

## Systemic Lidocaine Blocks Nerve Injury-induced Hyperalgesia and Nociceptor-driven Spinal Sensitization in the Rat

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**Background:** Repetitive C-fiber stimulation induces a state of facilitated processing of sensory information in the dorsal horn, while chronic nerve compression gives rise to a hyperalgesic state, characterized by spontaneous neuronal activity generated by voltage-sensitive sodium channels, as well as spinal facilitation.

This study investigates the effects of systemic local anesthetic on thermal hyperalgesia evoked by chronic nerve compression and on the pain behavior responses to subcutaneous formalin.

**Methods:** The effects of intravenous lidocaine were evaluated in rats with (1) the formalin test, a model of acute pain and centrally mediated delayed sensory sensitization, and (2) a model of chronic sciatic nerve compression leading to a neurogenic thermal hyperalgesia. Groups of rats (300 g) undergoing formalin testing were given intravenous lidocaine in doses of: 3 mg plus 25  $\mu$ g/min infusion (yielding serum levels of  $6.3 \pm 1.0$   $\mu$ g/ml) or 1.5 mg plus 12.5  $\mu$ g/min infusion (yielding serum levels of  $3.6 \pm 0.3$   $\mu$ g/ml) beginning 5 min before the subcutaneous injection of formalin in the left hind paw. In other studies, a group of six animals were rendered hyperalgesic in one hind limb by the placement of compressive ligatures about the left sciatic nerve (Bennett model) 3-5 days before these studies. These rats were treated with 0.6 mg in-

travenous lidocaine followed by an infusion of lidocaine at a rate of 5  $\mu$ g/min (yielding serum levels of  $1.0 \pm 0.1$   $\mu$ g/ml).

**Results:** Lidocaine had no significant effect on the first phase of the formalin test or on thermal response latencies in normal limbs. However, at a high dose, lidocaine significantly reduced phase 2 flinching behavior and at a low dose, reversed the thermal hyperalgesia produced by sciatic nerve ligation during 30 min of infusion for a period of 3 h after the infusion was discontinued.

**Conclusions:** Intravenous lidocaine acts by distinct mechanisms to diminish the hyperesthetic state induced by peripheral nerve injury and to reduce the degree of spinal sensitization induced by C-afferent fiber activation. (Anesthetics, local; intravenous lidocaine. Nerve, injury: hyperalgesia. Spinal cord: sensitization.)

SYSTEMIC administration of lidocaine has been shown to produce analgesia in a variety of neuropathic pain states.<sup>1-4</sup> The site of analgesic action in such conditions is not clear. At blood levels that do not produce side effects in humans (dizziness, tinnitus, tremor, or paresthesias), there is little or no appreciable effect of local anesthetics on impulse conduction in normal peripheral nerves<sup>5-8</sup> or on cutaneous C-fiber terminal function.<sup>5</sup> Therefore, possible mechanisms of action are likely to include effects of the drug on the impulse generation in injured nerves or on the processing of activity in the central nervous system. There is evidence that both of these mechanisms may be operative in neuropathic pain states. Systemic lidocaine has been shown to inhibit spontaneous impulse generation arising from injured nerves<sup>6-8</sup> and from dorsal root ganglia proximal to injured nerve segments.<sup>6</sup> The fact that the C-fiber-evoked polysynaptic reflex generated by sural nerve stimulation is suppressed by lidocaine at doses that do not block impulse conduction<sup>5</sup> provides evidence that this drug also has central inhibitory effects. Bach *et al.*<sup>1</sup> showed that lidocaine raised response thresholds of nociceptive flexion reflexes in diabetic patients, also suggesting a central action.

There is evidence that systemic local anesthetic acts on the hyperalgesic component of the pain state gen-

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erated by nerve injury either by an action at the injured site of the peripheral nerve or by an effect on sensory processing in the dorsal horn of the spinal cord. In the present study, we sought to examine the relative contributions of these distinct mechanisms systematically by considering the effects of intravenous lidocaine in two animal models: the formalin model and a model of thermal hyperalgesia induced by chronic nerve compression. In the former case, the injection of formalin into the paw resulted in a two-phased pain behavior, the first phase being representative of an acute effect mediated by the activation of nociceptive afferents, and the second phase being a composite of the ongoing barrage plus the generation of a facilitated state of afferent processing thought to result from the sensitization of the spinal cord ("wind-up").<sup>9,10</sup> The nerve compression model has been shown to be associated with the appearance of significant changes in peripheral nerve morphology,<sup>11</sup> increases in endoneurial pressure,<sup>11</sup> and the appearance of spontaneous activity arising from the injured regions as well as from the dorsal root ganglion.<sup>12</sup> In addition, over time, there were marked morphologic and biochemical changes that appeared in the ipsilateral dorsal horn, suggesting the reorganization of afferent processing.<sup>13</sup>

## Methods

The following studies were carried out under a protocol approved by the Institutional Animal Care Committee of the University of California at San Diego.

