Prolonged Alleviation of Tactile Allodynia by Intravenous Lido- caine in Neuropathic Rats

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Background: Lidocaine may be useful in the treatment of neuropathic pain states. The authors hypothesized that lido- caine would reduce tactile allodynia observed in a rat nerve injury model. In an effort to determine the site of drug action, effects after intravenous, intrathecal, and regional administration were compared.

Methods: Rats underwent ligation of the left fifth and sixth lumbar spinal nerves. The 50% thresholds (g) for left hind paw-withdrawal of awake rats to von Frey hairs were documented before, during, and after intravenous administration of lidocaine at programmed/documented pseudo-steady-state plasma concentrations, and correlated with measured plasma concentrations. Responses to lidocaine application intrathecally and regionally to the injured nerves were also recorded.

Results: In rats with tactile allodynia, intravenous lidocaine yielded 66 ± 11% of the maximal possible effect on thresholds (100% = normal threshold), versus 1.5 ± 2.7% for saline infusion. Twenty-one days after lidocaine infusion, 30–40% of the maximal possible effect persisted. Threshold increases depended on plasma concentration, rather than quantity of drug administered: rats receiving 15 mg/kg with higher plasma concentrations (1.2 ± 0.1 µg/ml) showed significant allodynia suppression throughout 7 days of follow-up, whereas rats receiving 15 mg/kg at a slower rate with lower plasma concentrations (0.6 ± 0.1 µg/ml) did not. The EC50 for acute allodynia suppression was 0.75 µg/ml. No such allodynia suppression was seen after intrathecal or regional administration of lidocaine despite transient neural blockade.

Conclusions: Intravenous, but not intrathecal or regionally applied, lidocaine produces dose-dependent suppression of allodynia associated with nerve injury. The effects far outlast plasma concentrations of lidocaine. The mechanism of these prolonged effects is unknown. (Key words: Anesthetics, local; lidocaine; nerve injury; peripheral neuropathy; rat; von Frey hairs. Pain, allodynia: mechanical; tactile. Pain, hyperalgesia: mechanical; tactile.)

A number of carefully executed clinical studies have shown that systemically administered local anesthetics may have analgesic properties specific to pain states resulting from damage to nerve tissue.1–7 Analgesia in such neuropathic pain states is attained in the absence of motor or sensory conduction blockade, and at doses without toxic effects. Because neuropathic pain is otherwise difficult to treat and is typically refractory to conventional analgesic agents, these studies have generated considerable interest.

Patients with painful diabetic neuropathy have been shown to benefit with reduced pain scores for several days from the intravenous administration of lidocaine, without alteration in thermal thresholds.8,9 Patients with pain due to peripheral nerve injury likewise reported decreases in spontaneous pain, albeit of short duration, after receiving intravenous lidocaine.6 Orally administered available congeners of lidocaine also may be effective, as demonstrated by the analgesic effects of mexiletine in painful diabetic neuropathy5 and peripheral nerve injury,1 and tocainide in trigeminal neuralgia.9

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portantly, human psychophysical studies have documented that the predominant evoked pain complaint in peripheral nerve injury sufferers is allodynia. Kim and Chung have reported that after ligation of the L5 and L6 spinal nerves in the rat, reliable, long-lasting allodynia develops. In particular, animals so prepared display readily quantifiable paw withdrawal reactions to light mechanical stimuli, comparable in character to the clinical syndrome of tactile allodynia evoked by light touch. We employed this model to study the efficacy and site of action of systemically administered lidocaine in the neuropathic state.

Materials and Methods

All procedures followed protocols approved by the Institutional Animal Use and Care Committee of the University of California, San Diego. Male Harlan Sprague-Dawley rats (weighing 100–200 g) were maintained in a standard facility with a 12-h day (0600–1800) and 12-h night cycle. Water and food pellets were supplied ad libitum. After surgery, rats were housed two or three to a cage with corn cob bedding. All surgeries were performed on separate occasions, allowing a minimum of 5 days between procedures for adequate recovery, except as specified later in the case of regional nerve catheter placement at the time of nerve ligation.

