

Concentration–Effect Relationship of Intravenous Lidocaine on the Allodynia of Complex Regional Pain Syndrome Types I and II

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Background: Several lines of evidence suggest that neuropathic pain (including Complex Regional Pain Syndrome [CRPS] I and CRPS II) is mediated in part by an increase in the density of voltage-sensitive sodium channels in injured axons and the dorsal root ganglion of injured axons. This study sought to characterize the effects of intravenous lidocaine (a sodium channel blocker) on acute sensory thresholds within the painful area and the size of the painful area in patients suffering from CRPS I and II.

Methods: This study used a randomized, double-blind, placebo-controlled design in 16 subjects suffering from CRPS I and II with a prominent allodynia. Each subject received an intravenous infusion of lidocaine and diphenhydramine separated by 1 week. A computer-controlled infusion pump targeted stair-step increases in plasma levels of lidocaine of 1, 2, and 3 $\mu\text{g}/\text{ml}$. At baseline and at each plasma level, spontaneous and evoked pain scores and neurosensory testing within the painful area were measured. The neurosensory testing consisted of thermal thresholds, tactile thresholds and the area of allodynia to punctate, and stroking and thermal stimuli.

Results: Intravenous lidocaine and diphenhydramine had no significant effect on the cool, warm, or cold pain thresholds. However, lidocaine caused a significant elevation of the hot pain thresholds in the painful area. Intravenous lidocaine caused a significantly decreased response to stroking and cool stimuli in the allodynic area. There was also a significant decrease in pain scores to cool stimuli at all plasma levels and the spontaneous pain at the highest plasma level.

Conclusions: This study demonstrates that intravenous lido-

caine affects pain in response to cool stimuli more than mechanical pain in subjects with neuropathic pain. There is a lesser effect on spontaneous pain and pain induced by stroking stimuli and no effect on the pain induced by punctate stimuli. (Key words: Anesthetic; local; neuropathic.)

COMPLEX Regional Pain Syndrome (CRPS) is a term used to describe a variety of painful conditions resulting from injury. Spontaneous pain or allodynia/hyperalgesia is the cardinal symptom of this syndrome. CRPS I develops after an initiating noxious event, and the pain is not limited to the territory of a single peripheral nerve. In contrast, CRPS II develops after a nerve injury with pain referred to a peripheral body region that includes, but typically extends beyond, the dermatome of the injured nerve. This pain may display several characteristics: (1) an ongoing sensation described as unpleasant or electrical shock-like (dysesthesia); (2) an exaggerated pain response to a given noxious stimulus (hyperalgesia); or (3) a report of pain secondary to a nonpainful stimulus (allodynia, both thermal and mechanical). Thus, patients with CRPS I and II often report pain to cool temperatures as high as 26°C ¹ and tactile stimuli that only activate low-threshold mechanoreceptive afferents.¹⁻⁵

Mechanisms underlying these anomalous sensory states are not resolved. However, as in humans, animal models of nerve injury demonstrate spontaneous pain behavior, allodynia (pain behavior secondary to light touch), or hyperalgesia (e.g., a reduced thermal escape latency).^{6,7} Several lines of evidence developed in such models suggest that both the spontaneous and evoked pain is mediated in part by an increase in the density of voltage-sensitive sodium channels in the neuroma and dorsal root ganglion of the injured axon.⁸ Evidence of the importance of this altered sodium channel expression to neuropathic conditions is that systemic delivery of use-dependent sodium channel blockers has no effect on acute nociceptive thresholds, but attenuates in a dose-dependent manner experimental neuropathic states.

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Table 1. Patient Characteristics

Patient No.	Sex	Age	Diagnosis	Pain Location	Pain Duration (months)	Cause of Pain	Injured Nerve
1	F	32	RSD	LLE	31	Bone fracture	
2	M	23	RSD	RLE	31	Bone fracture	
3	M	51	RSD	RLE	50	Soft tissue injury	
4	F	26	RSD	LUE	28	Soft tissue injury	
5	F	58	RSD	LUE	21	Soft tissue injury	
6	F	63	RSD	RUE	121	Postmastectomy	
7	F	43	RSD	RLE	27	Soft tissue injury	
8	F	62	RSD	LUE	40	Postmastectomy	
9	M	38	RSD	LLE	20	Bone fracture	
10	M	43	Causalgia	RLE	28	Surgery	Posterior Tibial
11	M	50	Causalgia	RUE	28	Surgery	Median
12	F	46	Causalgia	LLE	46	Surgery	L5 nerve root
13	M	40	Causalgia	RUE	128	Accident	Brachial plexus
14	M	25	Causalgia	LLE	7	Surgery	L5 nerve root
15	M	32	Causalgia	LLE	45	Surgery	Ilioinguinal
16	M	74	Causalgia	RLE	40	Hip fracture	Sciatic
Mean		44.1			43.2		

