 mg, and 1 mg) of lidocaine were compared between the injected three volumes (0.05 ml, 0.1 ml, and 0.2 ml) using the Wilcoxon rank sum test for the graded responses of proprioception and nociception and one-way ANOVA, followed by Scheffé test as a *post hoc* correction to compare the measured deficits of motor functions, expressed as %MPE. ANOVA was likewise used to compare results from the lidocaine uptake study. The fraction of animals with complete block was compared between dosing conditions by chi-square analysis. A probability value of 0.05 or less was considered statistically significant.

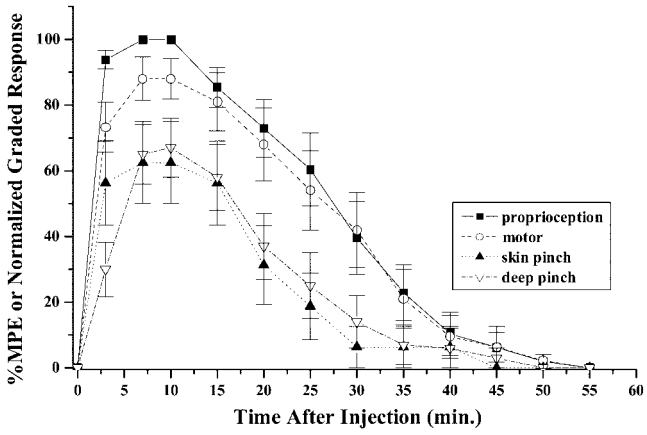

Fig. 1. Typical time course of four behavioral indices (percentage of maximal possible effect [%MPE] for motor and normalized graded responses for proprioception, skin pinch, and deep pinch) of functional nerve block. The results from rats injected with 1.125 mg lidocaine in 0.2 ml (0.5625%) represent a typical time course (n = 16, mean ± SE). Peak effect (%MPE or graded response), duration of block, and area under the curve were calculated from graphs such as this one.

Results

Effects of General Anesthetics

All animals given sevoflurane anesthesia awoke rapidly, permitting an evaluation of the neurologic functions as early as 1 to 2 min after injection of lidocaine.

Quantitative Description of Four Parameters after Injection of Single Dose

Typical time courses of the four behavioral parameters after a single lidocaine (0.5625%) injection are shown in figure 1. Proprioception function (first), motor function (second), and nociceptive function (third) in the form of responses to skin pinch and DP were blocked in this order after the injection of this and all other doses of lidocaine. Nociceptive functions completely recovered first (score < 3), followed by motor and proprioception, a pattern also seen with all other doses. All functions were restored to preinjection values after 1 h. There were no secondary later effects; other than the changes in the ipsilateral leg, the animals' behavior was unchanged.

Effects of Lidocaine Concentration

Peak effects of lidocaine that occurred during a block varied with dose and volume (fig. 2). Dose–response curves such as these show the critical importance of drug concentration in achieving the desired effects, as follows.

The ED_{50} of each function decreased with decreasing injected volumes (The range of ED_{50}s was determined by

