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Concentration–effect Relations for Intravenous Lidocaine Infusions in Human Volunteers

Effects on Acute Sensory Thresholds and Capsaicin-evoked Hyperpathia

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***Background*: Preclinical studies have emphasized that persistent small afferent input will induce a state of central facilitation that can be regulated by systemically administered lidocaine. The authors extended these preclinical studies to human volunteers by examining the concentration-dependent effects of intravenous lidocaine on acute sensory thresholds and facilitated processing induced by intradermal capsaicin.**

***Methods:* Fifteen healthy persons received a lidocaine or a placebo infusion. A computer-controlled infusion pump targeted sequential stepwise increases in plasma lidocaine concentration steps of 1, 2, and 3 μg/ml. At each plasma concentration, neurosensory testing (thermal and von Frey hair test stimulation) were performed. After completing the tests at the 3 μg/ml plasma lidocaine level, intradermal capsaicin was injected into the volar aspect of the left forearm, and the flare response and hyperalgesia to von Frey hair stimulation, stroking, and heat was assessed.**

***Results:* The continuous infusion of lidocaine and placebo had no significant effect on any stimulus threshold. Although intravenous lidocaine resulted in a decrease in all secondary hyperalgesia responses, this was only significant for heat hyperalgesia. Intravenous lidocaine resulted in a significant decrease in the flare response induced by intradermal capsaicin.**

***Conclusions:* These studies suggest that the facilitated state induced by persistent small afferent input human pain models may predict the activity of agents that affect components of nociceptive processing that are different from those associated with the pain state evoked by "acute" thermal or mechanical stimuli. Such insight may be valuable in the efficient development of novel analgesics for both neuropathic and post–tissue-injury pain states. (Key words: Capsaicin. Experimental. Intravenous. Lidocaine. Pain. Sensation.)**

PRECLINICAL studies have shown that persistent small afferent input can induce a state of facilitated processing that leads to hyperalgesia. These experimental hyperpathic states in animals are mediated by a pharmacologic mechanism distinct from that which mediates pain behavior induced by acute noninjurious stimuli.[1] One example of this novel pharmacologic mechanism in animal models is that associated with the action of systemic lidocaine, a use-dependent sodium channel blocker. Intravenous lidocaine, at plasma concentrations that do not block axonal conduction, diminishes facilitated states induced by tissue[2] and nerve injury[3] without altering acute nociceptive thresholds. In humans, systemic lidocaine can be effective in treating certain neuropathic pain disorders at doses that do not produce frank anesthesia[4-8] and at plasma concentrations less than those required to block axonal conduction.[9,10] Although the mechanisms of these actions are not certain, the effects of low concentrations of lido-

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caine in animal models in tests of facilitated processing and the parallels with lidocaine in human clinical pain states associated with hyperpathia suggest that parallel mechanisms may exist. An appropriate strategy would be to compare the activity of lidocaine on human pain states induced by acute, noninjurious stimuli (mimicking the acute nociceptive models) and hyperalgesia/allodynia in facilitated states of processing (mimicking the facilitated states in preclinical models). In humans, the intradermal delivery of capsaicin has been shown to produce an acute pain sensation followed by long-lasting hyperalgesia and allodynia.

The study of systemic lidocaine is complicated by a rapidly declining plasma concentration curve after acute delivery and by allied sensory effects, which make it difficult to blind the studied participant and the researcher to the presence of the drug. We recently characterized the pharmacokinetics of intravenous lidocaine and developed a computer-controlled infusion paradigm for lidocaine that permits the establishment of pseudo-steady-state plasma lidocaine levels after a brief interval.[11] This delivery system, in conjunction with the use of diphenhydramine as an active placebo, has several advantages. 1) It permits the measurement in a single sitting of the participant's response to several concentrations during a relatively brief interval. 2) It reduces the overshoot leading to side effects associated with a simple bolus/infusion technique. 3) It permits the sampling of plasma at each step, which allows the drug effect relation to be defined in terms of actual plasma levels rather than simply dose. 4) The crossover design using lidocaine and diphenhydramine allows a double-blinded paradigm in which each participant can be used as his or her own control. We used this model to study the effect of intravenous lidocaine on peripheral nerve injury.[12] In the present study, we wanted to establish the concentration-effect relation for intravenous lidocaine in human volunteers for thermal thresholds, mechanical thresholds, and a facilitated state generated with intradermal capsaicin.

