The Analgesic Response to Intravenous Lidocaine in the Treatment of Neuropathic Pain

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This study was performed in order to determine concentration-effect, and graded and quantal dose-response relationships for the clinical administration of intravenous (IV) lidocaine to patients with neuropathic pain. Thirteen patients were administered 500 mg of IV lidocaine at a rate of 8.35 mg/min over 60 min. Visual analog pain scores and venous blood samples were obtained concomitantly at 10 min intervals for 60 min. Blood samples were also obtained for determination of serum and serum water lidocaine concentrations at the onset of analgesia and at the time complete pain relief was attained. Lidocaine concentrations were determined by gas chromatography. Graded dose-response curves were prepared individually and for the group as a whole, and a quantal dose-response curve was prepared for the entire group. The dose-response relationship for IV lidocaine was characterized by large increases in pain relief for concomitant minimal increases in dosage. The difference between the ED_{50} (372.0 mg) and the ED_{90} (416.5 mg) was 44.5 mg of lidocaine (5.3 min of infusion). The concentration-effect relationship was also steep with pain scores abruptly decreasing over a range of 0.62 μg/mL of lidocaine. Interestingly, the free concentration of lidocaine had no better correlation with the onset of analgesia or the attainment of complete analgesia than the serum concentration of lidocaine. This suggests that the mechanism of analgesia to IV lidocaine may not be based upon a conventional concentration-effect relationship. In conclusion, the results of this study suggest that the analgesic response to IV lidocaine is best characterized by a precipitous "break in pain" over a narrow dosage and concentration range.

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The intravenous (IV) administration of lidocaine has long been used to provide analgesia in patients with neuropathic pain of varying etiologies (1–4). Unfortunately, basic pharmacologic relationships, such as dose-response curves, have not been fully defined. Previous work by Boas et al. (1) used a methodology involving a bolus injection of 3 mg/kg of lidocaine followed by a continuous infusion of 4 mg/min. The onset of analgesia was effectively immediate, and steady-state blood concentrations were achieved rapidly. Thus, neither dose-response relationships nor concentration-effect relationships could be defined. Furthermore, the study did not examine the significance of free versus total serum concentrations of lidocaine upon the production of analgesia. [Free drug concentration is generally accepted as a more accurate reflection of the active concentration (5).]

The object of this study was to define concentration-effect and dose-response relationships for the clinical administration of IV lidocaine for neuropathic pain states of varying etiology. The setting and the administration of IV lidocaine for this study was kept as close as possible to clinical practice. The correlation of free versus total serum concentrations of lidocaine and various stages of analgesia was also investigated.

Methods

Patients with neuropathic pain were recruited to participate in this preliminary study without regard for standardization of diagnosis (*i.e.*, central versus peripheral neuralgia, sympathetically maintained pain versus nonsympathetic mechanism, etc.). Participants were selected irrespective of gender and age. Patients with preexisting hepatic or renal disease were excluded from the study. Each patient had had neuropathic pain for at least 6 mo prior to enrollment. No

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patient had ingested oral lidocaine cogeners (tocainide [Tonocard], mexiletine [Mexitil]), or had received an IV infusion of local anesthetic for at least 6 wk prior to enrollment. There was no randomization or blinding. The study was approved by the institution's Human Research Committee, and informed consent was obtained from all patients.

Prior to treatment, all patients received a battery of psychometric tests including the short-form McGill Pain Questionnaire (6) and the Multidimensional Pain Inventory (7). Only the activities of daily living scales (Part III) of the Multidimensional Pain Inventory were scored. The short-form McGill Pain Questionnaire was again administered immediately after the IV infusion. The entire battery of tests was again completed at 1 and 2 wk postinfusion.

IV lidocaine was administered in a controlled environment with resuscitative drugs and equipment immediately available. IV catheters were inserted in contralateral limbs for the administration of lidocaine and the withdrawal of blood samples. Procaine was used to provide analgesia for catheter insertion via skin infiltration. Lidocaine was administered IV at a rate of 8.35 mg/min (500 mg in 250 mL of normal saline over 60 min). The effect of lidocaine on the intensity of neuropathic pain was assessed by subjective bioassay using a 10-cm visual analog scale. Pain scores were obtained before starting the infusion and at 10-min intervals until completion of the infusion.