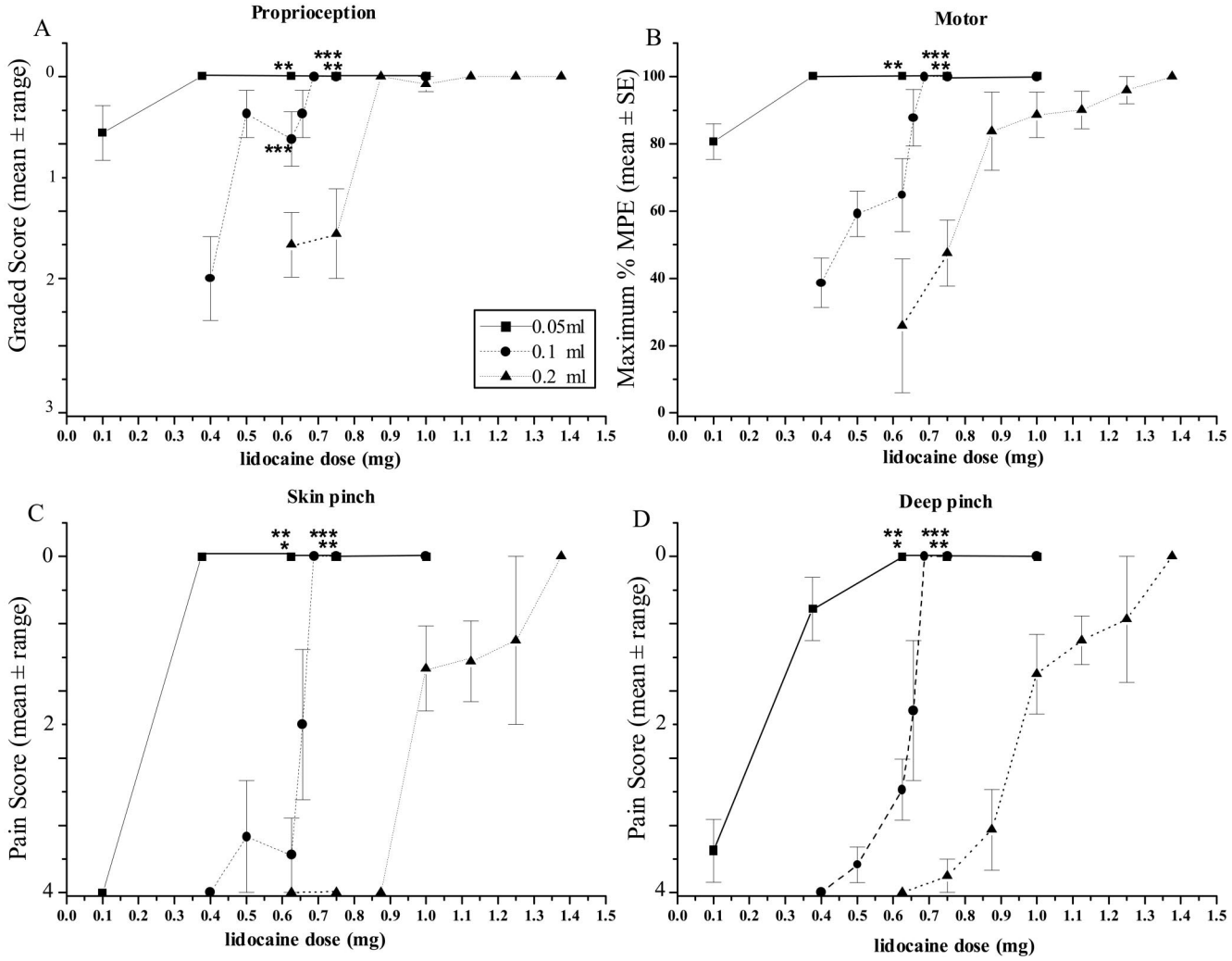

Fig. 2. Changes of percentage of maximal possible effect (mean ± SE) or in graded score for different doses of lidocaine in each volume. Proprioception (*A*), motor function (*B*), response to skin pinch (*C*), and response to deep pinch (*D*). The values for the same doses diluted in 0.05 ml, 0.1 ml, and 0.2 ml to yield different concentrations were compared (one-way ANOVA and Scheffé test as a *post hoc* correction or Wilcoxon rank sum test; see Methods section). *$P < 0.05$ comparing 0.05 ml with 0.1 ml, **$P < 0.05$ comparing 0.05 ml with 0.2 ml, ***$P < 0.05$ comparing 0.1 ml with 0.2 ml.

the intercepts of the range of graded score, or the SE of %MPE, with the interpolated dose–response line). For example, for inhibition of the nocifensive response to DP, the ED_{50} was 0.2 to 0.3 mg for the 0.05-ml volume, 0.60 to 0.65 mg for the 0.1-ml volume, and 0.95 to 1.0 mg for the 0.2-ml volume (fig. 2D; table 1). The same order held for minimal blocking doses for 100% effect. When the ED_{50}s, which differ by almost fourfold, are divided by their respective volumes, however, the resulting concentrations, defined as EC_{50}s (table 1), vary by only about 20%.

Similarly, when the fraction of fully blocked animals was assessed by DP, smaller doses were required for the same population effect with lower volumes of lidocaine (fig. 3). Although the variance in this "quantized" parameter for block is not calculable from data on a single cohort of animals (as it is for the graded parameter or for %MPE), the interpolated ED_{50}s have about the same relative values as those for the graded one (fig. 2D).