### *Intravenous Lidocaine Administration*

Male Sprague Dawley rats weighing 250–350 g were anesthetized with 2–3% halothane. The right internal jugular vein was surgically exposed, and a 3.3 cm length of Silastic catheter (Dow Corning, Midland, MI) attached to 15 cm of PE 50 tubing was introduced into the jugular vein and sutured to the vein at its junction with the PE 50. The PE 50 portion of the catheter was tunneled subcutaneously to the posterior cervical region, flushed with a saline and heparin solution, and occluded during recovery.

The drug delivery protocol employed a fixed bolus volume of lidocaine and saline (300  $\mu$ l) followed by the continuous infusion of 2.5  $\mu$ l/min. The use of fixed volumes prevented possible effects related to volume loading across different dose groups. Dose was adjusted by varying the drug concentration. Concentra-

tions of local anesthetic used were 10 mg/ml, 5 mg/ml, 2 mg/ml, or 0.2 mg/ml, calculated to achieve and maintain blood levels of approximately 10, 5, 2, or 0.2  $\mu$ g/ml, respectively, in a 300-g animal.<sup>14</sup> Normal saline was infused at the same rate in control animals. All injections were made with a Harvard Compact Infusion Pump, model 975 (Harvard Apparatus, South Natick, MA).

### *Formalin Test*

The formalin test was performed as previously described.<sup>15</sup> In brief, the animals were individually allowed to breathe 3% halothane until observers noted the rats' loss of the righting response. Each animal was removed quickly from the anesthesia and given a subcutaneous injection of 50  $\mu$ l 5% formalin into the dorsum of the right hind paw with a 30-G needle. The rat was placed in a clear plexiglass chamber for observation. Coordinated spontaneous movement and the return of righting reflex typically was noted < 30 s after the injection. Animals routinely displayed a flinching, withdrawal movement of the injected hind paw. The number of flinches per minute then was recorded at 1 and 5 min after injection (phase 1) and at 5-min intervals thereafter for 1 h (phase 2). The animals then were killed with an overdose of barbiturate.

### *Chronic Sciatic Nerve Compression*

Loose ligation of the sciatic nerve was performed according to the method described by Bennett and Xie.<sup>16</sup> Animals were anesthetized with 2–3% halothane. After an incision was made in the skin, the biceps femoris of each leg was dissected bluntly at midthigh to expose the sciatic nerves. Each nerve then was carefully mobilized, with care taken to avoid undue stretching. Four 4-0 chromic sutures were tied with a square knot around the right sciatic nerve, approximately 2 mm apart, with enough tension to produce a single brief twitch of the innervated muscles. The left sciatic nerve was mobilized but not ligated. The muscles were reapproximated and the skin closed with 3-0 silk suture. Animals were allowed to recover for 5 days before nociceptive threshold testing. After sciatic nerve ligation, the animals were maintained individually in clear plastic cages with solid floors covered with 3–6 cm sawdust. Animals appropriately prepared showed mild flexion of the ligated leg and slight curling of the digits. All animals exhibited normal feeding, drinking, and grooming behaviors postoperatively.

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Thermal nociceptive threshold in rats with chronic nerve compression was measured with a device similar to that used by Hargreaves *et al.*<sup>17</sup> Animals were placed in clear plastic cages on a 2-mm thick, clear glass floor, the temperature of which was maintained at 30° C with a thermostatically controlled forced hot air heater directed into the chamber beneath the glass. A radiant heat source (halogen projector lamp CXL/CXP 50 W, 8V, Ushio, Tokyo, Japan) with a 4-mm aperture was contained in a movable holder beneath the glass floor. Voltage to the lamp was controlled with a constant voltage regulator. The voltage of the lamp was calibrated to produce a mean response latency of 10 s in untreated animals. Animals were placed in the box for 10–15 min before testing. Before each latency test, the lamp was positioned directly under the midpalmar aspect of the footpad, with low-voltage illumination used to target the beam. When the radiant heat source was turned on, it activated a timing circuit. Time-to-brisk-withdrawal of the paw was measured to the nearest 0.1 s. The cut-off time in the absence of a response was 20 s, and this latency was assigned to nonresponders.