A brief neurologic examination was performed prior to the administration of IV lidocaine and every 10 min during the infusion until completion. Neurologic examination included assessment of alertness, orientation, pupillary size, extraocular muscle function, nystagmus, VIIIth cranial nerve function, gross motor strength, reflexes, and coordination. The complete examination required 2–3 min to perform. Patients were told to report immediately any subjective responses to the infusion (light-headedness, circumoral numbness, etc.) to the observer.

Blood samples (3 mL) to determine lidocaine concentration were obtained prior to the IV infusion and at 10, 20, 30, 40, 50, and 60 min during the infusion. Samples were stored in heparinized tubes at −20°C until required for analysis. Additional blood samples (10 mL) to determine serum and serum water concentrations of lidocaine were obtained at initial onset of analgesia and when complete pain relief was attained. These samples were allowed to clot at room temperature, centrifuged to obtain serum, and stored as above. Serum pH was adjusted to physiologic pH using microliter quantities of 0.1 M HCl or 0.1 M NaOH as required. Serum water was then obtained using an ultrafiltration technique (8), and the percentage of protein binding of lidocaine was calculated.

Lidocaine concentrations in whole blood, serum, and serum water were determined using gas chromatography and reported as micrograms of lidocaine HCl per milliliter of fluid (9). Assay variability was typically <5% over the concentration range of the samples.

Graded dose-response curves were prepared individually and for the entire group of patients, and subjected to logarithmic regression analysis. A quantal dose-response curve was constructed for achievement of complete analgesia by plotting the cumulative frequency distribution of responders versus log dose. ED_{50} was estimated by means of a quadratic regression equation as there was no empiric observation of the ED_{50}. The percent of patients attaining complete pain relief was the dependent variable. The dose of lidocaine and the square of the dose were the independent variables.

A plot of lidocaine concentration versus time was prepared, and logarithmic regression was performed. Concentration-effect curves were prepared individually for each patient and for the entire group.

All patients were included in statistical analyses where appropriate. The median was used as a measure of central tendency for ordinal data (visual analog pain scores and scores from the short-form McGill Pain Questionnaire and the Multidimensional Pain Inventory). The Wilcoxon signed rank test was used to determine differences between paired groups for ordinal data. Mean ± SD are reported for interval data. The paired Student's *t*-test was used to determine differences between group means for interval data. For all statistical analyses, $P < 0.05$ was considered significant.

Results

Thirteen patients were enrolled in the study. Ten patients achieved complete pain relief. The "incomplete" responders obtained 55% (Patient 3), 40% (Patient 7), and 62% (Patient 9) relief from their baseline pain at the end of infusion. The age, gender, diagnosis, initial pain score prior to infusion, and dose of lidocaine for complete analgesia for each patient are listed in Table 1.

The time of initial onset of analgesia (14.8 min ± 6.6) and the calculated corresponding dose of lidocaine (123.0 mg ± 55.0) exhibited significant interpatient variability (coefficient of variation [CV] = 0.45). However, the time of onset of complete analgesia (45 min ± 8.6) and the calculated corresponding dose of lidocaine (374.9 mg ± 22.7) exhibited minimal interpatient variability (CV = 0.2).

The graded dose-response curve (and the concentration-effect curve for the entire group; see

Table 1. Patient Demographics and Response to Treatment

Patient	Age (yr): gender	Diagnosis	Complete analgesia?	Lidocaine dose for complete analgesia (mg)
1	47:M	Central pain (spinal cord injury)	Yes	416.5
2	67:M	Burning dysesthesia (L5)	Yes	358.2
3	42:M	Saphenous neuropathy	No	>500?
4	70:F	Burning dysesthesia (L5)	Yes	374.9
5	35:F	Diabetic polyradiculopathy	Yes	441.5
6	65:M	Intercostal neuralgia	Yes	399.8
7	66:M	Phantom foot pain	No	>500?
8	32:F	Central pain (Dejerine-Roussy syndrome)	Yes	416.5
9	52:M	Sympathetically maintained pain	No	>500?
10	30:F	Diabetic neuropathy	Yes	333.2
11	48:M	Sympathetically maintained pain	Yes	408.2
12	39:F	Diabetic radiculopathy	Yes	408.2
13	57:F	Meralgia paresthetica	Yes	191.6