Neuropathy
Rats were anesthetized with halothane, 1–3%, in a 34%/oxygen/mixture. The left fifth and sixth lumbar spinal nerves were exposed via a dorsal midline incision and ligated tightly with 6-0 silk suture according to the method described by Kim and Chung. Rats were studied between 5 and 60 days after nerve ligation.

Intrathecal Catheters
Intrathecal PE-10 catheters were implanted under halothane/oxygen anesthesia. The catheters were 9 cm in intrathecal length and terminated near the lumbar enlargement. A rostral 3-cm extension of catheter was tunneled under the skin and externalized between the ears for injection. Rats with neurologic deficits were not used. Catheters were flushed with 10 μl preservative-free physiologic saline after insertion and after use for drug delivery.

Intravascular Access
Catheters made from PE-50 tubing were inserted into an external jugular vein under halothane/oxygen anesthesia. Similar catheters with the addition of a small boulon 1 cm from the intravascular tip, for suture retention, were inserted into a carotid artery, taking care to spare the adjacent vagus nerve. All catheters were tunneled subcutaneously to emerge at the base of the neck, flushed before and after each use with heparinized saline (10 units/ml), and capped when not in use.

Indwelling Nerve Blockade Catheters
To allow drug delivery at the nerve injury site in the six rats described later, catheters were fashioned from PE-10 gently bent into a U shape and fused to a PE-50 extension, as previously described. During creation of the nerve ligation, the PE-10 loop was tied down to the newly lesioned nerve pump, with the catheter lumen directed proximally toward the dorsal root ganglion. Catheters were externalized through the wound closure to the subcutaneous level, secured to the fascia, then tunneled subcutaneously to exit at the neck. These catheters were periodically flushed with sterile normal saline to ensure patency.

Infusion Method
A computer program (Stanpump) designed to rapidly achieve and maintain constant plasma drug concentrations (pseudo-steady-state concentrations) was used to drive a syringe infusion pump (Harvard Apparatus, South Natick, MA). A modification of Rowland's kinetics set using experimentally derived rat parameters (Chapman, Bach, Shafer, and Yaksh; unpublished data) enabled prediction of plasma concentrations and stable maintenance of pseudo-steady-state concentrations in plasma (fig. 2).

Mechanical Thresholds
Rats were placed in a plastic cage with an open wire mesh bottom and accommodated to approach approximately 15 min. A series of eight von Frey-type filaments with exponentially incremental stiffness (0.41, 0.70, 1.20, 2.00, 3.63, 5.50, 8.50, and 15.10 g; Stoelting, Wood Dale, IL) was employed to determine the 50% threshold for paw withdrawal to light mechanical stimuli, using a previously described up-and-down paradigm summarized later. The left hind paw was tested, because (1) the ability or willingness of the rat to bear weight on the left hind paw may have altered any results of testing applied to the normal right hind paw; and (2) other investigators have shown alterations in both left and right spinal cord dorsal horn neurochemical environments after unilateral lesions.

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Fig. 1. After a single intravenous lidocaine infusion to complete allodynia suppression or a maximum of 30 mg/kg over approximately 60 min on day 0, neuropathic rats were followed for 3 weeks (N = 6) and simultaneously compared with rats that received saline infusions of equivalent volume using the same paradigm (N = 5). Blinded assessment revealed a highly significant difference between groups, with sustained allodynia suppression in the lidocaine-treated rats, and an absence of spontaneous neuropathy resolution in the saline controls (P = 0.0002, repeated measures analysis of variance). X-axis, day relative to lidocaine infusion; y-axis, paw withdrawal thresholds expressed as percent of maximum possible effect ± SE.

The following equation was used to compute %MPE:

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\%MPE = \frac{\text{new threshold}(g) - \text{baseline threshold}(g)}{15 \text{ g} - \text{baseline threshold}} \times 100
\]

Experimental Design: Effect of Lidocaine on Normal Rats

Normal (i.e., nonlesioned) rats prepared with both intrathecal and intravenous catheters (N = 12), were divided into two groups. The first group (N = 6) received an infusion of lidocaine designed to rapidly achieve a plasma concentration of 2.5 μg/ml and maintain that plasma concentration for 30 min. The second group (N = 6) received the same volume of infusate containing only saline. Paw withdrawal thresholds were measured after 30 min of infusion and compared. These animals were not further used in the present studies.