#### Experimental Protocols

**Local Anesthetic Infusion and Formalin Test.** Infusion of lidocaine solution or saline was begun 8 min before the animals were anesthetized. After 3 min for the bolus administration and 5 min of maintenance infusion, animals were anesthetized briefly and injected with formalin. Maintenance infusions were continued uninterrupted throughout the testing period. Syringe labels were covered during testing so that the investigator did not know which solution was used until each test run was completed. Based on preliminary studies, several dose groups were used to assess the dose-dependent effects of intravenous lidocaine on phases 1 and 2 of the formalin test (Groups 1, 2, and 3). In addition, to determine whether potential effects of lidocaine on the phase 2 of the formalin response were due to effects of the drug during the immediate post-formalin period or to ongoing analgesic effects of the drug during phase 2, a separate group of animals, designated Group 4, underwent formalin testing as described but were administered a bolus dose and infusion of 10 mg/ml lidocaine beginning 2 min after formalin injection (as soon as 1-min results were recorded) at the rates previously described. These groups are summarized in table 1.

**Local Anesthetic Infusion and Chronic Nerve Compression.** Latency to retraction from the radiant

**Table 1. Summary of Drug Treatment Groups Employed in the Formalin and Chronic Nerve Compression Studies**

Group: Infusion Paradigm	Time Course of Drug Delivery
<b>Formalin testing</b>	
Group 1 (n = 8): saline (0.3-ml bolus + 2.5- $\mu$ l/min infusion)	8-min preformalin → 60-min postformalin
Group 2 (n = 7): 5 mg/ml lidocaine (1.5-mg bolus + 12.5- $\mu$ g/min infusion)	8-min preformalin → 60-min postformalin
Group 3 (n = 5): 10 mg/ml lidocaine (3-mg bolus + 25- $\mu$ g/min infusion)	8-min preformalin → 60-min postformalin
Group 4 (n = 5): 10 mg/ml lidocaine (3-mg bolus + 25 $\mu$ g/min infusion)	2-min postformalin → 60-min postformalin
<b>Chronic nerve compression</b>	
Study 1 (n = 6): 2 mg/ml lidocaine (0.6-mg bolus + 5- $\mu$ g/min infusion)	30-min infusion
Study 2 (n = 5): Saline (0.3-ml bolus + 2.5- $\mu$ l/min infusion)	30-min infusion
0.2 mg/ml lidocaine (60- $\mu$ g bolus + 0.5- $\mu$ g/min infusion)	30-min infusion
2 mg/ml lidocaine (0.6-mg bolus + 5- $\mu$ g/min infusion)	30-min infusion

heat stimulus, or paw withdrawal latency (PWL) was measured on the normal and ligated paws in all animals on the fifth day postoperatively. Animals that demonstrated at least 1.5 s latency difference between the normal and ligated extremities on two tests, administered 30 min apart, underwent intravenous line placement as previously described and were allowed to recover for 24 h. Animals that did not exhibit such latency differences were tested again on the sixth day. If they exhibited appropriate latency differences, they underwent intravenous placement, otherwise they were excluded from further investigation. The two following studies then were performed 48 h apart (table 1, summary):

**Study 1.** Twenty-four hours after intravenous placement, infusion lines were connected to the intravenous catheters and the animals were placed in plexiglass chambers on the testing apparatus. After 30 min, animals underwent baseline latency testing and then remained undisturbed for 1 h. They then were given an infusion of a bolus injection of 2 mg/ml lidocaine (0.6 mg), delivered over 3 min, followed by maintenance infusion (5  $\mu$ g/min) for 30 min. Tests for PWL re-

**Table 2. Mean Plasma Lidocaine Levels after Intravenous Bolus Plus Infusion**

Bolus Dose (mg)	Infusion Rate ( $\mu\text{g}/\text{min}$ )	Sampling Time (min)	n	Blood Level ( $\mu\text{g}/\text{ml}$ )
0.6	5	10	3	$1.0 \pm 0.1$
1.5	12.5	5	3	$3.6 \pm 0.3$
3	25	5	3	$6.3 \pm 1.0$

sponses were repeated at 10 and 30 min after the maintenance infusion was begun, and the infusion was discontinued. Withdrawal latencies were repeated 1, 3, and 24 h after the infusions were discontinued.