Materials and Methods

Participants

All work was done according to protocol approved by the Institutional Review Board of the University of California, San Diego. With informed consent, 15 healthy persons (four women and 11 men) were recruited for the study. Their average age (± SD) was 33 ± 11 yr (range, 18–48 yr), and their average weight was 75 ± 15 kg (range, 53–97 kg). After explaining the protocol and obtaining their informed consent, we entered the participants into the following experimental trials.

Clinical Methods

Infusion. This study used a randomized, double-blind, placebo-controlled design. Each participant received a lidocaine (Astra Pharmaceuticals, Westboro, MA) and saline (0.9% sodium chloride USP, for injection) or diphenhydramine (Parke-Davis, Morris Plains, NJ) infusion in separate study sessions. The order of the study sessions was randomized and separated by 1 week. Because intravenous lidocaine causes significant side effects that may lead to a placebo response, we studied the efficacy of diphenhydramine as a placebo drug. Thus, one half of the participants received diphenhydramine, and one half received saline as the placebo infusion.

During each study session, two 20-gauge intravenous cannulas 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.[11] Briefly, parameters were estimated in those studies from the pooled analysis of arterial concentration *versus* time profile of those volunteers for the purpose of optimizing CCIP performance. Based on those parameters, plasma lidocaine concentration steps of 1, 2, and 3 μg/ml were targeted and maintained for 20 min. This results in a pseudo-steady-state of lidocaine because we cannot assume that the lidocaine has equilibrated in all body compartments. To reach a true steady state, a prolonged infusion is required, which would be difficult in this study. After a baseline neurosensory test (described subsequently) and heart rate and blood pressure were measured, the CCIP was initiated to achieve a plasma lidocaine

level of 1 μg/ml and allowed to reach pseudo-steady state for 20 min. At 20 min, the following tests were performed in this order: 1) Blood pressure and heart rate were recorded, 2) a venous blood sample (2 ml) was collected, 3) side effects were assessed (described subsequently), and 4) neurosensory testing was done. After completing these tests, the process was repeated at the 2 and 3 μg/ml plasma lidocaine levels. After completing the tests at the 3 μg/ml plasma lidocaine level, intradermal capsaicin was injected into the volar aspect of the left forearm, and hyperalgesia was assessed. The infusion was stopped if the following side effects occurred (which usually occur at plasma lidocaine levels greater than 5 μg/ml)[13]: 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 were reported because they usually occur at plasma lidocaine levels less than 5 μg/ml.[13] Electrical activity of the heart (*via* a three-lead electrocardiograph), heart rate, and blood pressure were monitored throughout the study.

Testing.

Neurosensory Testing. Three neurosensory tests were performed: warm and cool sensation, hot and cold pain, and touch. These tests were performed on the volar aspect of the left forearm and the left anterior thigh. The same order of the stimuli was used in all participants: cool, warm, cold pain, and hot pain. This order was chosen because it progresses from the lowest (cool) to the highest (hot pain) stimulus.

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 × 29 mm. The temperature of the thermode can either increase or decrease (at a rate of 1°C/s) depending on the direction of current flow through the device. The participant holds a switch that he or she presses at the first sensation of warmth or cold; pressing the switch reverses the temperature change, returning to a neutral temperature of 32°C.

The thermal sensory analyzer is used for warm and cold pain measurements, but the endpoint is pain instead of temperature change sensation. It also uses a temperature change rate of 1.5°C/s.

Touch was measured using von Frey hairs. Calibrated von Frey hairs are filaments of various sizes. The filament 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 micronewtons and measured as positive if the participant felt any one of the three successive stimuli. At the stimulus intensity evoking a report of discomfort, the next stimulus is one unit lower. This stimulus reversal is repeated twice, and the average reversal intensity is defined as the threshold. This is a modification of the widely used method of Dixon in animal and human psychophysical testing (see, for example, Chaplan *et al.*[14]).

Side Effects. Side effects were measured by the participant using a visual analog scale. This consists 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 participant 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, measured in millimeters, from the no-side-effect end to the location of the mark gives a measurement of the side effect.