The duration of complete block was generally longer in rats injected with the smaller volumes of more concentrated lidocaine containing the same doses (*e.g.*, 0.625 mg, 0.75 mg), although at 1.0 mg, the complete block lasted as long after a 0.1-ml injection as after one of 0.2-ml injections (fig. 4).

The area under the curve function integrates the degree and the duration of analgesia to DP. This area for graded analgesia *versus* time blocked increased with increasing lidocaine dose; as with other parameters, the greater potency occurred with the smaller volume (fig. 5). As with the duration of block (fig. 4), it appears that at the smallest volume (0.05 ml), the area under the curve had reached a limiting value of approximately 1,250 min and did not change despite a further increase

Table 1. Volume-dependent Parameters for Analgesia and Lidocaine Content in Nerve

Volume (ml)	0.05	0.1	0.2
ED_{50}, mg	0.25	0.656	0.96
EC_{50}, mg/ml	5	6	5
Peak LID content at ED_{50}, nM/mg wet	1.0 ± 0.2	3.3 ± 0.6	5.8 ± 0.7
Total LID content at ED_{50}, nM/mg wet	2.3 ± 0.6†	8.6 ± 2.8‡	10.8 ± 2.3
Total LID content:injected dose at ED_{50}	$0.25 \pm 0.07 \times 10^{-2}$	$0.36 \pm 0.11 \times 10^{-2}$	$0.29 \pm 0.06 \times 10^{-2}$
Total LID content at MBD_{100}, nM/mg wet	4.8 ± 2.4*†	8.0 ± 1.3‡	19.1 ± 2.4
Total LID content to injected dose at MBD_{100}	0.21 ± 0.10	0.32 ± 0.35	0.36 ± 0.11
Longitudinal spread, cm	1	1.4	1.9

The respective ED_{50} doses were determined from the data in figure 2D. For 0.05-ml, 0.1-ml and 0.2-ml injections, the MBD_{100} doses were 0.625 mg, 0.688 mg, and 1.38 mg, respectively. The values (mean ± SE) at ED_{50} and MBD_{100} in three volumes were compared (one-way ANOVA and Scheffé test as *post hoc* correction).

* $P < 0.05$ comparing 0.05 ml with 0.1 ml. † $P < 0.05$ comparing 0.05 ml with 0.2 ml. ‡ $P < 0.05$ comparing 0.1 ml with 0.2 ml.

ED_{50} = dope for 50% maximum possible effect; LID = lidocaine; MBD_{50} = minimal blocking done for 100% effect.

in concentration. Such a result suggests an important pharmacokinetic property of lidocaine (see Discussion).

Lidocaine Content in the Nerve at 10 Min

Intraneural lidocaine uptake was measured 10 min after lidocaine injection, at which time the maximum behavioral effect was achieved for all dosing (fig. 1). Doses for 50% (ED_{50}) and minimal blocking dose for 100% effect block were decided according to the previously analyzed neurobehavioral results (fig. 3; table 1), and the degree of the nocifensive response to DP was assessed for all rats (n = 5 in each volume) just before sacrifice.

The hypothesis being tested was that the same functional deficit would be matched by the same intraneural content of lidocaine resulting from equivalent ED_{50}s. Intraneural lidocaine contents at the respective equivalent doses were not equal, however, but increased with increasing volume and thus with increasing dose, disproving the hypothesis. In contrast to the functional effects, nerve lidocaine content was poorly related to concentration but was almost proportional to dose (table 1). The longitudinal spread of lidocaine was also greater for increasing volume of the injected solution, and the peak of the distribution was slightly shifted to a more distal position as the volume rose (fig. 6). This locus is one to two segments distal to the locus of injection, at segment 2, as determined by methylene blue dye injections (data not shown).

Comparing the ratio of intraneural lidocaine content with total mass of injected lidocaine to reach 100% block in each group showed that there was no statistically significant difference between groups (0.0021 ± 0.0010 in 0.05 ml, 0.0032 ± 0.0035 in 0.1 ml, and 0.0036 ± 0.0011 in 0.2 ml; $P > 0.10$). This uptake equivalence was also found among the doses for 50% MPE (0.25 ± 0.07% in 0.05 ml, 0.36 ± 0.11% in 0.1 ml, and 0.29 ± 0.06% in 0.2 ml; $P > 0.05$). Thus, the efficiency for delivery of drug into the nerve was constant over the range of doses