**Study 2.** Forty-eight hours later, the animals underwent a similar testing protocol. However, on this occasion, three separate testing dosages were used, with a 1 h period between tests. The first consisted of a bolus dose plus a 30-min infusion of normal saline, the second consisted of a bolus dose plus an infusion of 0.2 mg/ml lidocaine (60  $\mu\text{g}$  bolus, 0.5  $\mu\text{g}/\text{min}$  infusion), and the third consisted of a bolus dose plus an infusion of 2 mg/ml lidocaine, as described for study 1. As in the first experiment, latency testing was performed at 10 and 30 min after infusions were begun, then the infusions were discontinued. Latencies again were measured 1, 3 and 24 h after the 2 mg/ml infusion was discontinued.

**Measurement of Lidocaine Blood Levels.** Lidocaine blood levels were determined in three animals (not study animals) at each of the following doses and times: 0.3 ml and 2 mg/ml bolus plus 25  $\mu\text{l}/\text{min}$  infusion, 10 min after initiation of infusion; 0.3 ml and 5 mg/ml bolus plus infusion, 5 min after initiation of 25  $\mu\text{l}/\text{min}$  infusion; 0.3 ml and 10 mg/ml bolus plus infusion, 5 min after initiation of 25  $\mu\text{l}/\text{min}$  infusion. Assays were not performed after the administration of 0.2 mg/ml bolus plus infusion, because anticipated blood levels were below sensitivity levels of the assay. Animals were used for only one sample. One ml of blood was removed from the central venous catheter and discarded, then 4 ml was removed, allowed to clot, and centrifuged. Serum then was frozen for later analysis. Animals were killed by an intravenous overdose of barbiturate immediately after sampling. Lidocaine levels were analyzed by radioimmunoassay (Syva, Palo Alto, CA).

#### *Data Analysis and Statistics*

**Formalin Test.** The total number of flinches was determined for all of the phase 1 (1–5 min) and phase

2 (10–60 min) observations for each animal, and groups were compared by one-way analysis of variance (ANOVA; Sheffé's F test). For display purposes, mean values of phase 1 and phase 2 data were expressed as percentages of control, using the method described by Tallarida and Murray<sup>18</sup> to calculate the ratios of the means and standard errors.

**Chronic Nerve Compression.** Differences in PWL were recorded at each testing period, and differences between baseline values and values at 10 and 30 min after the beginning of each infusion and at 1, 3, and 24 h after discontinuing the 2 mg/ml infusion were compared by repeated-measures ANOVA. Differences in PWL between the normal and ligated limbs were compared by one-way ANOVA (Sheffé's F test).

## **Results**

### *Lidocaine Blood Levels*

The mean serum lidocaine levels are shown in table 2. As shown, the infusion model led to levels that were somewhat lower than anticipated but proportional to the infusion dose.

### *Formalin Test*

Animals that received a bolus dose plus infusion of normal saline (Group 1) showed the typical response to formalin injection, *i.e.*, a brief period of flinching during the first 5 min, a period of relative quiescence for 5–10 min, and a resumption of flinching beginning 15–20 min postinjection and lasting through the remainder of the test period (fig. 1). There was no significant difference in mean phase 1 flinching activity among the four groups (table 3). Animals that received the lower concentration (5 mg/ml) of lidocaine (Group 2) exhibited a modest (27%) but nonsignificant reduction in flinching activity during phase 2. Animals that received the higher concentration (10 mg/ml) of lidocaine before formalin injection (Group 3) exhibited  $53 \pm 11\%$  of the mean phase 2 flinching activity of saline control animals ( $P < 0.05$ ; fig. 1 and table 3).

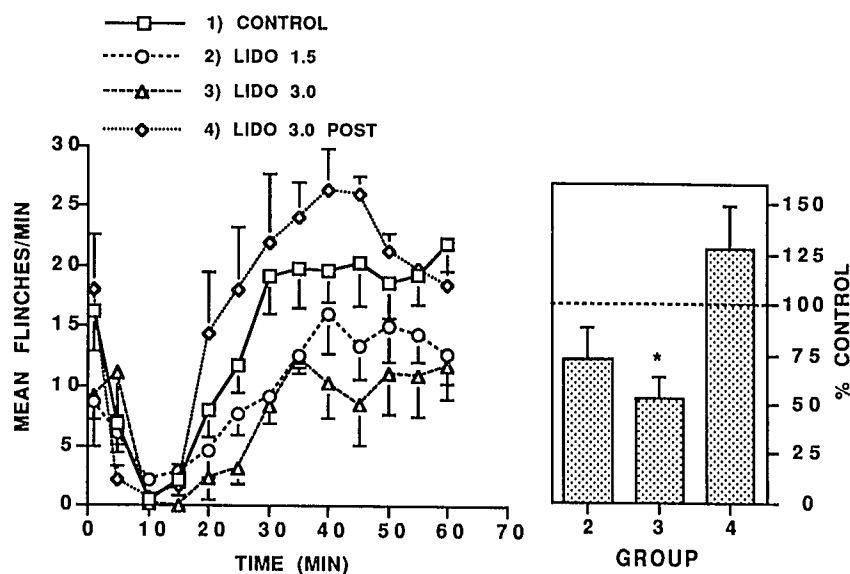
In the animals that received 10 mg/ml lidocaine beginning 2 min after formalin injection (Group 4), phase 2 responses showed no effect of the drug (flinches =  $128 \pm 21\%$  of control; table 3).