Intradermal Capsaicin Injection. One hundred milligrams of capsaicin (8-methyl N-vanillyl 6-nonamide), dissolved in 10 ml of a 20% cyclodextran vehicle to achieve a concentration of 10 μg/μl, was prepared in accordance with aseptic precautions. A volume of 10 μl was injected intradermally on the volar aspect of the left forearm with a sterile tuberculin syringe. The investigator recorded at the time of injection and at 5-min intervals the magnitude of the pain score. After 15 min, the region of secondary hyperalgesia and flare response was determined. The edge of the region of secondary hyperalgesia was established with a 5.18 von Frey hair, with cotton wisp gently stroked on the skin, and with a 2 cm × 2 cm probe heated to 40°C (in that order). These stimuli were begun away from the injection site in an area of skin that did not produce pain. These stimuli were repeated tangentially to the injection site at a progressively closer radius until the participant 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 bor-

ders of secondary hyperalgesia were outlined on the skin. These three borders were outlined onto a transparency for area (measured in square centimeters) determination. The area of the flare response resulting from the intradermal injection of capsaicin was similarly determined by outlining the borders onto a transparency for area determination. The neurosensory thresholds already described were established at a distance half way between the edge of the assessed area of hyperalgesia and the center of the injection site.

Pain Scores. Pain scores were measured using a visual analog scale. This consists of a 100-mm line with "no pain" written at one end and the "worst imaginable pain" written at the other end. The participant 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.

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.[14a] Total run time was 5 min, and lidocaine and bupivacaine eluted at 2.4 and 4 min, respectively. The limit of detection for lidocaine by this method was 0.05 ng/ml plasma. The interassay precision (coefficient of variation) was 7.5% and 3.5%, respectively, for lidocaine levels of 0.1 and 1.0 ng/ml in serum. Accuracy in the range of 0.5 - 10 ng/ml was more than 99%.

Data Analysis. Data are expressed as the means ± SD. Analysis of variation with repeated measures was used for intergroup comparisons of neurosensory thresholds, pain scores, blood pressure, and heart rate. Analysis of variation with repeated measures was also used to determine if a dose *versus* side effect relation existed and to make an intergroup comparison of each side effect. Tukey's *t* test was used for *post hoc* testing. An unpaired Student's *t* test was used to make an intergroup comparison of percentage reduction in secondary hyperalgesia. Bonferroni's *t* test was used for *post hoc* testing. Results of all tests were considered significant at $P < 0.05$.

The time course of analgesia produced by the intravenous lidocaine and placebo was compared using the area under the curve of the pain score *versus* time plot. Area was calculated using the trapezoid rule.

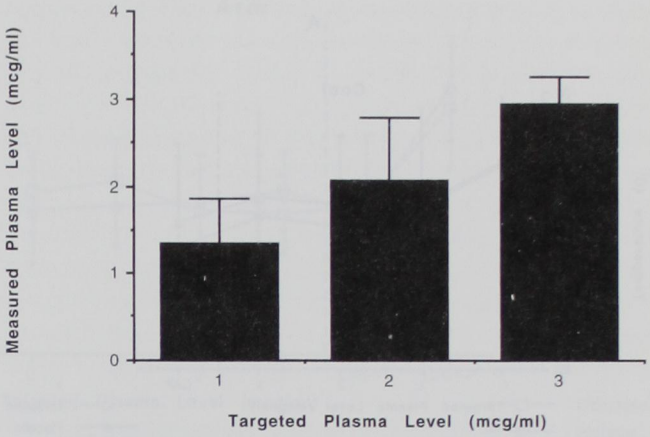

Fig. 1. Measured *versus* targeted plasma lidocaine levels (expressed in micrograms per milliliter) in volunteers receiving intravenous lidocaine *via* a computer-controlled infusion pump. This pump was programmed to increase the plasma lidocaine levels by 1-μg/ml increments.

Results

Lidocaine Infusion and Plasma Lidocaine Levels

The mean dose of lidocaine (plus SD) infused was 763 (±240) mg (range, 311 - 1,072 mg). Based on the CCIP parameters used, measured venous lidocaine levels were considered very close to targeted levels. Mean measured plasma levels for each targeted level (1, 2, and 3 mg/ml, respectively) were 1.3 μg/ml (range, 0.7 - 2.4 mg/ml), 2.1 mg/ml (range, 1 - 3.2 μg/ml), and 2.9 mg/ml (range, 2.6 - 3.5 mg/ml) (fig. 1). Thus, the mean percentage difference (concentration error = [(Real − Targeted)/Targeted] × 100)(±SD) between the targeted and measured concentration at targeted plasma concentrations of 1, 2, and 3 μg/ml received by each patient was 32 ± 46%, 2 ± 0.7%, and -2 ± 10%, respectively.