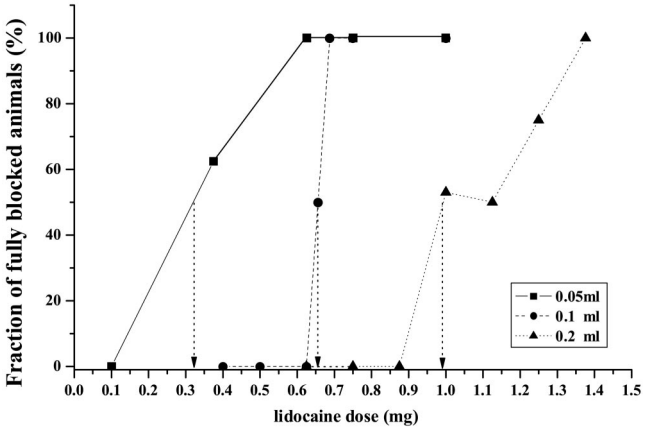

Fig. 3. Fraction of animals fully blocked (deep pinch) *versus* dose in each volume (0.05 ml, 0.1 ml, and 0.2 ml). The *vertical dotted lines* point with *arrowheads* to the doses that correspond to the interpolated population 50% maximum possible effect, as shown by the intercepts of the experimental curves by the *horizontal bars* drawn at "50% fully blocked."

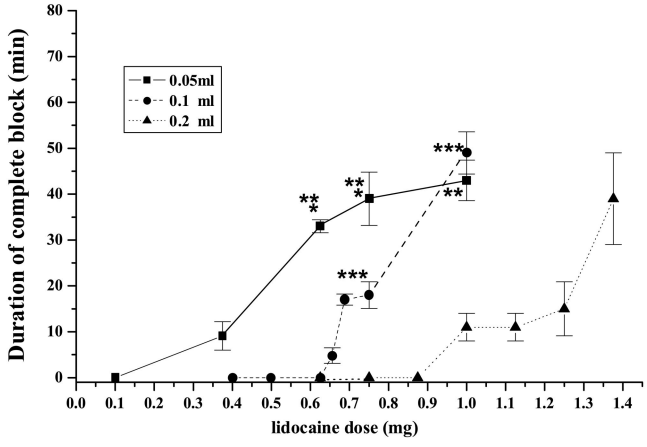

Fig. 4. Duration of complete nocifensive block *versus* dose. Each value (mean ± SE) represents the duration of block assessed with response to deep pinch. Full block was defined as the time after injection when response to deep pinch returned (score > 3) minus the first time after injection when the analgesia began (score < 1). The values at the same dose (0.625 mg, 0.75 mg, and 1 mg) in different concentrations (0.05 ml, 0.1 ml, and 0.2 ml) were compared as described for figure 2. *$P < 0.05$ comparing 0.05 ml with 0.1 ml, **$P < 0.05$ comparing 0.05 ml with 0.2 ml, ***$P < 0.05$ comparing 0.1 ml with 0.2 ml.

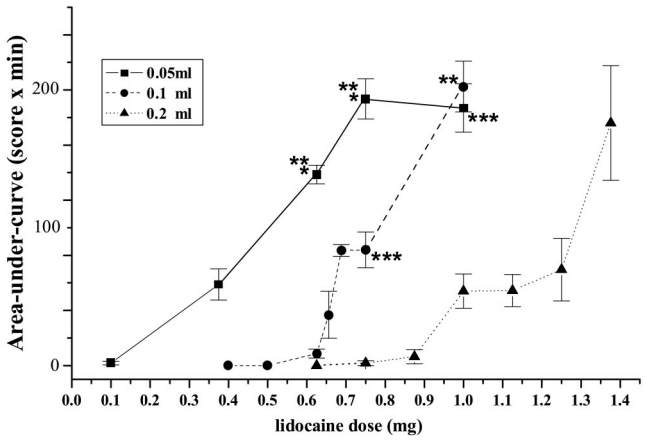

Fig. 5. Area under the curve (percentage of maximal possible effect *vs.* min) for deep pinch in each volume of lidocaine (0.05 ml, 0.1 ml, and 0.2 ml). The values (mean ± SE) at the same dose (0.625 mg, 0.75 mg, and 1 mg) at different concentrations were compared as described for figure 2. *$P < 0.05$ comparing 0.05 ml with 0.1 ml, **$P < 0.05$ comparing 0.05 ml with 0.2 ml, ***$P < 0.05$ comparing 0.1 ml with 0.2 ml.

and volumes that gave the same effect, suggesting that this parameter also depends on lidocaine concentration rather than on injected mass or the tissue area over which the drug spread.