### *Chronic Nerve Compression*

Six animals exhibited at least 1.5 s shorter latency to noxious radiant heat stimulation and were used in the

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Fig. 1. (Left) Mean number of flinches per min ( $\pm$  SEM), plotted as a function of time after injection of formalin. The treatment groups were the following: (1) control (intravenous saline), (2) low-dose lidocaine (1.5-mg bolus), (3) high-dose lidocaine (3.0-mg bolus), (4) high-dose lidocaine, 2 min after formalin administration (3.0 mg bolus). (Right) Mean values for phase 2 activity for groups 2, 3, and 4 expressed as a percent of control values (from Tallarida RJ, Murray RB: Manual of Pharmacologic Calculations with Computer Programs. 2nd edition. New York, Springer, 1987, pp 137-139). \* = significantly different from control (one-way ANOVA,  $P < 0.05$ ).



initial testing protocol. The mean latencies to hind limb withdrawal of the normal and ligated limbs and the mean differences between normal and ligated limbs are shown in figure 2.

In Study 1, as figure 2 illustrates, the hyperalgesia of the ligated limb, evident before drug infusion, was no longer present 10 min after the administration of the bolus dose (600  $\mu$ g) and infusion (5  $\mu$ g/min) of lidocaine. The difference between normal and ligated-limb withdrawal latencies was not significantly different at any of the times through 3 h postinfusion. By 24 h postinfusion, the difference was again significant. Likewise, there was a significant change in the difference scores over the course of the 24-h observation period by repeated-measures ANOVA ( $P < 0.001$ ). The difference scores after 10 and 30 min of lidocaine infusion were significantly different from baseline levels and remained significantly different through 3 h postinfusion ( $P < 0.05$ ). At 24 h postinfusion, the difference scores again were not significantly different from baseline.

By 24 h after the initial lidocaine infusion, five of the six animals had difference scores greater than 1.5 s. The animal that did not show a difference in latency at 24 h still failed to exhibit hyperalgesia of the affected limb after 48 h and was eliminated from the second portion of the study. The mean latencies for the normal and ligated limbs and the mean difference scores for the animals at the start of Study 2 are shown in figure 3. There was a significant difference in PWLs between the normal and ligated limbs at baseline and at 10 and

30 min after saline infusion ( $P < 0.05$ ). The difference scores did not change significantly during saline infusion or during the infusion of 0.2 mg/ml lidocaine. During the infusion of 2 mg/ml lidocaine, at both 10 and 30 min, there was a significant reduction in the difference scores ( $P < 0.05$ ), again indicating the loss of hyperalgesia in the ligated limb. Significant suppression of the difference score was still evident 1 and 3 h after the lidocaine was discontinued ( $P < 0.01$ ). Although the group as a whole did not show significant suppression of the difference score at 24 h, two of the five animals still did not demonstrate hyperalgesia in the ligated limb.

## Discussion

The infusion of lidocaine, to blood levels as high as 8.3  $\mu$ g/ml, had no effect on motor function and did not produce detectable alterations in general behavior. In contrast, as will be discussed below, lidocaine resulted in a modest alteration in the sensitization-dependent component of the behavior induced by protracted afferent input (formalin test) and a selective reduction in the hyperalgesia associated with chronic compression of the sciatic nerve.