Acute/Long-term Effect in Rats with Neuropathy: Lidocaine Versus Saline

Four weeks after nerve ligation, rats were assigned to groups for either lidocaine or saline infusion, using a random number table. The investigator assessing mechanical thresholds was blinded to the treatment. Lidocaine (Abbott, Abbott Park, IL, 2%, diluted in normal saline to 5 mg/ml; N = 6), or an identical volume of saline (N = 5), was continuously infused intravenously at an incremental rate to an endpoint of complete allodynia suppression, or a maximum infusion volume corresponding to a lidocaine dose of 30 mg/kg, over a period of approximately 60 min. At the conclusion of this acute phase of the experiment, intravascular catheters were left trimmed and cuffed, and rats were returned to the animal facility. Testing was performed daily on days 1-14, and then on days 17, 19, and 21.

Acute Time Effect

To examine the relationship between plasma concentration and time, neuropathic rats with intrajugular...
catheters (N = 6) received lidocaine at rates calculated to maintain a pseudo-steady-state plasma concentration (plateau) close to 2 μg/ml, to a cumulative dose of 15 mg/kg. Paw withdrawal thresholds were tested 5, 10, 20, 30, and 40 min into the plateau phase of the infusion, after completion of the approximately 9-min rapid bolus infusion phase required to achieve the targeted concentration. A parallel group of noninjured rats with both intratracheal and intraarterial catheters received identical infusions (N = 4), and arterial blood samples were drawn at all time points corresponding to threshold measurements in the neuropathic rats.

**High Versus Low Plasma Concentration Lidocaine**

To examine the importance of plasma concentration achieved versus total dose of lidocaine administered, rats with both intratracheal and intraarterial catheters were randomly assigned to receive a dose of lidocaine in such a fashion as to achieve a plasma target concentration previously found to suppress mechanical allodynia as above (high target: group A), or the same total dose in mg/kg, but delivered in such a way that plasma concentrations remained at approximately half the demonstrated effective target concentration (low target: group B). Intravenous infusions of lidocaine designed to achieve and maintain plasma concentrations in the vicinity of 2 μg/ml were administered to group A to a cumulative dose of 15 mg/kg (n = 11). Group B received an infusion designed to maintain a plateau concentration of half the concentration in group A, administered over 85 min, for a cumulative dose again of 15 mg/kg (n = 9). Paw withdrawal thresholds were tested every 10 min, and arterial blood samples were drawn when allodynia suppression was achieved, or at the end of the infusion. At the conclusion of the experiment, rats were returned to the animal facility, and paw withdrawal thresholds were recorded on posttreatment days 1, 5, and 7 (n = 8, group A, and n = 6, group B).

**Effect Site**

**Spinal Cord.** To determine whether lidocaine has an antiallostatic action when directly applied to the spinal cord, a dose of 500 μg/kg lidocaine was administered intrathecally in a volume of 10 μl, followed by 10 μl saline flush (N = 6). This dose was chosen to grossly exceed any cerebrospinal fluid concentration of lidocaine that might be achieved by systemic infusion, and to produce obvious transient motor dysfunction as a marker of effective drug placement. Paw withdrawal thresholds were tested at baseline before dosing (0 min) and at time points beginning when motor function completely returned to normal after lidocaine instillation (30, 45, 60 min). The effects on mechanical thresholds, expressed as %MPE, were compared to baseline values.

**Spinal Nerve.** To explore the possibility of a site of action at the injured axon, rats prepared as described earlier with indwelling nerve block catheters were dosed with 1 mg lidocaine regionally applied to the nerve ligation site, in a volume of 50 μl (20 mg/ml, N = 6). Paw withdrawal thresholds were tested at 5, 10, 15, 30, and 60 min after drug treatment, and compared to pretreatment baseline values.

**Lidocaine Assays**

Samples were obtained by withdrawing and discarding approximately 0.5 ml of blood from the arterial cannulae, and then withdrawing samples of approximately 0.5 ml volume. These samples were centrifuged and the plasma supernatant was frozen at −20°C until analysis. Lidocaine was extracted from the thawed samples by solid-phase extraction chromatography.