Effect of Lidocaine on Neurosensory Thresholds

Baseline sensory thresholds expressed in degrees centigrade for the arm (± SD) were cool, 30.5 ± 1.4; warm, 34.5 ± 2.0; cold pain, 12.8 ± 10.7; hot pain, 45.6 ± 2.9; and von Frey, 3.86 ± 0.38. Baseline sensory thresholds for the thigh were cool, 27.2 ± 2.8; warm, 36.2 ± 2.5; cold pain, 12.2 ± 12.6; hot pain, 46.8 ± 2.2; von

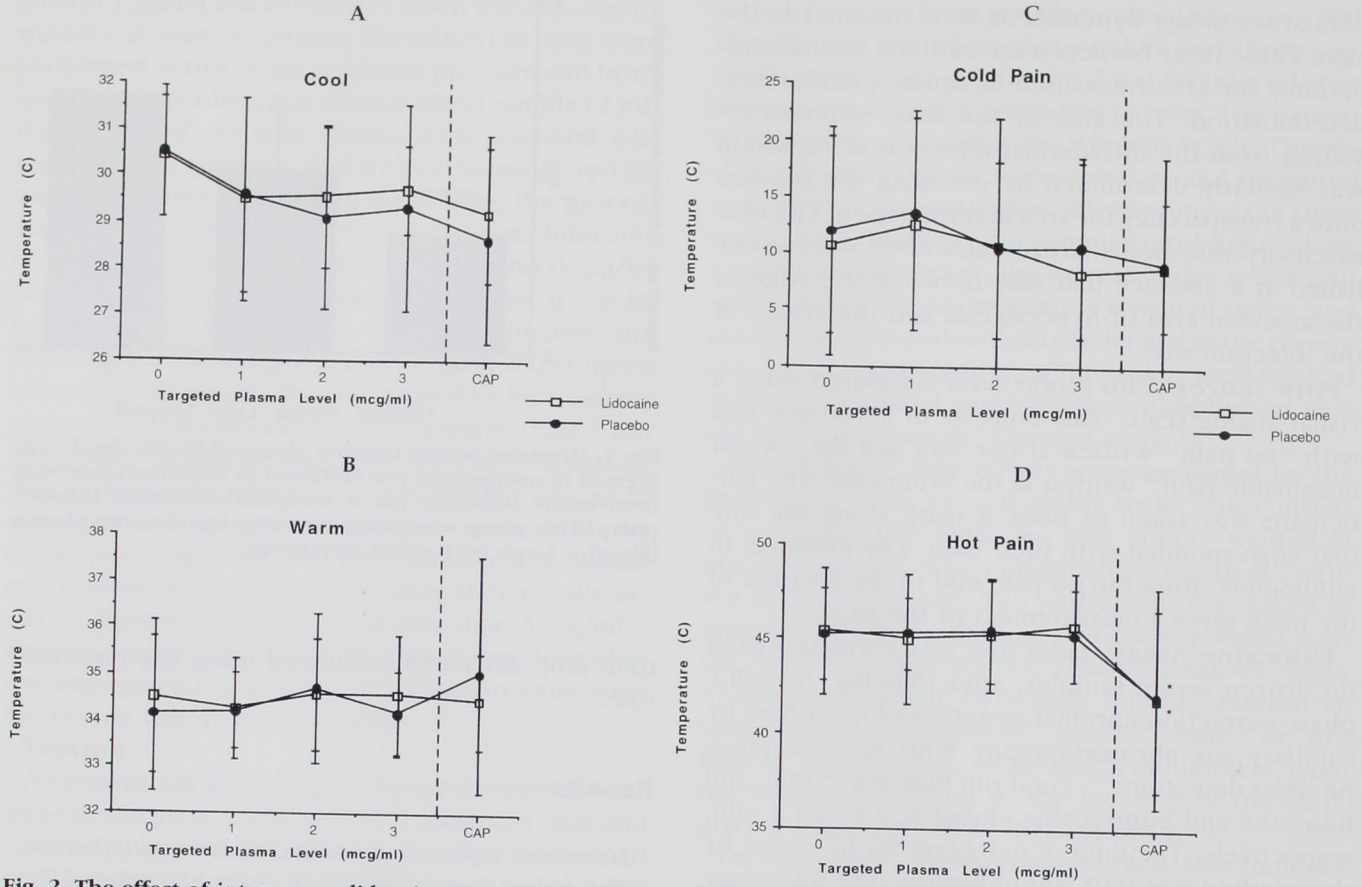

Fig. 2. The effect of intravenous lidocaine, at three different plasma concentrations, on cool (*A*), warm (*B*), cold pain (*C*), and hot pain (*D*) thermal thresholds of the volar aspect of the left forearm. After measuring the thresholds at the 3-μg/ml targeted plasma level, intradermal capsaicin was administered on the volar aspect of the left forearm and the thermal thresholds were repeated at 15 min (CAP).