Discussion

We undertook this study to resolve the importance of anatomic factors (*i.e.*, volume) *versus* pharmacodynamic factors (*i.e.*, concentration) in the establishment of functional peripheral nerve block. Earlier results from our laboratory had shown that with steady-state drug concentrations controlled *in vivo* by a small superfusion chamber, lidocaine must be present at 1.0 mM to block all C-fiber nociceptors and at 0.5 mM to block all Aδ-fiber nociceptors and Aβ-mechanoreceptors of rat sciatic nerve.[1] (The same order of block susceptibility in this nerve occurs for percutaneous injections of lidocaine, analogous to clinical peripheral nerve blocks.[2]) The length of nerve fiber exposed to the drug is also an important factor in determining block; too short an exposure length prevents blockade of propagated impulses by even the highest drug concentration, whereas a long length of axon exposed to a low drug concentration can result in a decremental reduction of impulse amplitude and its associated action currents over centimeter distances, which is nevertheless able to stimulate normal conduction when eventually reaching a drug-free segment.[3] To avoid local and systemic toxicity, clinicians use a limited dose of local anesthetic whose absolute value depends on the patient's physical characteristics and medical condition and on the site of administration.[4,7,10,11] Whether that dose should be concentrated in a small volume or spread over a larger one depends on how the minimal blocking concentration at the critical blocking length can be achieved.

The present results show clearly that concentration is more important than volume or dose *per se* for block in rat sciatic nerve. Lidocaine concentrations used here were considerably lower than used clinically (> 1%), because we sought to explore the range from zero to complete block so as to define drug potency, whereas anesthetists require full analgesia in patients. When comparing identical doses, the one contained in a smaller volume produced a more intense and a longer lasting blockade. This finding is similar to that reported by Smith and Siggins[4] using prilocaine for sciatic nerve block, although they accompanied this procedure with other blocks, had a varying concentration of vasopressin with the prilocaine, and did not report any effort to control pH (an important determinant of block kinetics in experimental studies).[8]

Although the more concentrated lidocaine dose injected in the rat was distributed over only half the nerve length of the more dilute dose (fig. 6), this length was sufficient for functional blockade. Indeed, the equipotent formulations over the fourfold volume difference used here had final concentrations that were within 20% agreement of each other, supporting the thesis that concentration is the critical determinant and that spread under these conditions is always adequate for blockade. It is therefore likely that the much longer volumes used for major peripheral nerve blocks in humans will always cover an adequate length, although volumes used for blockade of smaller and less accessible nerves might be a factor in determining adequate spread for successful blocks.

Although our detailed analysis emphasized analgesic action, the primacy of concentration for determining functional blockade applied to all four modalities that were tested. The effective potencies were about the same for proprioceptive and motor block, with both being approximately 1.5 times greater than analgesic potencies (fig. 2). Both the qualitative order of susceptibility and the quantitative potency ratios are consistent with results from lidocaine's blockade of impulses in individual axons of sciatic nerve measured *in vivo* in the anesthetized rat[2]; loss of motor performance corresponds to blockade of the most sensitive Aγ-efferents, whose inactivity leads to toneless spindles and thus, through spinal reflex modulation, to flaccid muscles, whereas the onset of pinch analgesia corresponds to blockade of the less sensitive C-mechanosensitive nociceptors.[1,2]

The results of radiolabeled lidocaine uptake after injections of equipotent doses in the three volumes were anomalous. Despite the comparable lidocaine concentrations of the injected equipotent doses, the intraneural content was far greater in nerves treated with the larger volume. In one sense, this result seems logical, consid-