**Gas Chromatography Instrumentation and Chromatographic Conditions**

Lidocaine was quantitated by capillary gas chromatography with nitrogen-phosphorus detection. A Hewlett-Packard 5890 II gas chromatograph (Palo Alto, CA) was equipped with a methyl-silicone gum (HP-1) capillary column (25 M × 0.2 mm × 0.33 μM), programmed with injector and detector temperatures of 265°C. Split injections (1:5) were performed with a Hewlett-Packard 7673A automatic sampler, and the chromatograms were recorded and analyzed with HP Chemstation (MSDOS) software. The helium carrier gas flow rate was 0.9 ml/min (32 psi). Hydrogen and air flow rates in the detector were 5 and 120 ml/min, respectively. The oven temperature was programmed at 240°C for 1 min, raised over 1 min to a final temperature of 270°C, and held at 270°C for 4 min. Total run time was 5 min; lidocaine and bupivacaine (used as an internal standard) eluted at 2.4 and 4.0 min, respectively. The absolute limit of detection by this method was 0.05 ng lidocaine/μl serum. The interassay and intraassay coefficients of variation were 4.2% and 2.5%, respectively, for serum lidocaine concentrations between 0.1 and 1.0 ng/μl.

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Fig. 2. Two groups of rats underwent identical intravenous lidocaine infusion protocols, in which a pseudo-steady-state level was sustained over 40 min. One group, consisting of six neuropathic animals, had repeated paw withdrawal threshold testing. The second group consisted of four normal rats equipped with arterial catheters for blood sampling. Samples were drawn at all time points corresponding to paw testing in the neuropathic group; mean plasma lidocaine concentration overall was 1.34 ± 0.07 μg/ml. Significant increases in paw withdrawal thresholds were seen beginning 30 min after attaining targeted plasma lidocaine levels (P < 0.001, repeated measures analysis of variance with mean squares contrasts). X-axis: time; left y-axis: paw withdrawal thresholds expressed as percent of maximum possible effect ± SE; right y-axis: plasma lidocaine levels, μg/ml ± SE.

Statistical Analysis

Results are expressed as mean ± SE, or median (95% confidence intervals). Median paw withdrawal thresholds before and after infusion were compared using the Wilcoxon signed-rank test if paired and the Mann-Whitney U test if unpaired. Changes in %MPE, designating pretreatment paw withdrawal thresholds as 0% effect and threshold values of ≥15 g as 100% effect (see above), were compared using repeated measures analysis of variance. When P values were less than 0.05, we identified significant differences between pairs by contrast calculations (means comparisons). Nonparametric repeated-measures analyses were performed using the Friedman test. Lidocaine blood concentrations were compared using a two-tailed t test.

Acute Time Effect

Paw withdrawal was inhibited in a cumulative fashion by the continuous administration of intravenous lidocaine at a pseudo-steady-state plasma concentration (in the parallel group) of 1.34 ± 0.07 μg/ml for a period of 40 min. Median paw withdrawal threshold increased gradually during the 40-min infusion period to a final value of 12.68 g (7.07–14.87 g), compared to a baseline value of 1.56 g (1.00–2.80 g). Figure 2 shows both the stable plasma concentrations generated by the software-driven infusion and the steady increase in paw thresholds, expressed as %MPE, as a function of time. Although plasma concentrations achieved were slightly lower than the targeted levels, more importantly, concentrations were steady over time and correlated in a linear fashion with targeted values. Repeated measures analysis of variance yielded a P value of <0.001 for %MPE during lidocaine infusion; using contrasts (means...
comparison), the 30- and 40-min time points were shown to be the points that significantly differed from baseline.