Frey, 4.27 ± 0.21. Thresholds were not different during the 7-day observation period. The continuous infusion of diphenhydramine or saline or lidocaine at nominal plasma concentrations as high as 3 μg/ml did not have a significant effect on any measured stimulus threshold (figs. 2 and 3).

Effect of Lidocaine on Capsaicin-induced Secondary Hyperalgesia, Flare Response, and Pain Scores

The intradermal injection of capsaicin reliably produced a flare response and secondary hyperalgesia to von Frey hairs in all participants. Secondary hyperalgesia to stroking and heat occurred in 70% and 75% of participants, respectively. The heat hyperalgesia induced by intradermal capsaicin was associated with a significant decrease in hot pain thresholds in the hyperalgesic area.

Although intravenous lidocaine decreased all secondary hyperalgesia responses, this effect was significant only for the heat hyperalgesia (fig. 4). Intravenous lidocaine also resulted in a significant decrease in the flare response induced by intradermal capsaicin (fig. 5).

Although intravenous lidocaine slightly decreased intradermal capsaicin-induced pain intensity and duration, it was not statistically significant (fig. 6).

Side Effects of Lidocaine

Participants reported significantly more side effects during the lidocaine infusion than during infusions of diphenhydramine and saline (table 1). Lido-

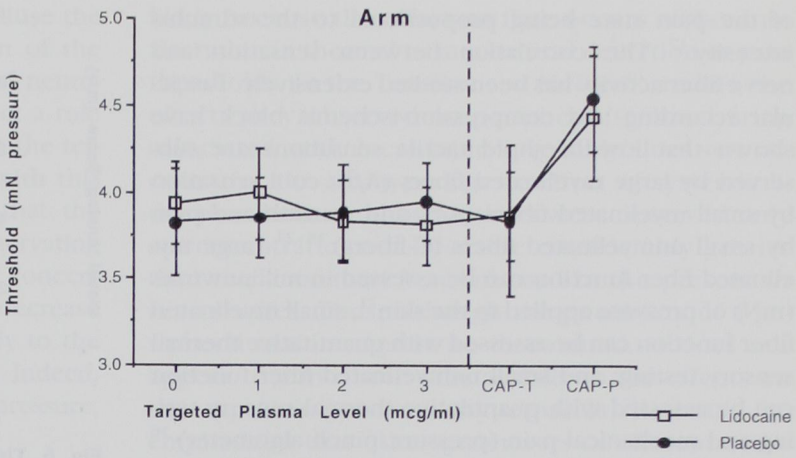

Fig. 3. The effect of intravenous lidocaine, at three different plasma concentrations, on von Frey hair thresholds of the volar aspect of the left forearm. After measuring thresholds at the 3-μg/ml targeted plasma level, intradermal capsaicin was administered on the volar aspect of the left forearm, and von Frey hair thresholds were repeated for sensation (CAP-T) and pain (CAP-P).

caine produced significantly more light-headedness, sedation, perioral numbness, and dry mouth than did saline and significantly more sedation and dry mouth than did diphenhydramine. Lidocaine resulted in a significant dose-dependent incidence of light-headedness, sedation, perioral numbness, metallic taste, and dry mouth. Diphenhydramine resulted in significant dose-dependent incidence of sedation and dry mouth. Saline did not result in any notable effects. Because the infusions were discontinued if the participants experienced nausea, muscle twitching, tinnitus, or blurred vision, it was difficult to measure dose-response curves for these side effects. Nonetheless, lidocaine resulted in a significant dose response for muscle twitching (table 1).

Effect of Lidocaine on Blood Pressure and Heart Rate

Intravenous lidocaine produced a significant dose-dependent increase in blood pressure and heart rate. Intradermal capsaicin produced a slight increase in heart rate that was not attenuated by intravenous lidocaine.

Discussion

Plasma Lidocaine Levels

Previous studies of intravenous lidocaine on experimental pain states in humans have used bolus dosing of intravenous lidocaine, which results in a continuously changing plasma concentration.[10,15] To define the relation 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 appears to achieve this goal.