below) are shown in Figure 1. The graded dose-response curve is described using logarithmic regression analysis by the equation: $y = 18.845 - 43.946 \cdot \log(x)$; $R^2 = 0.968$. The data point for the 500-mg dose of lidocaine (median visual analog pain score = 0) was excluded in the regression analysis as a median pain score of 0 was already achieved at a lidocaine dose of 416.5 mg.

The quantal dose-response relationship for IV lidocaine is shown in Figure 2. This relationship is described using quadratic regression analysis by the equation:

$$\% \text{ patients with complete analgesia} = -9.8 - (0.062 \times \text{dose}) + (0.0006 \times \text{dose}^2);\ R^2 = 0.93.$$

Using this equation, the ED_{50} was calculated to be 372.0 mg of lidocaine. This agrees quite well with the mean calculated dose of lidocaine (374.9 mg ± 22.7) at the time complete analgesia was achieved.

The slope of the linear portion of the quantal dose-response curve for IV lidocaine is extremely steep (Fig. 2). The difference between the ED_{50} (372.0 mg) and the ED_{90} (416.5 mg) was 44.5 mg of lidocaine (5.3 min of infusion). The difference between the ED_{20} (330.0 mg) and the ED_{90} (the end-points of the linear portion of the dose-response curve) was 86.5 mg of lidocaine (10.4 min of infusion).

A plot of lidocaine concentration as a function of time of infusion is shown in Figure 3. There was appreciable variation in the lidocaine concentrations in whole blood at each time point. (CV at each time point ≈ 0.3)

Concentration-effect curves were prepared individually for each patient (Fig. 4) and for the group as a whole (Fig. 1). Examination of individual concentration-effect curves defined two types of plots (Fig. 4): (a) curves with a precipitous decrease in pain score over a narrow concentration range with or without the immediate onset of analgesia ($n = 10$), and (b) partial analgesic response curves with a similar, abrupt decrease in pain score over a narrow concentration range ($n = 3$). The plot for the entire group of patients demonstrated that pain scores decreased rapidly over a narrow concentration range of 0.62 μg/mL of lidocaine (Fig. 1).

The total serum concentration of lidocaine at the initial onset of analgesia (2.43 μg/mL ± 1.01) was highly variable (CV = 0.42). The total serum concentration of lidocaine at the time of onset of complete analgesia (3.79 μg/mL ± 1.00) was less variable (CV = 0.26) (Table 2). The mean difference between the lidocaine concentration associated with the initial onset of analgesia and complete analgesia ($[\text{Serum}]_{\text{complete analgesia}} - [\text{Serum}]_{\text{onset}}$) (a measure of the range of analgesic concentrations) was 1.32 μg/mL ± 0.69 (CV = 0.52) (Table 2). Thus the range of the analgesic concentrations between the initial onset of analgesia and the onset of complete analgesia was appreciable and highly variable.

The free concentration of lidocaine at the initial onset of analgesia (0.67 μg/mL ± 0.26) was also highly variable (CV = 0.4), although variability diminished by the onset of complete analgesia (1.28 μg/mL ± 0.35; CV = 0.28) (Table 2). The mean difference between the free lidocaine concentration associated with the initial onset of analgesia and complete analgesia ($[\text{Free}]_{\text{complete analgesia}} - [\text{Free}]_{\text{onset analgesia}}$) was 0.60 μg/mL ± 0.34 (CV = 0.57) (Table 2).