High Versus Low Plasma Concentration Lidocaine

Rats receiving the higher target concentration of lidocaine (group A) achieved allodynia suppression. The median baseline value for paw withdrawal threshold in this group was 1.56 g (1.19–2.19 g), which was significantly below that recorded at the end of the infusion period, 15.00 g (12.41–15.76 g; \( P = 0.0033 \), Wilcoxon signed-rank test). Rats receiving the lower target concentration (group B), receiving the same cumulative dose (15 mg/kg) administered over a longer period (85 min), did not achieve significant allodynia suppression (baseline thresholds of 2.80 g (1.64–3.15 g) versus postinfusion, 3.31 g (2.22–4.39 g; \( P = 0.067 \), Wilcoxon signed-rank test). Paw withdrawal thresholds in group A were significantly higher than in group B immediately after infusion (\( P = 0.002 \), Mann-Whitney). At the end of the infusion period, blood concentrations in the higher target infusion group (A) were 1.21 µg/ml ± 0.09 and in the lower target infusion group (B), 0.61 µg/ml ± 0.10 (\( P = 0.0007 \), two-tailed t test). Rats in group A continued to show significant allodynia suppression during the 7 days of follow-up (\( P = 0.0006 \), Friedman test). No suppression of allodynia appeared during the follow-up period for rats in group B (\( P = 0.67 \), Friedman test; fig. 3).

Effect Site: Intrathecal and Regional Nerve Application

Rats receiving 500 µg of intrathecal lidocaine exhibited transient motor block (flaccidity) of 10–15 min maximum duration affecting the hind quarters but not the forequarters. During this time paw withdrawal could not be assessed. Testing of paw withdrawal thresholds after resolution of motor block (as evidenced by normal stance, gait, and righting reflexes) revealed no differences from baseline at 30 and 60 min; a mean threshold elevation at 45 min representing a 13.7 ± 4% MPE was statistically significant (\( P = 0.02 \), repeated-measures analysis of variance with contrasts). Application of lidocaine directly to the site of nerve injury by means of indwelling catheters caused conduction blockade of a transient nature, manifested as transient paw flaccidity with decreased withdrawal responses to pinch as well as to light tactile stimuli. After resolution of acute blockade, no further effect on allodynia was detectable with regional administration. Figure 4 shows the mechanical thresholds after both intrathecal and regional lidocaine administration.

Dose-Response Analysis

After determination of the delayed onset of allodynia blockade as demonstrated in figure 2, all plasma lidocaine concentrations obtained after at least 30 min of intravenous lidocaine administration were correlated with simultaneously determined paw withdrawal thresholds. This analysis resulted in a sigmoidal dose-response curve. Logit analysis (log(y)/(100 – y)) was performed to linearize the sigmoidal curve (fig. 5). The plasma lidocaine concentration corresponding to 50% suppression of allodynia was calculated as 0.75 µg/ml using this analysis.

Discussion

The major findings of this study are that (1) intravenously administered lidocaine produces plasma-
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Fig. 4. (A) Lidocone 500 μg was administered intrathecally to six neuropathic rats (10 μl of 5% lidocone in saline). This dose was chosen to exceed hypothetical cerebrospinal fluid concentrations of lidocone achieved with intravenous infusion. All rats developed complete, transient lower body flaccidity (effective spinal anesthesia). After resolution of motor weakness, paw withdrawal thresholds were compared to predrug values. The significant albeit small effect at 45 min (P = 0.02, repeated measures analysis of variance with means comparisons contrast tests) was not present at 30 min and was absent by 60 min. (B) Catheters were implanted at the site of nerve ligation with orifices directed centrally (6 rats). After full recovery and documentation of withdrawal thresholds to von Frey hairs, catheters were injected with 50 μl of 2% lidocone (1 mg = approximately 1 mg/kg in a 250 g rat). Transient analgesia to paw pinch and partial paw weakness were seen in all six rats (data not shown), demonstrating satisfactory delivery to the ligation site. By 15 min after treatment, von Frey hair thresholds were again indistinguishable from pre-treatment (P = 0.97, repeated measures analysis of variance, means comparisons contrasts). X-axes: time; y-axes: paw withdrawal thresholds expressed as percent of maximum possible effect.

Fig. 5. Intravenous infusion of lidocone, using a software-driven syringe pump, produced pseudo-steady-state plasma lidocone levels during which paw withdrawal thresholds were measured. Arterial lidocone levels drawn ≥30 min after start of infusion correlated with the degree of suppression of allodyney. There were no signs of toxicity at the levels illustrated. Untransformed data (Inset): x-axis = log measured lidocone concentration, y-axis = percent of maximum possible effect. In the surrounding figure, percent of maximum possible effect has been given logit transformation (y = log [y/(100 − y)]) for linear depiction of the sigmoid dose-response curve. R = 0.76, P < 0.01, linear regression. X-axis: log measured plasma lidocone concentration; y-axis: logit transformation of percent of maximum possible effect as above.