RSD = reflex sympathetic dystrophy; LLE = left lower extremity; RLE = right lower extremity; LUE = left upper extremity; RUE = right upper extremity.

Importantly, these effects occur at plasma concentrations that do not produce an afferent conduction block.⁸⁻¹¹ Comparable results have been noted in humans. Systematic studies in humans using experimental models of threshold detection have demonstrated that lidocaine has no effect on acute thermal and mechanical thresholds in normal volunteers.^{12,13} However, systemic lidocaine has significant attenuating effects on the regional hyperalgesia otherwise evoked by intradermal capsaicin.¹² When examined in patients reporting significant pain secondary to a variety of neuropathic states, subanesthetic doses of systemic lidocaine produce clinically relevant relief in diabetes,^{13,14} nerve injury pain states,^{15,16} and late-stage cancer.^{9,16,17} These results suggest that in humans, as in animals, sodium channels mediate a substantive facilitation of afferent processing after nerve injury.

There are several reports in the literature on the effects of sympathetic blockade on quantitative neurosensory testing in CRPS I and II. All of these studies have demonstrated a significant reduction in pain and hyperalgesia after sympathetic blockade.¹⁸⁻²⁰ However, there are no studies using quantitative neurosensory testing for evaluating the effects of systemic lidocaine on this interesting syndrome. In the present study, we sought to examine the effects of lidocaine on the decreased pain threshold to cold and tactile stimuli and the size of the receptive field to which these decreased thresholds are referred in patients with CRPS I and II. An important question relates to whether these several components

are similarly dependent on sodium channel activity. Accordingly, we must define the plasma concentration dependency of these measures under steady-state drug conditions. To accomplish that, we have validated a lidocaine infusion paradigm that uses pseudo-steady-state kinetics to permit the patient to be exposed over a reasonable period to several plasma lidocaine concentrations.²¹

Methods

Subjects

All work was conducted according to protocol approved by the institutional review board of the University of California, San Diego. With informed consent, 16 subjects (7 women and 9 men) suffering from CRPS I (9 patients) and CRPS II (7 patients) were recruited for the study. The mean subject age (\pm SD) was 44 ± 15 yr (range, 23-74 yr), the mean weight was 80 ± 15 kg (range, 53-109 kg), and the mean duration of pain was 43 ± 34 months (range, 7-128 months). Table 1 summarizes the demographics of the cohort. After the protocol was explained and informed consent obtained, they were entered into the following experimental trials.

Clinical Methodology

Infusion. This study used a randomized, double-blind, placebo-controlled design. Each subject received in separate sessions an intravenous infusion of lidocaine (Astra,

Westboro, MA) or diphenhydramine (Parke-Davis, Morris Plains, NJ). The order of the study sessions was randomized and separated by 1 week. Because intravenous lidocaine results in significant side effects that may lead to a placebo response, diphenhydramine was used as the placebo control. Previous studies have demonstrated that diphenhydramine produces side effects similar to lidocaine but does not affect sensory thresholds.¹⁷

During each study session, two 20-gauge intravenous cannulae were inserted into the right arm: one into the antecubital vein and one into a hand or distal forearm vein. Procaine was used to anesthetize the skin to avoid interference with the lidocaine assay. The antecubital cannula was connected to a computer-controlled infusion pump (CCIP) and the other was capped with a saline flush and used to collect venous blood samples. The CCIP was programmed with the pharmacokinetic data obtained from a previous pharmacokinetic study of intravenous lidocaine in healthy volunteers.²¹ In brief, parameters were estimated in those studies from the pooled analysis of arterial concentration-*versus*-time profiles of those volunteers for the purpose of optimizing CCIP performance. Based on those parameters, plasma lidocaine concentration steps of 1 $\mu\text{g/ml}$, 2 $\mu\text{g/ml}$, and 3 $\mu\text{g/ml}$ were targeted and maintained for 20 min. This resulted in a pseudosteady state of lidocaine, so named because we cannot assume that the lidocaine has equilibrated in all body compartments.