Effect of Lidocaine on Neurosensory Thresholds in Humans

In humans, skin temperatures greater than 33°C or less than 30°C will evoke an initial report of warmth or coolness, respectively. At further extremes of temperature, participants report the stimulus as painful, with the magnitude of the pain state being proportional to the stimulus intensity.[16] A low-intensity mechanical stimulus yields a sensation of touch, whereas higher intensities leading to physical distortion or injury will prompt participants to report pain, with the magnitude

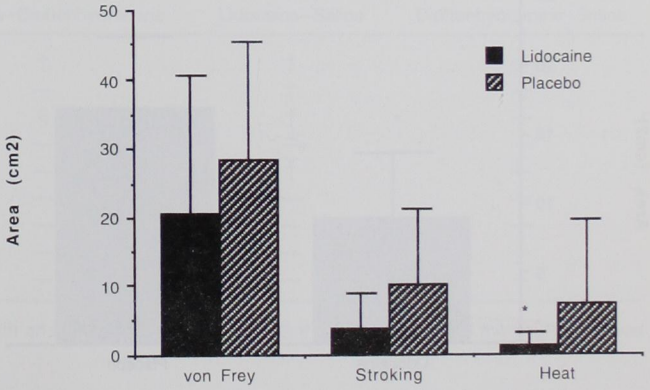

Fig. 4. The effect of intravenous lidocaine on the area of secondary hyperalgesia (in square centimeters) to von Frey hairs, stroking, and heat after intradermal injection of capsaicin in the volar aspect of the left forearm. *$P < 0.05$.

of the pain state being proportional to the stimulus intensity.[17] The correlation between sensation and nerve fiber activity has been studied extensively. Fascicular recording and compression-ischemia block have shown that low-threshold tactile sensations are subserved by large myelinated fibers (Aβ), cool sensation by small myelinated fibers (Aδ), and warmth and pain by small unmyelinated fibers (C-fibers).[18-24] Large myelinated fiber function can be assessed in millinewtons (mN) of pressure applied to the skin[21]; 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).[16] These are the premises that established the model used to study the effects of intravenous lidocaine on neurosensory processing.

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 seen in our study, we observed no prominent effects on acute heat, cold, or mechanical thresholds. These findings are consistent with previous reports by Bach *et al.*,[6] in a small group of healthy human volunteers.[6] Their study concluded that intravenous lidocaine, at plasma concentrations that have been shown to decrease neuropathic pain,[10,12] do not affect acute neurosensory processing in the unaltered system. This lack of effect of intravenous lidocaine on acute thermal and mechanical stimuli appears different from several

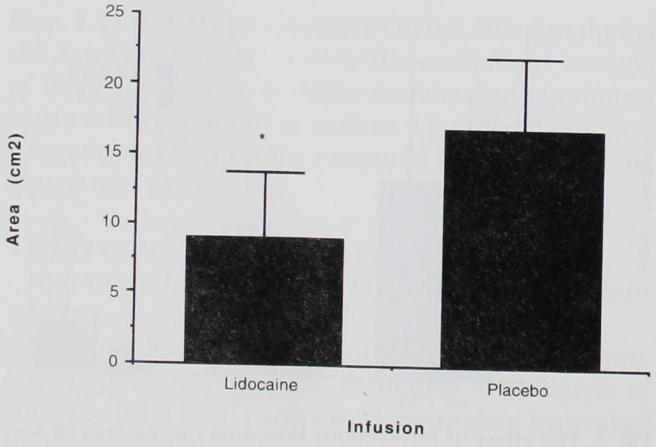

Fig. 5. The effect of intravenous lidocaine on the flare response (in square centimeters) after intradermal capsaicin injection in the volar aspect of the left forearm. *$P < 0.05$.

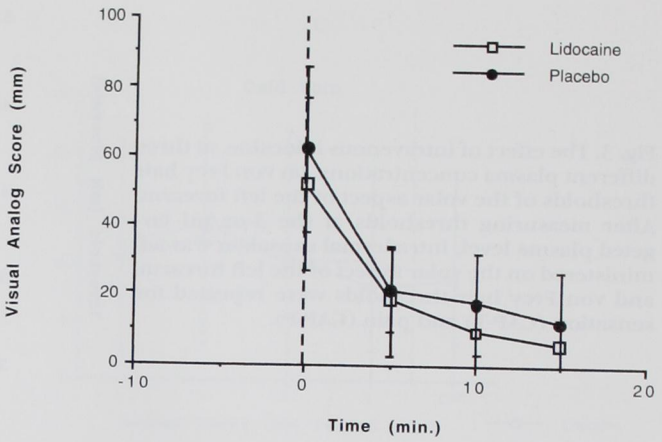

Fig. 6. The effect of intravenous lidocaine (3 μg/ml plasma concentration) on the pain resulting from intradermal capsaicin injection in the volar aspect of the left forearm.