### Formalin Test

The injection of formalin into the paw results in an acute afferent C-fiber barrage, followed by an ongoing

Table 3. Mean (±SEM) Number of Flinches during Phase 1 (1–5 min) and Phase 2 (10–60 min) after Saline or Lidocaine Infusion

Treatment	Mean Phase 1	% of Control*	Mean Phase 2	% of Control*
Saline	22.5 ± 3.6	—	160.2 ± 22.0	—
Lidocaine (5 mg/ml)	14.9 ± 2.3	72 ± 16	111.0 ± 16.2	73 ± 15
Lidocaine (10 mg/ml)	20.4 ± 6.2	98 ± 33	79.6 ± 13.5†	53 ± 11
Lidocaine (10 mg/ml), post‡	17.0 ± 6.1	82 ± 31	192.8 ± 17.5	128 ± 21

\* From Tallarida and Murray.<sup>18</sup>  
† Significantly different from control (one-way analysis of variance, *P* < 0.05).  
‡ Infusion begun 2 min after formalin injection.

but progressively declining level of afferent activity.<sup>10</sup> The first phase of the post-formalin response reflects the acute afferent barrage, although it now seems likely that the second phase reflects the afferent input, continuing at a much reduced rate, plus facilitation in afferent processing, leading to an exaggerated pain state. This second-phase activity is thought to be the behavioral parallel of the “wind-up” phenomena evoked by repetitive C-fiber stimulation in dorsal horn wide dynamic-range neurons.<sup>19,20</sup> In the present study, pread-

ministered intravenous lidocaine at the highest dose examined had no effect on phase 1 but significantly suppressed the second phase response in a concentration-dependent fashion.

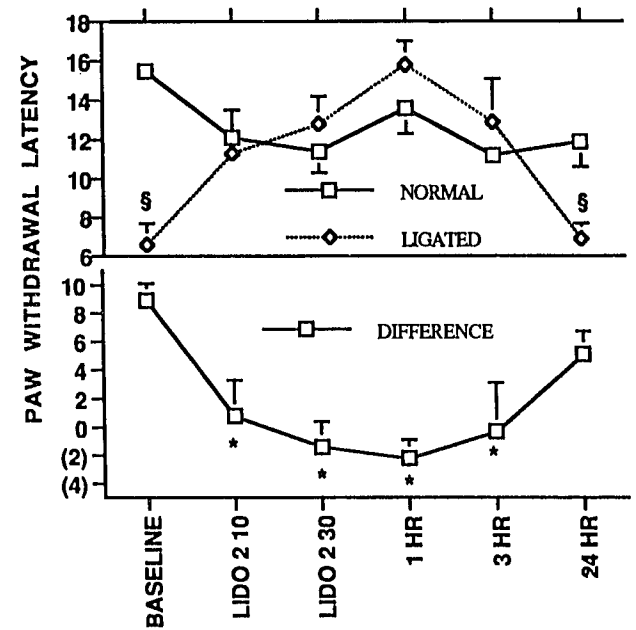


Fig. 2. Results of Study 1. Mean paw withdrawal latencies (± SEM) for normal and ligated limbs 10 and 30 min after a bolus injection of 3 ml 2 mg/ml lidocaine (Lido 2 10, Lido 2 30) and 1, 3, and 24 h after the infusion was discontinued. § = significantly different from nonligated paw (one-way ANOVA, *P* < 0.05); \* = significantly different from baseline (repeated-measures ANOVA, *P* < 0.05).