After a baseline neurosensory test of the painful area (described in the following section), heart rate, and blood pressure, the CCIP was initiated to achieve a plasma lidocaine level of 1 $\mu\text{g/ml}$ and allowed to reach a pseudosteady state for 20 min. At 20 min the following procedures were performed in the order indicated: (1) blood pressure and heart rate were recorded; (2) a venous blood sample (2 ml) was collected; (3) side effects were assessed (described in the following section); (4) spontaneous and evoked pain scores were measured; and (5) neurosensory testing of the painful area was performed. After completing these tests, the process was repeated at the targeted 2- and 3- $\mu\text{g/ml}$ plasma lidocaine level. The infusion was stopped if the following side effects occurred (which usually occur at plasma lidocaine levels $> 5 \mu\text{g/ml}$):²² arrhythmias, nausea, tinnitus, visual hallucination, and muscle twitching. Light-headedness, sedation, perioral numbness, metallic taste, and dry mouth were allowed, and the infusion was continued if these effects were reported because they usually occur at plasma lidocaine levels $< 5 \text{ mg/ml}$.²² Three-lead

electrocardiogram, heart rate, and blood pressure were monitored throughout the study.

Testing.

Determination of Area of Allodynia to Frey's Hair and Stroking. The region of allodynia was determined before initiating the study. The edge of the region of allodynia was established with a 5.18 Frey's hair and a cotton wisp gently stroked on the skin. These stimuli were started away from the painful area of skin and were repeated tangentially to the allodynic area at a progressively closer radius until the subject reported pain or tenderness. That site was marked on the skin with a felt-tip pen, and a new series was started from the periphery at a different angle until at least eight determinations of the borders of allodynia were outlined on the skin. These two borders were outlined onto a homunculus for area determination (in squared centimeters). The process was repeated at the completion of the infusion at the highest targeted plasma level.

Neurosensory testing. Once the area of allodynia was established, three neurosensory thresholds were established in the central portion of the allodynic area: (1) warm and cool sensation; (2) hot and cold pain; and (3) touch. The same order of the stimuli was used in all subjects: cool, warm, cold pain, and hot pain. This order was chosen because it goes from the lowest stimulus (cool) to the highest stimulus (hot pain).

Warm and cool sensation were measured using a Thermal Sensory Analyzer (Medoc Advanced Medical Systems, Minneapolis, MN). This device consists of a thermode measuring $46 \times 29 \text{ mm}$. The temperature of the thermode can either increase or decrease (at a rate of 1.0°C/s) depending on the direction of current flow through the device. The patient holds a switch that is pressed at the first sensation of warmth or cold; pressing the switch reverses the temperature change, returning to a neutral temperature of 32°C .

Warm and cold pain measurements also use the Thermal Sensory Analyzer, but the end point is pain instead of temperature change sensation. It also uses a temperature change rate of 1.5°C/s .

Touch was measured using Frey's hairs. Calibrated Frey's hairs are filaments of varying size. The filaments are selected at random, and three successive stimuli are applied for 2 s at 5-s intervals per filament, applied in an ascending pattern. The patient is instructed to report if the stimulus is felt. Thresholds are expressed in millinewtons and measured as positive if the patient felt any of the three successive stimuli.

Determination of the Area of Thermal Allodynia.

Patients who reported pain at temperatures $< 40^{\circ}\text{C}$ or $> 20^{\circ}\text{C}$ were classified as having thermal allodynia. The area of the allodynia was established using the same method previously described for the Frey's hair and cotton wisp. The temperature used was halfway between the sensory threshold temperature and the temperature that produced pain. This border was outlined onto a homunculus for area determination (in squared centimeters). The process was repeated at the completion of the infusion at the highest targeted plasma level.

Pain Measurements. Both spontaneous pain scores and evoked pain scores were measured. Pain scores were measured using a visual analog scale that consisted of a 100-mm line with "no pain" written at one end and the "worst imaginable pain" written at the other end. The subject was asked to place a mark along the line that corresponded with their pain. The distance (in millimeters) from the no-pain end to the location of the mark gives a measurement of the pain. Evoked pain was established with a 5.18 Frey's hair applied for 2 s, cotton wisp gently stroked on the skin for 2 s, and a 2×2 -cm probe heated to a predetermined temperature applied for 2 s (see previous section).