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 Aδ fibers after intravenous lidocaine, although the difference suggests that these modest changes may not be relevant to detection thresholds.[25-27] Second, in previous human studies, we evaluated the effects of intravenous lidocaine on perception thresholds for electrocutaneous stimulation. The three different frequencies used, 2,000, 250, and 5 Hz, are thought to recruit at threshold intensities progressively smaller afferent populations (Aβ, Aδ, and finally C-fibers) as stimulation frequency is decreased.[28,29] In those studies, lidocaine appeared to elevate threshold for the 250 and 5 Hz, but not the 2,000 Hz stimuli. Inspection of the data, however, emphasizes that the repeated epochs of stimulation at 250 and 5 Hz were associated with a progressive decrease in threshold, which may reflect the initiation of a facilitated state, and we think that it is this facilitated component evoked by small afferent stimulation that is affected by the intravenous lidocaine injection.

Effect of Lidocaine on Capsaicin-induced Flare Response

Intradermal capsaicin causes the transient (less than 20-30 min) and selective activation of C-fibers. In addition, intradermal capsaicin results in a rapid onset of a flare response, which peaks at about 3-5 min.[30] Our study showed a significant reduction in the flare re-

sponse induced by intradermal capsaicin. Because the flare response represents antidromic invasion of the axon collaterals and the subsequent release of neuropeptide,[31] this blockade of the flare may reflect a role played by voltage-sensitive sodium channels at the terminals of unmyelinated axons.[32] Consistent with this possibility, Tanelian and MacIver[26] showed that the spontaneous activity arising from an axon-innervating injured tissue can be diminished by lidocaine at concentrations that do not block conduction. The decrease in the flare response also could be due simply to the vasoconstrictive effect of systemic lidocaine. Indeed, we found a significant increase in blood pressure, which supports this conclusion.

Mechanisms of the Antihyperalgesic/Antiallodynic Action of Systemic Lidocaine

After a focal tissue injury, or the injection of capsaicin, the local skin site is surrounded by a large area of secondary hyperalgesia.[33] The mechanisms of the hyperalgesia and allodynia are not completely understood, but two lines of reasoning are relevant: 1) peripheral sensitization of sensory terminals secondary to injury (and the release of local active factors), and 2) a central (spinal) sensitization secondary to persistent small afferent.

With regard to an action at the peripheral terminal, an effect on peripheral transduction appears unlikely because the effect on flare occurs without an alteration in thermal or mechanical detection or pain thresholds. In the Tanelian and McIver[26] studies, the effects they observed on peripheral terminal firing associated with local injury probably does not account for the antihyperalgesic effect of systemic lidocaine, because those actions were observed only at concentrations of lidocaine considerably greater than the maximum 3 μg/ml used in the present *in vivo* studies. Thus, although the possibility of a peripheral action cannot be discounted, it does not appear to contribute substantially to the effects on the capsaicin-generated hyperpathia. It should be emphasized that other generators of afferent activity, notably neuromas and the traffic arising from dorsal root ganglia after peripheral nerve injury, have been shown to respond to low concentrations of systemic lidocaine, and the "peripheral" action of lidocaine at these spike generator sites may contribute to the effects of systemic lidocaine in a post-nerve-injury pain model in animals[3] and humans.[12,15]

Several lines of evidence emphasize that intravenous lidocaine can exert a central action. Plasma lidocaine concentrations estimated to be between 1 and 10 mg/ml will 1) selectively inhibit the nociceptive response in the isolated rat spinal cord;[34] 2) reduce the late discharge component of spinal wide dynamic range neurons;[35] and 3) reduce the dis-

Table 1. Summary of Side Effects

	Dose–Response			Intergroup Comparison		
	Lidocaine	Diphenhydramine	Saline	Lidocaine–Diphenhydramine	Lidocaine–Saline	Diphenhydramine–Saline
Light-headedness	*	—	—	†	†	—
Sedation	†	‡	—	—	†	—
Oral numbness	‡	—	—	§	†	—
Met taste	§	—	—	—	—	—
Dry mouth	‡	*	—	—	†	—
Nausea	—	—	—	—	—	—
Muscle twitch	§	—	—	—	—	—
Tinnitus	—	—	—	—	—	—
Blurred vision	—	—	—	—	—	—

Statistical analysis was performed to determine (1) if the side effect increased with an increase in the dose and (2) if the appearance of the side effect was significantly greater between groups.