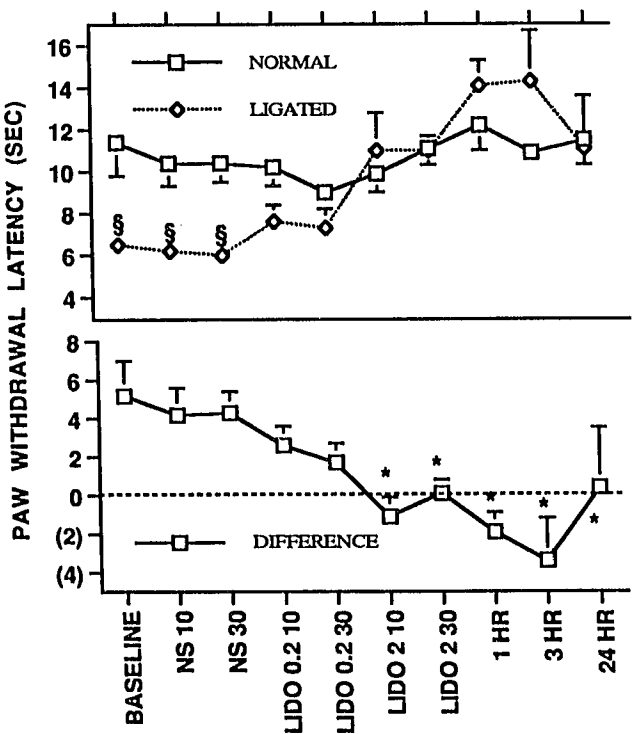


Fig. 3. Mean paw withdrawal latencies (± SEM) for normal and ligated limbs 10 and 30 min after a bolus injection of 3 ml normal saline (NS 10, NS 30), 10 and 30 min after a bolus injection of 3 ml 0.2 mg/ml lidocaine (Lido .2 10, Lido .2 30), 10 and 30 min after a bolus injection of 3 ml 2 mg/ml lidocaine (Lido 2 10, Lido 2 30), and 1, 3 and 24 h after the lidocaine 2 mg/ml infusion was discontinued. § = significantly different from nonligated paw (one-way ANOVA, *P* < 0.05); \* = significantly different from baseline (repeated-measures ANOVA, *P* < 0.05).

The possibility that lidocaine exerts its analgesic effect in this model by blockade of afferent input is remote, because, unlike spinal morphine,<sup>15</sup> it caused no suppression of the phase 1 component; and initiation of even high-dose lidocaine treatment *after* the formalin injection produced *no* inhibition of the phase 2 activity. This interesting observation has particular significance in this model. Previous work has shown that n-methyl d-aspartate (NMDA) antagonists can produce a highly significant but subtotal reduction in the phase 2 response when the agents are given before but not after formalin.<sup>15,21</sup> This characteristic has been thought to reflect the fact that a specific component of the afferent barrage is necessary to evoke the facilitated state, but this component is not required to sustain it. Therefore, pretreatment with lidocaine appears to partially block this initiating sequence but fails to affect the process once it is initiated. It should be noted that the dose of systemic lidocaine required to block central facilitation is fairly large, and the blood levels required to produce a significant effect are high enough to produce subconvulsant symptoms in humans.<sup>22</sup>

#### *Nerve Injury Model*

Application of loose unilateral sciatic nerve ligatures resulted in lower paw withdrawal latencies on the lesioned side 5–6 days later. This phenomenon indicates thermal hyperalgesia on the lesioned side rather than analgesia on the nonlesioned side, because the PWL on the lesioned side is significantly lower than that of nonlesioned animals, as well as that of the contralateral, nonlesioned limb.<sup>23</sup> Although the origin of the hyperesthetic state is not certain, there are several possible alternatives. First, the hyperalgesic state induced in the nerve-lesioned extremity may result from spinal sensitization (wind-up) induced by ectopic activity of small diameter afferents originating from the injured site on the sciatic nerve. After ligation of the peripheral nerve, persistent small afferent fiber activity originating from the lesioned site<sup>†</sup> and the dorsal root ganglion<sup>12</sup> has been documented. As noted above, such ongoing repetitive activity can lead to dorsal horn sensitization.<sup>21,24,25</sup> In addition, after peripheral nerve compression, prominent morphologic changes have been identified in the spinal dorsal horn ipsilateral to the site of ligation.<sup>13</sup> The mechanism of these changes

is not clear, but the possibility of persistent changes secondary to the chronic afferent barrage or to a change in factors transported from the lesioned site seems likely. In the present study, lidocaine appeared to block selectively the hyperalgesia observed in the ligated paw. Importantly, this effect occurred at approximately 20% of the concentrations required to produce a significant effect on the second phase of the formalin test.

#### *Mechanisms of the Analgesic Actions of Systemic Lidocaine*

**Peripheral Neural Blockade.** Although the systems that mediate the two pain states sensitive to systemic lidocaine are distinct, the lidocaine-sensitive component is invariably that behavioral element associated with hyperalgesia. Lidocaine is able to reduce the excitability of axons stimulated to fire at high frequencies at concentrations 40-times lower than those used clinically to produce nerve block.<sup>26</sup> One might postulate, therefore, that a reduction in the maximum firing rate of peripheral nociceptors might produce an analgesic effect peripherally. However, within the dose ranges used in this study, there was no evidence that lidocaine was able to alter normal nociceptive thresholds. This is particularly emphasized in the observation that even the highest dose of lidocaine was unable to diminish the second phase of the formalin response when administered after the formalin. We feel strongly that these observations indicate that the demonstrated effects are not due to a simple blockade of afferent traffic in the axon. Several alternative mechanisms can be considered.