Side Effects. Side effects were measured by the subject using a visual analog scale that consisted of a 100-mm line with "no side effect" written at one end and the "worst imaginable side effect" written at the other end. The patient was asked to place a mark along the line that corresponded with the following side effects: sedation, nausea, light headedness, muscle twitching, tinnitus, blurred vision, perioral numbness, metallic taste, or dry mouth. The distance (in millimeters) from the no-side-effect end to the location of the mark gives a measurement of the side effect.

Lidocaine Assay

Lidocaine was extracted from the frozen serum samples after thawing by solid-phase extraction chromatography and quantified by capillary gas chromatography with nitrogen-phosphorous detection.²³ Total run time was 5 min, and lidocaine and bupivacaine eluted at 2.4 and 4.0 min, respectively. The limit of detection for lidocaine by this method was 0.05 ng/ml plasma. The interassay precision (C.V) was 7.5% and 3.5% for lidocaine levels of 0.1 ng/ml and 1.0 ng/ml in serum, respectively. Accuracy in the range of 0.5–10 ng/ml was $> 99\%$.

Table 2. Baseline Experimental Measurement Thresholds

Experimental Measure	Week 1	Week 2
Cool threshold ($^{\circ}\text{C}$)	23.2 ± 4.7	22.4 ± 6.6
Warm threshold ($^{\circ}\text{C}$)	41.2 ± 4.8	41.6 ± 3.8
Cold pain ($^{\circ}\text{C}$)	13.8 ± 8.2	15.7 ± 10.3
Hot pain ($^{\circ}\text{C}$)	44.9 ± 3.8	44.9 ± 3.2
Frey's detectable threshold (mN pressure)	4.29 ± 0.37	4.15 ± 0.47

Values are mean \pm SD.

Data Analysis

Data are expressed as mean \pm SD. Baseline sensory thresholds and pain scores before lidocaine and placebo infusion were compared using a one-factor repeated-measure analysis of variance to ensure that no differences existed before onset of treatment. Subsequently, data for each sensory threshold measure and pain score were compared using a two-factor repeated-measures analysis of variance with both drug treatment (lidocaine *vs.* placebo) and titrated drug level as within-subjects factors. Allodynic areas (preadministration, postadministration) were analyzed by a paired Student *t* test, and, as appropriate, follow-up comparisons of individual means consisted of paired *t* tests, with significance held at a constant level of $P < 0.05$ through the correction method of Bonferroni.

Results

Lidocaine Infusion and Plasma Lidocaine Levels

The mean dose of lidocaine (\pm SD) infused was 488 ± 98 mg (range, 329–700 mg). Based on the CCIP parameters used, measured venous lidocaine levels were considered to be close to targeted levels. Mean measured plasma levels for each targeted level (1, 2, and 3 $\mu\text{g/ml}$, respectively) were 1.3 $\mu\text{g/ml}$ (range, 0.8–1.8 $\mu\text{g/ml}$), 2.4 $\mu\text{g/ml}$ (range, 1.4–3.9 $\mu\text{g/ml}$), and 3.4 $\mu\text{g/ml}$ (range, 2.4–4.8 $\mu\text{g/ml}$). Thus, the mean percent difference (concentration error = $[(\text{Real} - \text{Targeted})/\text{Targeted}] \times 100$)(\pm SD) between targeted and measured concentration at targeted plasma concentrations of 1, 2, and 3 $\mu\text{g/ml}$ received by each patient was $+29\% \pm 46\%$, $+21\% \pm 46\%$, and $+16\% \pm 26\%$, respectively.