Mechanism of Action

Widespread Consequences of Peripheral Nerve Injury. After injury to a peripheral nerve, substantial functional alterations occur in both the peripheral and central nervous systems. Sustained, low-level ectopic spontaneous activity originates at the site of neuroma formation in large peripheral axons as well as in dorsal root ganglion cells. While the basis of this spontaneous electrical activity is not known, abnormalities of axonal sodium channel distribution have been described in association with demyelination after periph-

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eral nerve injury,25, 26 that may lead to spontaneous fiber activity.27 In addition, the appearance after nerve injury of an unusual type of "modified rapidly adapting" cutaneous mechanoreceptor has been identified, which although not spontaneously active, shows abnormally prolonged, weak, irregular discharges to light mechanical stimuli.28 Prominent increases are also seen in the evoked activity of dorsal horn neurons, which project supraspinally.29, 30 Similar sustained central activity is demonstrable after the application of N-methyl-D-aspartate type glutamate agonists,31 which leads not only to electrophysiologic facilitation of neuronal responses but also to the behavioral manifestation of tactile allodynia.32 Thus, continued afferent pathway activity is linked to behavioral states wherein modest stimuli may evoke pronounced responses. These changes in electrical activity are associated with peripheral and central changes including alterations in receptor expression33, 34 second messenger function,35, 36 neurotransmitter production,37, 38 likely neuronal dropout,39 and possibly altered balance of inhibitory/excitatory neurotransmitters.40 The sum total of these mechanisms may provide a scenario whereby nerve injury leads to an anomalous pain state.

**Effect of Lidocaine on Neuronal Activity.** Owing to its well known properties of conduction blockade, lidocaine has been assayed in afferent systems primarily using electrophysiologic assessments. A number of investigations have examined the effects of lidocaine on evoked or spontaneous neural activity such as described earlier. A systematic examination in patients with painful diabetic neuropathy4 has suggested a spinal or supraspinal effect site because of suppression of the centrally organized nociceptive flexion response. In addition, considerable evidence from the preclinical literature supports a spinal cord or supraspinal site of action of intravenously administered lidocaine in facilitated pain states.40-44 Lidocaine, with an octanol: water distribution coefficient of 110 at 36°C, pH 7.4,45 distributes promptly to central nervous system structures after systemic administration.46 The effects of a systemically delivered dose appear more potent in central than in peripheral nervous structures. Although peripheral terminals clearly respond to lidocaine, they appear to do so only at a relatively high concentration. A single study has derived in vitro dose-response curves for the suppressant effect of lidocaine on spontaneous activity in acutely injured peripheral terminals. The reported ED50 of 5.7 μg/ml however, reflects drug in an artificial, protein-free system; a substantially higher plasma concentration would in all likelihood be required for a comparable investigation in vivo, considering that lidocaine is extensively protein-bound in circulation. In whole animals, the ED50 of intravenous lidocaine for discharge suppression in neurumata has been reported to be 6 mg/kg, whereas that for the dorsal root ganglion is lower, at 1 mg/kg,48 a dose that also yields suppression of polysynaptic (spinal cord) sural nerve evoked afterdischarges.49 Dose-related suppression of neurons in Rexed lamina V to high threshold mechanical and noxious thermal stimuli is seen in decerebrate cats (plasma concentration = 3-10 μg/ml).49 Intravenous lidocaine (1-5 mg/kg) suppresses polysynaptic C-fiber evoked flexor responses to mustard oil and noxious heat, without evidence of conduction block at the peripheral terminal.49 Intravenous lidocaine (3-4 mg/kg) suppresses noxious-evoked activity in wide dynamic range neurons in the rat, and, in addition, selectively suppresses the increased wide dynamic range neuronal activity seen ipsilateral to chronic peripheral nerve injury.52, 53 To date, no studies have specifically examined the effects of systemically administered lidocaine on supraspinal structures or descending pathways in the context of hyperalgesia or increased evoked responses.