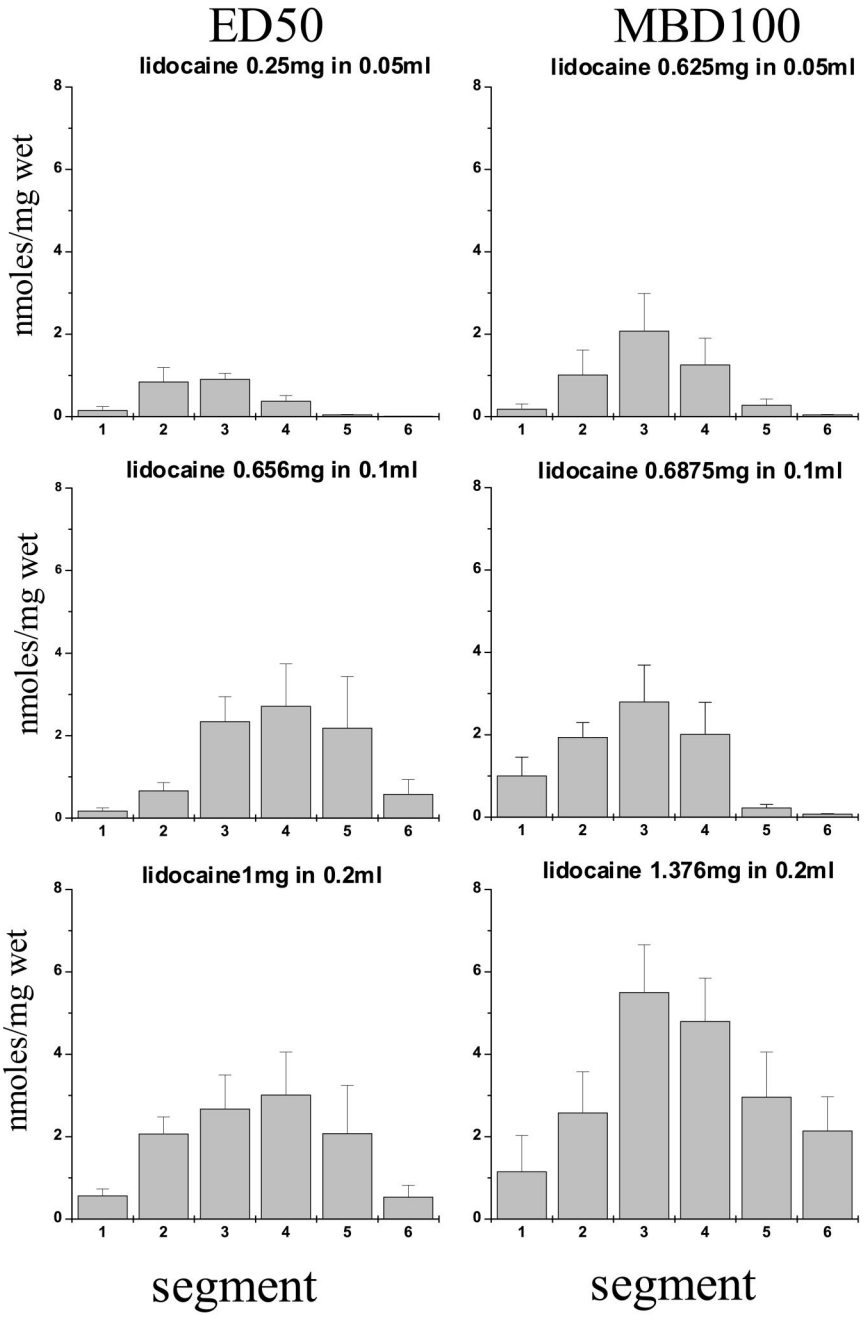

Fig. 6. Lidocaine distribution along the sciatic nerve 10 min after injection. The lidocaine distribution over the different longitudinal segments after injecting the 50% maximum possible effect and minimal blocking dose for 100% effect corresponding to each of the three volumes is graphed as the mean ± SEM from unilateral injections of five rats each for each of the six conditions. The specific doses and volumes are given above each graph.

ering that the total injected mass of drug in the largest volume is four times greater than in the smallest one and should lead to a greater mass in nerve. The odd finding is that the peak functional effects were the same despite the large difference in both the total and maximum intraneural drug contents at the time of these effects. We surmise that the lidocaine molecules are distributed radially within the nerve in different patterns, depending on the injected volume, and that the critical concentration at the axon membrane that establishes the reversible blockade of impulses is the same within these differing profiles of gross uptake. In other words, the larger uptake detected for large injected volumes does not occur in the effector compartment for neural blockade and may occur in the superficial epineural compartment of these ensheathed nerves.