Effect of Lidocaine on Neurosensory Thresholds

Table 2 summarizes the baseline neurosensory thresholds. Thresholds were not significantly different over the 7-day interval between observations. In addition, there was no significant difference in baseline neurosensory

EFFECT OF SYSTEMIC LIDOCAINE ON ALLODYNIA

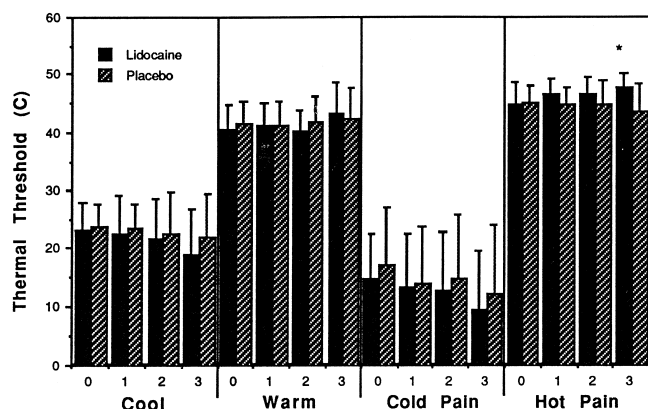


Fig. 1. The effect of intravenous lidocaine at three different plasma concentrations (0 = baseline; 1, 2, 3 = the targeted plasma concentration in $\mu\text{g/ml}$) on cool, warm, cold pain, and hot pain thermal thresholds of the painful area in patients with neuropathic pain and allodynia. * $P < 0.05$.

thresholds between the CRPS I and II subgroups. Continuous infusion of lidocaine or diphenhydramine had no statistically significant effect on cool, warm, or cold pain thresholds (fig. 1). At the highest plasma level, intravenous lidocaine caused a significant elevation of hot pain thresholds (from a mean baseline of 44.7°C to a mean of 47.9°C ; fig. 1).

Effect of Lidocaine on Allodynic Area and Pain Scores

All of the subjects had allodynia to Frey's hair and stroking stimulation. Eight of 16 (50%) reported pain to cold stimuli, and in 5 of these patients (62.5%), it was possible to map the distribution of the cold-evoked allodynia. No patients had allodynia to heat. Mapping of the allodynic area showed that it was greatest for the Frey's hair stimulus ($113 \pm 107.8 \text{ cm}^2$), followed by stroking ($76.8 \pm 77.9 \text{ cm}^2$) and cold stimuli ($61 \pm 97.1 \text{ cm}^2$).

Intravenous lidocaine resulted in a significant decrease in response to stroking and cold in the area of allodynia. This effect was greatest for cold allodynia (fig. 2). Intravenous lidocaine also resulted in a significant decrease in pain in response to cooling stimuli and in spontaneous pain (fig. 3). There was no effect of intravenous lidocaine on pain scores evoked by Frey's hair and stroking stimulation (fig. 3).

Side Effects of Lidocaine

Lidocaine produced significantly more light headedness than diphenhydramine. Sedation and dry mouth were similar in both groups (fig. 4). All other side effects measured were negligible in both groups.

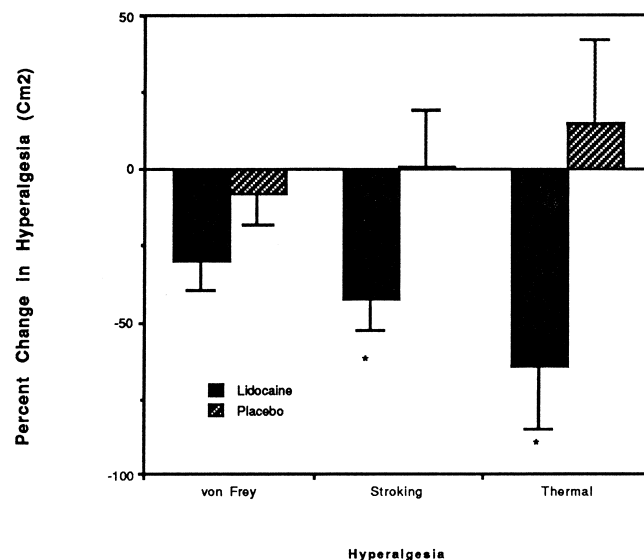


Fig. 2. The effect of intravenous lidocaine (3 $\mu\text{g/ml}$ plasma concentration) on the area of allodynia (in squared centimeters) to Frey's hairs, stroking, and cool stimuli in patients with neuropathic pain and allodynia. * $P < 0.05$.

Effect of Lidocaine on Blood Pressure and Heart Rate

Intravenous lidocaine produced a significant increase in systolic blood pressure at the high plasma level only (from a mean baseline of $134.9 \pm 20.2 \text{ mmHg}$ to a mean of $150.6 \pm 21 \text{ mmHg}$). There was no significant effect on heart rate.