**Novel Lidocaine Pharmacology.** The possibility that lidocaine may be acting in a novel fashion, such as through an opioid receptor mechanism or by the release of endogenous opioids,<sup>5</sup> appears unlikely in light of: (1) the failure of lidocaine to affect phase 1 of the formalin test or to affect phase 2 when given after formalin; and (2) the fact that, unlike intrathecal opioids and  $\alpha_2$ -adrenergic-agonists, which produce dose-dependent blockade in both normal and nerve lesioned paws,<sup>23</sup> lidocaine produced a significant increase in PWL only on the lesioned side. The fact that both models are sensitive to NMDA-receptor antagonists leads to the speculation that lidocaine may interact through a similar mechanism. We know of no data suggesting that lidocaine interacts with the NMDA channel, and, although lidocaine may interact with voltage-sensitive calcium channels, its principle effect remains on voltage-sensitive sodium channels.<sup>27</sup>

† Kajander KC, Bennett GJ: Analysis of the primary afferent neurons in a model of neuropathic pain in the rat (abstract). Soc Neurosci 14:912, 1988.

**Effects on Central Conduction.** At low concentrations, local anesthetics may serve to reduce the safety factor of the conducting systems responsible for the central generation of the facilitated state. Therefore, we have speculated that such an action might influence input at the level of the dorsal horn, where an extensive ramification of small afferent axons might be sensitive to low levels of local anesthetics. If the facilitatory component is dependent for its initiation on a critical level of afferent transmitter release, then such a modest reduction in safety factor might not be sufficient to alter the initial input evoked by a barrage in all afferents, but might prevent the generation of a facilitated state, mediated by a particular fiber class, such as the small unmyelinated primary afferents.

**Effects on Spontaneous Generator Activity.** A common factor in these studies is that the injury model is thought to yield an increase in spontaneous nerve activity in the periphery. Devor *et al.*<sup>6</sup> demonstrated a reduction in spontaneous activity originating from neuromas after the intravascular (carotid artery) injection of 0.5 mg lidocaine in rats and complete cessation of ectopic activity originating from dorsal root ganglia after administration of the same dose. Tanelian *et al.*,<sup>7</sup> using an *in vitro* corneal nerve injury model, demonstrated the suppression of spontaneous discharge from A $\delta$  and C fibers with lidocaine concentrations of 2–15  $\mu$ g/ml. Therefore, there is evidence that spontaneous activity is suppressed at doses and blood levels of lidocaine similar to those we found effective at reversing thermal hyperalgesia. In the present study, the fact that thermal hyperalgesia following nerve ligation was reversed at much lower doses than were needed to block phase 2 of the formalin test suggests a peripheral nerve locus for lidocaine's analgesic effect on neuropathic pain.

### Clinical Significance

Systemic administration of local anesthetics has been shown to diminish the severity of neuropathic pain<sup>1–4</sup> and to reduce the intensity and extent of associated allodynia<sup>4</sup> at doses that do not produce symptoms of systemic toxicity. While lidocaine is not an ideal therapeutic agent for long-term therapy because of the need for parenteral administration and the potential accumulation of a toxic metabolite, monoethyl glycine xylidide,<sup>28,29</sup> it has been used chronically as a subcutaneous infusion,<sup>28,29</sup> and some patients experience days to weeks of pain reduction after receiving a single administration.<sup>2</sup> On the other hand, orally effective so-

dium-channel blocking agents, such as mexilitene, have been shown to be efficacious for some patients with neuropathic pain that is temporarily responsive to lidocaine.<sup>29</sup>

Because of the ability of systemically administered local anesthetics to attenuate neuropathic pain and its associated hyperalgesia, one must be cautious in interpreting the results of diagnostic local anesthetic blocks. An epidural injection of as little as 1 mg/kg lidocaine will produce blood levels of about 1  $\mu$ g/ml, a level we have shown to attenuate the thermal hyperalgesia associated with nerve injury, while an injection into more vascular areas, such as with the intercostal blocks, will yield still higher blood levels.<sup>30</sup> Therefore, analgesia can be achieved in the absence of blockade of the intended target nerves, leading to false positive results.

### Conclusions

In conclusion, we have demonstrated that systemic local anesthetics can affect the behavioral responses to noxious stimulation by two distinct mechanisms. While they are capable of blocking nociceptor-induced spinal sensitization, they do so incompletely and only at blood levels that are close to those associated with symptoms of toxicity. They also appear to have no effect on previously established spinal hypersensitivity. Therefore, it appears likely that the predominant effect of systemic lidocaine on neuropathic pain is through suppression of spontaneous impulse generation arising from injured nerve segments or associated dorsal root ganglia.

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