Pharmacokinetics are important for peripheral nerve block.[12] It was previously reported that in the rat sciatic nerve, only a small percent of the molecules in an administered dose of 1% lidocaine is contained in the nerve at the time of maximum block.[6,9] Because vasoconstrictors (*e.g.*, epinephrine) coinjected with lidocaine can extend the block duration from this dose by several fold, vascular removal is probably the major process that limits drug uptake and, correspondingly, block duration.[11,12] Given that less than 1% of administered lidocaine is found in the nerve (table 1), even a modest increase in vascular flow could substantially influence

the effective delivery of drug to its neural target tissue. Importantly, lidocaine itself alters the local vascular flow.[12–14]

Local anesthetics exert complex actions on vascular tone. Blood flow in nerve and surrounding skeletal muscle can be increased or decreased depending on the concentration and type of local anesthetic. Lidocaine is known to dilate as well as to constrict blood vessels, depending on its concentration[14,15] and, perhaps, on the particular vascular bed studied.[16] Rat skeletal muscle arterioles *in vivo* were constricted by 0.01–1.0 mg/ml lidocaine but dilated by 10 mg/ml lidocaine.[15] Constriction of mesenteric capacitance veins isolated from rabbits and stimulated by neuronal norepinephrine release was inhibited by 0.01–0.1 mg/ml lidocaine.[16] By comparison, direct application of concentrated (10–20 mg/ml) lidocaine solutions to exposed sciatic nerve of anesthetized rats *in vivo* produced constriction of neurally associated vessels, which was detected as reduced blood flow by the laser Doppler technique.[17,18] At the lidocaine concentrations injected here, which are well above 1 mg/ml (0.1%), the *initial* effect on total *neuronal blood flow* would be vasoconstrictive, but *skeletal muscle arterioles* would be vasodilated.[15] The local lidocaine concentration may drop quickly, however, as a result of tissue adsorption, for example, leading rapidly to a different balance in constrictive–dilative dynamics. We speculate that for the larger volumes of equipotent solutions, the larger total dose will require a longer time for local clearance, local vasoconstriction will persist for longer, and the initial concentration will fall more slowly, resulting in a greater net amount of lidocaine entering the nerve, even though the same initial concentration was injected. Thus, the total neural content and the peak content are both greater for injection of larger equipotent doses, but most of this may be in the more superficial mantle regions of the nerve.[19] We propose that in the deeper perineurially contained fascicle core regions, the same effective concentration produces equivalent impulse blockade in those fibers that innervate the distal sensory and motor tissues tested by the behavioral routines used here.

How do the findings in rats compare with those in humans? For one, the order of loss and recovery of motor and nociceptive activities observed here is remarkably similar to that reported by Winnie *et al.*[19] for brachial plexus blockade by 1% lidocaine in humans. Second, the doses are also similar when scaled to mass. To accomplish a successful sciatic nerve block from a single injection in humans, 10–20 ml lidocaine, 2% to 1%, respectively, is recommended.[7] When scaled to body mass (*e.g.*, a 75-kg human being, who is 250–300 times larger than the rats used here), the corresponding dose of lidocaine would be 0.67–0.80 mg, equal to 1% lidocaine in a volume of 0.07 to 0.08 ml or 0.5% (5 mg/ml) in a volume of 0.14–0.16 ml, which is a scaled value similar to the one we determined experimentally (table 1). This agreement may be fortuitous, however, because the anatomic relations between nerve mass and surface area and the surrounding and endoneurial vasculature importantly affect the potency of clinically administered local anesthetics, and these specific relations are likely different between rats and humans. Nevertheless, Winnie *et al.*[19] reached a similar conclusion to ours about the importance of endoneurial blood flow in determining brachial plexus block duration, implying that some conclusions from experiments on small animals have clinical relevance.

Third, because the microanatomic properties of nerve fibers are not different among mammals,[20] the intraneural longitudinal spread of local anesthetic required for complete nerve block in humans is unlikely to be longer than that in rats. We therefore hypothesize that these similar findings can be generalized to humans and that local anesthetic concentration rather than dose will be the parameter critical for successful nerve block. One practical limit to this conclusion is that larger volumes permit more successful blocks when nerves are not well located or are poorly accessible. Another important limit is that more concentrated solutions of lidocaine are more likely to have irreversible neurotoxic effects.[21,22]