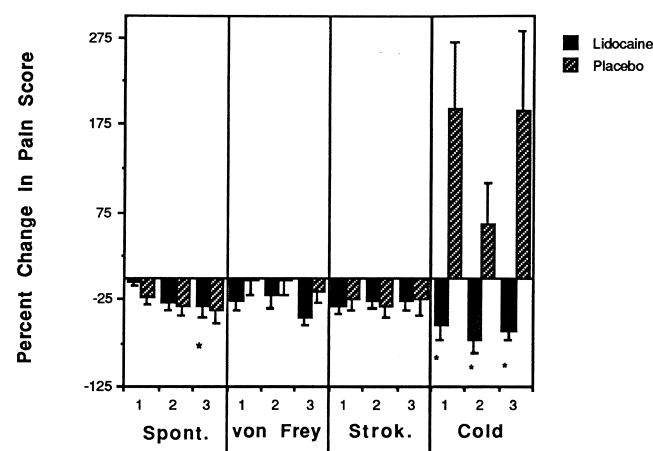


Fig. 3. The effect of intravenous lidocaine at three different plasma concentrations (0 = baseline; 1, 2, 3 = the targeted plasma concentration in $\mu\text{g/ml}$) on the spontaneous pain and pain scores to Frey's hair, stroking, and cool stimuli. Pain scores were measured on a visual analog scale from 0 (no pain) to 100 (worst imaginable pain). * $P < 0.05$.

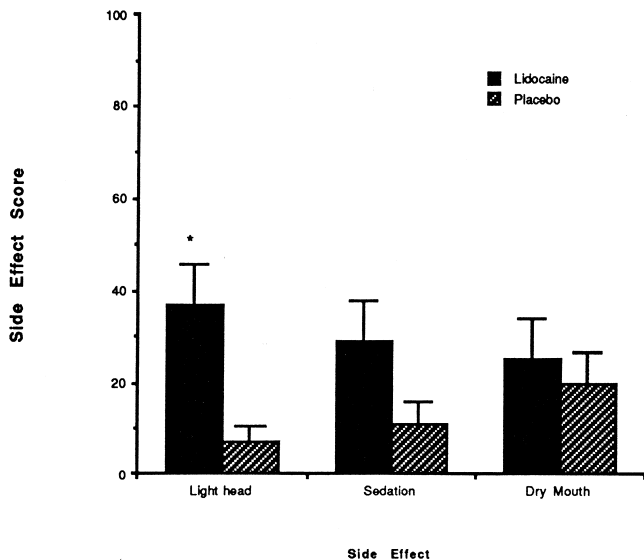


Fig. 4. The side effects produced by intravenous lidocaine (3 μ g/ml plasma concentration) vs. diphenhydramine (70–80 mg). Side effects were scaled on a visual analog scale from 0 (no side effect) to 100 (worst imaginable side effect). * $P < 0.05$.

Discussion

Description of the Study Cohort

In humans, skin temperatures $> 33^{\circ}\text{C}$ or $< 30^{\circ}\text{C}$ will evoke an initial report of warmth or coolness, respectively. At further extremes of temperature, the subject reports the stimulus as painful, with the magnitude of the pain state being proportional to the stimulus intensity.¹ A low-intensity mechanical stimulus yields a sensation of touch, whereas higher intensities leading to physical distortion/injury will yield a report of pain, with the magnitude of the pain state being proportional to the stimulus intensity.²⁴ The correlation between sensation and nerve fiber activity has been extensively studied, and no definite conclusions can be made as to what nerve fibers correlate with certain sensations. Fascicular recording and compression-ischemia block have shown that low-threshold tactile sensations are subserved by large myelinated fibers ($A\beta$), cool sensation by small myelinated fibers ($A\delta$), and warmth and pain by small unmyelinated fibers (C fibers).^{2,4,25–29} Large myelinated fiber function can be assessed with milliNewtons of pressure applied to the skin,²⁷ small myelinated fiber function can be assessed with quantitative thermal sensory testing, and small unmyelinated fiber function can be assessed with quantitative thermal sensory testing and mechanical pain (pressure/pinch algometer).¹ Although we cannot make a definite conclusion on what

nerve fibers are being stimulated with these techniques,^{30,31} the basic theories are the premises that established the model used to study the effects of intravenous lidocaine on neurosensory processing.