**Effect Site of Lidocaine.** These potent central effects strongly suggest that lidocaine can exert a central action. Although our local spinal delivery work demonstrates that the prolonged effects cannot be accounted for by a simple direct local action of lidocaine, the spinal cord should not be excluded from further consideration based solely on the current results. Our observations, including the delay in onset of the antiallodynic effect of intravenous lidocaine and the need for systemic delivery, raise the possibility, among other hypotheses, that biotransformation of the administered drug may be a prerequisite. Several metabolites with local anesthetic/antiarrhythmic activity, and half-lives as long as or longer than the parent compound, are produced in the liver, including monoethylglycinexilidide and glycineexilidide.59 It should be noted that the activity of intravenous lidocaine in a dorsal horn recording preparation exceeds that of iontophoresed lidocaine, suggesting that the species active in producing effects at the spinal cord level could in fact be a metabolite.50

We have considered the possibility that lidocaine might be acting via sympathetic nervous system blockade in this model, known to be responsive to sympa-thectomy.51, 52 The minimal and transient sympatheticic

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In all likelihood, this potentiation in vitro, conclusively protein-bound is the ED50 of intravenous block contribution that the dose of lidocaine (5 mg/kg), 44 a dose that the effects of sympathetic (spinal cord) and somatic (lower motor neuron) Dose-related suppression in the V to high threshold, central sensitization is seen in anesthesia = 3-10 μg/kg) suppresses perioperative responses to nociceptive stimulation. Evidence of conduction block.4,41 Intravenous lidocaine is axonally-evoked axons is in the rat, and in other species, the increased wide potential can be seen ipsilateral afferent axons.42 To date, no studies have examined the effects of systemic lidocaine suppression in the context of hyperalgesia and the possibility of potent central effects that can be observed in the central nervous system. In this study, we have observed that the effects after intravenous administration of lidocaine can be limited to the central nervous system and spinal cord with far less effect than exposures to lower concentrations by intravenous administration. The prolonged effects of several weeks might appear to point to some form of persistence of the drug at an active tissue site. We attempted to address the possibility of a depot drug action by administering an identical total dose in mg/kg to groups of rats using two different plasma concentration profiles, subjecting one group to a shorter infusion with a higher plasma concentration and the second to a longer infusion attaining half the plasma concentration. The observation that persistent allodynia suppression was only seen in the group receiving the higher plasma concentration appears to argue against any hypothesis whereby a depot of accumulated drug might explain persistent drug action.

Reversible sodium channel blockade is the most often described major pharmacologic property of lidocaine. It is possible that the action of lidocaine may be different in excitable tissues after injury, in a way that remains to be elucidated. For example, after injury, the expression of different isoforms of both acetylcholine receptors and sodium channels at the neuromuscular junction 45-49 leads to a distinct pharmacology of the postinjury state. Functionally differing subpopulations of sodium channels have already been well described within the normal dorsal root ganglion. Channels associated with the smaller dorsal root ganglion cells, which likely give rise to small unmyelinated fibers (C-fibers), display the particular characteristic of use-dependent blockade with lidocaine. 50 Although the role of C-fibers per se has been questioned in both the induction and maintenance of tactile allodynia, 51-55 it is speculated that a channel isoform, hypothetically expressed in afferent pathways after neuronal damage, could be subject to exaggerated use-dependent blockade by lidocaine.

We raise the additional hypothesis that lidocaine may be acting at a novel locus, one other than the sodium channel, perhaps by a mechanism of action that leads somehow to long-term “switching” of neuronal function. Several reports have suggested that lidocaine has second messenger blocking effects, 56-58 however, the concentrations employed in those studies far exceeded the physiologic range used in our study. Of note, a recent report 59 delineates a mechanism whereby the metabotropic glutamate receptor functions as an “on-off” switch through the activation of protein kinases/phosphatases to regulate the inducibility of long-term potentiation in the hippocampus. Such regulation, with durable consequences for the facilitation/inhibition of postsynaptic impulisses, may provide one example of a theoretical construct as to how an isolated pharmacologic intervention can exert a persistent effect.

In summary, we have described suppression of allodynia in a rat surgical neuropathy model during acute administration of lidocaine, accompanied by very prolonged continued effects. The site of effect and means of action remain to be elucidated. Further studies are needed to determine which mechanisms are most relevant to the persistent allodynia suppression observed in our study.
necessary to clarify the mechanisms involved in this potentially very clinically useful effect.

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