References

1. Huang JH, Thalhammer JG, Raymond SA, Strichartz GR: Susceptibility to lidocaine of impulses in different somatosensory afferent fibers of rat sciatic nerve. J Pharmacol Exp Ther 1997; 292:802–11
2. Gokin AP, Philip B, Strichartz GR: Preferential block of small myelinated sensory and motor fibers by lidocaine: *In vivo* electrophysiology in the rat sciatic nerve. ANESTHESIOLOGY 2001; 95:1441–54
3. Raymond SA, Steffensen S, Gugino LD, Strichartz GR: The role of length of nerve exposed to local anesthetics in impulse blocking action. Anesth Analg 1989; 68:563–70
4. Smith BE, Siggins D: Low volume, high concentration block of the sciatic nerve. Anaesthesia 1988; 43:8–11
5. Thalhammer JG, Vladimirova M, Bershadsky B, Strichartz GR: Neurologic evaluation of the rat during sciatic nerve block with lidocaine. ANESTHESIOLOGY 1995; 82:1013–25
6. Popitz-Bergez FA, Leeson S, Strichartz GR, Thalhammer JG: Relation between functional deficit and intraneural local anesthetic during peripheral nerve block. ANESTHESIOLOGY 1995; 83:583–92
7. Bridenbaugh PO, Wedel DJ: The lower extremity: Somatic blockade, Neural Blockade in Clinical Anesthesia and Management of Pain, 3rd edition. Edited by Cousins MJ, Bridenbaugh PO. Philadelphia, Lippincott-Raven, 1998, pp 378–9
8. Sinnott CJ, Garfield JM, Thalhammer JG, Strichartz GR: The addition of sodium bicarbonate to lidocaine decreases the duration of peripheral nerve block in the rat ANESTHESIOLOGY 2000; 93:1045–52
9. Sinnott C, Cogswell LP III, Johnson A, Strichartz GR: On the mechanism by which epinephrine potentiates lidocaine's peripheral nerve block. ANESTHESIOLOGY 2003; 98:181–8
10. Covino BG, Vasallo HG: Local Anesthetics: Mechanisms of Action and Clinical Use. Orlando, Grune & Stratton, 1976, p 97
11. Collingsworth KA, Strong JM, Atkinson, AK Jr, Wrinkle RA, Perlroth F, Harrison DC: Pharmacokinetics and metabolism of lidocaine in patients with renal failure. Clin Pharmacol Ther 1975; 18:59–64
12. Mather LE, Tucker GT: Pharmacokinetics and biotransformation of local anesthetics. Int Anesthesiol Clin 1978; 16:23–51
13. Wildsmith JAW, Tucker GT, Cooper S, Scott DB, Covino BG: Plasma concentrations of local anaesthetics after interscalene brachial plexus block. Br J Anaesth 1977; 49:461–6
14. Altura BM, Altura BT: Effects of local anesthetics, antihistamines, and glucocorticoids on peripheral blood flow and vascular smooth muscle. ANESTHESIOLOGY 1974; 41:197–214

15. Johns RA, DiFazio CA, Longnecker DE: Lidocaine constricts or dilates rat arterioles in a dose-dependent manner. ANESTHESIOLOGY 1985; 62:141–4

16. Hogan QH, Stadnick A, Bosnjak ZJ, Kampine JP: Effects of lidocaine and bupivacaine on isolated rabbit mesenteric capacitance veins. Reg Anesth Pain Medic 1998; 23:409–17

17. Myers RR, Heckman HM: Effects of local anesthesia on nerve blood glow: Studies using lidocaine with and without epinephrine. ANESTHESIOLOGY 1989: 71;757–62

18. Partidge BL: The effects of local anesthesia and epinephrine on rat sciatic nerve blood flow. ANESTHESIOLOGY 1991; 75:243–51

19. Winnie AP, Tay C-H, Patel KP, Ramamurthy S, Durrani Z: Pharmacokinetics of local anesthetics during plexus blocks. Anesth Analg 1977; 56:852–61

20. Northcutt RG: The comparative anatomy of the nervous system and the sense organs, Hyman's Comparative Vertebrate Anatomy. Edited by Wake MH. Chicago, University of Chicago Press, 1992, pp 615–769

21. Bainton CR, Strichartz GR: Concentration dependence of lidocaine-induced irreversible conduction loss in frog nerve. ANESTHESIOLOGY 1994; 81:657–67

22. Schneider MC, Hampl KF, Kaufmann M: Transient neurologic toxicity after subarachnoid anesthesia with hyperbaric 5% lidocaine (comment). Anesth Analg 1994; 79:610