All patients in this cohort were suffering from allodynia. Neurosensory testing in this area (compared with norms in healthy volunteers¹²) showed grossly elevated warm, cool, and Frey's hair thresholds, modest elevation in hot pain thresholds, and normal cold pain thresholds. Because we used a small electrode for the thermal thresholds, the warm and cool thresholds may have been overestimated because these measurements are more dependent on spatial summation.^{32,33} However, even taking this into account, it can still be concluded that these thresholds were elevated.

Plasma Lidocaine Levels

Previous studies of intravenous lidocaine on pain states in humans have used bolus dosing of intravenous lidocaine, which results in a continuously changing plasma concentration.^{10,34} To define the relationship between drug concentration and the observed effect, a technique is required that achieves and maintains a plasma concentration rapidly with minimal overshoot. The technique described in this study seems to achieve this goal.

Effect of Lidocaine on Neurosensory Thresholds in Humans

Although direct application of lidocaine to a nerve results in axonal conduction block, systemic delivery can exert potent effects on sensory processing at doses that do not produce conduction block. At the concentrations used in our study, we observed no prominent effects on acute thermal or mechanical thresholds. This is similar to a study in human volunteers in which it was demonstrated that there is no effect of intravenous lidocaine, in the same plasma concentrations used in the present study, on acute thermal or mechanical thresholds.¹² These findings are consistent with those of a previous report by Bach *et al.*¹⁵ in a small group of normal human volunteers. Their study concluded that intravenous lidocaine, at plasma concentrations that have been shown to decrease neuropathic pain,^{10,17} do not effect acute neurosensory processing in the unaltered system. Therefore, it can be concluded that systemic lidocaine exerts similar effects on acute neurosensory processing on the altered sensory system *versus* the unaltered sensory system. This lack of effect of intravenous lidocaine on acute thermal and mechanical stimuli seems different from several previous observations. First,

the lack of a robust effect of intravenous lidocaine on acute neurosensory thresholds is somewhat inconsistent with preclinical findings showing a depressed conduction velocity in C fibers, and to a lesser extent A δ fibers, after intravenous lidocaine, although the difference suggests that these modest changes may not be relevant to detection thresholds.³⁵⁻³⁷ In addition, this selective effect of lidocaine in unmyelinated fibers is supported by the observation that lidocaine decreases the flare response induced by intradermal capsaicin. We previously demonstrated a reduction in this flare response without demonstrating an effect on warm or hot pain thresholds.¹² These different C-fiber-mediated events may be served by different voltage-sensitive channels in the same nociceptor membrane.³⁸ Therefore, the different sensitivities of these channels to systemic lidocaine may explain the differential psychophysical responses. It could also be argued that the explanation for the decrease in the flare response has nothing to do with voltage-sensitive channels, but rather is the result of vasoconstriction produced by lidocaine. In this study, we demonstrated a significant elevation of systolic blood pressure, a finding consistent with previous studies.¹² This elevation of blood pressure could be interpreted as the result of vasoconstriction from the low plasma level of lidocaine, thus resulting in a decrease in the flare response. However, recent studies using laser Doppler imaging have demonstrated no change in basal perfusion in the flare after intradermal capsaicin in the presence of systemic lidocaine (M. Schmelz, personal communication, April 1999). Another explanation is that lidocaine stabilizes the membranes of other cells (*i.e.*, mast cells) that release peptides or vasodilator agents.

Effect of Systemic Lidocaine on Mechanical and Cool Allodynia and Pain Scores

The mechanism of hyperalgesia and allodynia after peripheral nerve injury is not completely understood. There are lines of evidence that static allodynia is mediated by unmyelinated fibers and dynamic allodynia is mediated by myelinated fibers.^{25,38} The exact mechanism of cool allodynia is yet to be determined, because not every patient with mechanical allodynia has cool allodynia. All of the patients in this study had both static and dynamic allodynia, and only eight had cool allodynia (with only five having mappable allodynia to cool stimuli). Although there were not enough subjects with mappable allodynia to cool stimuli to make firm conclusions, the large decrease in the area of allodynia to cool stimuli coincided with a significant decrease in pain

scores induced by cool stimuli. There was no consistency between the area of allodynia to mechanical stimuli and pain induced by mechanical stimuli, which suggests two different mechanisms of mechanical and cool allodynia. These two mechanisms seem to have different sensitivities to intravenous lidocaine.