— = no statistical significance.

* $P < 0.0001$.
† $P < 0.01$.
‡ $P < 0.001$.
§ $P < 0.05$.

charge of dorsal horn neurons evoked by iontophoretically applied glutamate.[36] Recent work has suggested that lidocaine also may induce a blockade of spinal substance P receptor function.[37] These several observations suggest the additional likelihood that there is a central action of low doses of intravenous lidocaine occurring at plasma concentrations that could be achieved by the present dosing regimen; and this effect is manifested in systems that are relevant to facilitated processing. Preclinical behavioral studies using cutaneous irritants (such as formalin) injected into the hindpaw of rats have emphasized the development of facilitated states of processing initiated by the persistent afferent input.[38–40] Intravenous lidocaine, at concentrations that did not alter acute thermal nociception, produced a selective blockade of the facilitated (phase 2) but not the acute (phase 1) component of the postformalin pain state.[2] These observations emphasize the possibility but do not prove a central effect. Nevertheless, these properties of lidocaine action, along with the failure in the human as well as animal experimental models to alter acute nociceptive processing strengthen the possibility of a central mechanism. Such an action has also been suggested by Bach and colleagues.[6]

If the action of lidocaine relative to hyperalgesia and allodynia lidocaine is functional as described before, we would have expected to see a decrease in the pain scores produced by the intradermal injection of capsaicin. As shown in figure 6, there was no significant effect on the pain.

Lidocaine Side Effects

In our previous study, we raised the possibility of a placebo effect of intravenous lidocaine on pain relief in patients with peripheral nerve injury. This assumption was based on the fact that the onset of pain relief occurred with the onset of side effects.[12] In an attempt to address this problem, we used diphenhydramine in one half of the placebo infusions. We chose this drug because it causes a prominent sedation (which is a prominent side effect of intravenous lidocaine). Because diphenhydramine frequently induces mouth dryness, we added this to the list of side effects studied. Diphenhydramine better mimics lidocaine-induced side effects than does saline. Therefore, we conclude that diphenhydramine is a suitable agent for placebo-controlled studies of systemic lidocaine.

None of our volunteers experienced serious side effects from the lidocaine infusion. Nine of the 15 participants completed the infusion. The infusion was discontinued in the remaining six volunteers because of unacceptable side effects. The mean peak plasma concentration for persons who completed the infusion was 2.94 ± 0.31 μg/ml which was considerably higher than the concentration seen in those subjects that had the infusion discontinued because of unacceptable side effects (1.56 ± 0.61 μg/ml). We chose to discontinue the infusion in the presence of tinnitus, blurred vision, and muscle twitching because these side effects can be signs of convulsions. We had a high incidence of the minor side effect of light-headedness. This may reflect how abruptly the targeted plasma levels were achieved in our study. However, we could infuse relatively higher doses of lidocaine (average total doses of 350 mg) compared with other studies.

Effects of Lidocaine on Heart Rate and Blood Pressure

Intravenous lidocaine resulted in a dose-dependent significant increase in blood pressure and heart rate. We monitored blood pressure and heart rate to show the systemic cardiovascular effects of intravenous lidocaine at the plasma levels we achieved. 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.[42] Our observations are consistent with these reports and show that the plasma concentrations we used to study the neurologic effects also exerted a systemic cardiovascular effect.

Clinical Relevance

These studies suggest that the facilitated human pain models may serve to predict the activity of agents that exert their effects on components of nociceptive processing that are different from those associated with the acute pain state. The preclinical literature and the growing body of clinical observations suggest that this facilitated condition may be of primary importance in many post-injury pain states in humans. The present studies showing the similarity of the effects in the experimental pain

models compared with the clinical state does not prove that their mechanisms are the same, but it does provide support for the hypothesis that these models can predict the efficacy of agents that are believed to act on these facilitated states. In that event, the pain models provide an experimental approach to define the human mechanisms. To the extent that these models do predict the human clinical condition, they can serve as important methods for defining the analgesic efficacy of drugs in phase 1 clinical trials. Such insight may be of extreme value in the efficient development of novel analgesics for neuropathic and non-neuropathic pain states.

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