The observation that intravenous lidocaine has a significant effect on cool and stroking allodynia and not Frey's allodynia is interesting. If both cool and mechanical allodynia are mediated by the same population of nerve fibers, one would expect systemic lidocaine to decrease the area of both. However, we demonstrated a consistent effect on cool allodynia only (both area of allodynia and evoked pain). There are several possible explanations for this observation. First, as previously mentioned, thermal and mechanical allodynia may be served by different voltage-sensitive channels in the same nociceptor membrane (on C fibers) that have different sensitivities to lidocaine. Second, a focal punctate stimulus is a higher-intensity stimulus than a diffuse non-noxious cool stimulus, and these two stimuli may activate a different population of nociceptors with different sensitivities to systemic lidocaine. It has been demonstrated that all C-polymodal nociceptors respond to mechanical and heat stimuli, and a subgroup of these nociceptors respond to noxious low temperatures.³⁹ Patients with cool allodynia report pain to cool stimuli at temperatures that do not result in pain. Whether this represents a sensitization of primary C-polymodal nociceptors to low temperatures or release of an inhibitory action of myelinated fibers on second-order nociceptor neurons in the spinal cord is unclear. Third, the discrepancies in Frey's hair testing of allodynia and the area of mapping to stroking and cooling may be a result of spatial summation effects. The Frey's test may not have the sensitivity to detect minor changes. On the other hand, the thermal testing is performed with a bigger probe that may be more sensitive in detecting changes. Likewise, stroking also stimulates a larger surface area. Fourth, previous reports have shown an absence of correlation between mechanical allodynia and cool allodynia in neuropathic patients.^{38,40} Our study also demonstrated this and suggests different mechanisms for mechanical and cool allodynia. The effect of systemic lidocaine on the pain scores is consistent with the aforementioned observations because systemic lidocaine had no effect on spontaneous or mechanically induced pain scores but had a significant effect on cool-induced pain scores.

The lack of effect of systemic lidocaine on spontaneous pain scores and mechanical allodynia is inconsistent

with previous reports of lidocaine on neuropathic pain.¹³⁻¹⁷ However, this can be explained by the fact that this study involved intense neurosensory testing that may have resulted in some wind-up (as demonstrated by the increase in pain scores to cooling in the placebo group; fig. 3), which masked the effects of lidocaine. In addition, most studies have shown a greater effect of systemic lidocaine in the area of allodynia than on pain scores.¹²

Physiologic Effects of Lidocaine

When studying the analgesic efficacy of a drug, it is important to determine if the analgesic effect is occurring below, at, or above the plasma concentration that results in known physiologic effects. To determine this, we monitored side effects, heart rate, and blood pressure. To rule out the possibility of a placebo effect of lidocaine, we used diphenhydramine as a placebo control. We chose this drug because of the prominent sedation (which is a prominent side effect of intravenous lidocaine) that usually results from its delivery. The most prominent side effects in both groups were light headedness, sedation, and dry mouth. All other side effects measured were negligible in both groups. Light headedness was the only side effect that was significantly higher in the lidocaine group than in the placebo group. Therefore, we conclude that diphenhydramine is a suitable agent for placebo-controlled studies on systemic lidocaine. These results are consistent with our previous reports.¹² Intravenous lidocaine resulted in a dose-dependent significant increase in systolic blood pressure and a modest increase in heart rate. Because lidocaine exerts an arterial vasoconstriction at plasma levels between 10 and 103 ng/ml, we assumed that an elevation in blood pressure should occur in our study.⁴¹ In addition, plasma concentrations of local anesthetics that produce central nervous system toxicity will result in an increase in heart rate.

Clinical Relevance

This study demonstrates that drugs may have a specificity for certain components of the pain syndrome. By characterizing the pain, one can begin to sort out which drugs to select for a given pain characteristic. It may be possible to characterize the pain through neurosensory testing and select one or a combination of drugs to alleviate the pain. Lidocaine is an example of a drug that may be the choice for pain that has a strong cool-evoked component. Until further studies are completed with

different classes of agents, we can make no further conclusions on how to select the drugs.

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