Mean percent protein binding at the time of initial onset of analgesia and at time of onset of complete analgesia were, respectively, 68.5% ± 5.1% (range = 61.0%–75.1%) and 62.9% ± 8.8% (range =

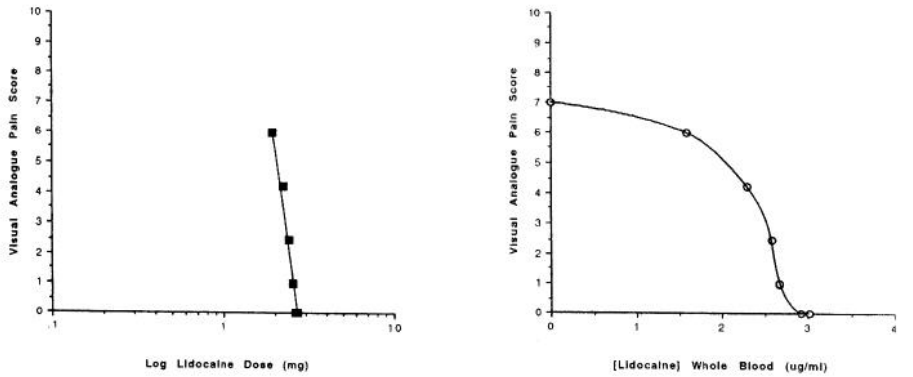

Figure 1. Graded dose-response and concentration-effect curves for entire group. (Lines in the figure represent computer-modeled interpolation, not regression analyses.)

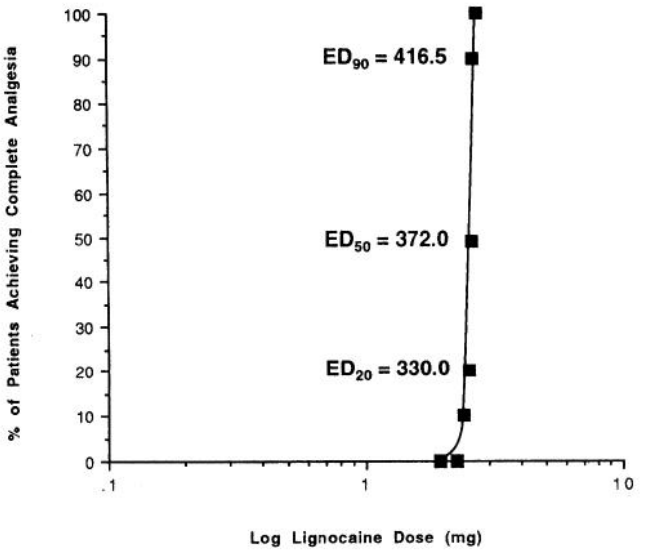

Figure 2. Quantal dose-response curve. The slope of the linear portion of the dose-response curve for intravenous (IV) lidocaine (lignocaine) is extremely steep and almost reminiscent of an "all-or-none" phenomenon. The analgesic action of IV lidocaine is best characterized by an abrupt "break" in neuropathic pain. Large increases in pain relief are achieved for very minimal increases in dosage.

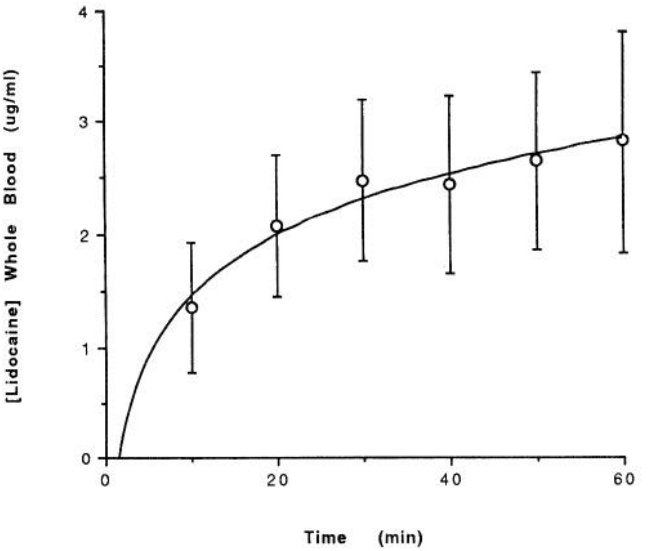

Figure 3. Lidocaine concentration versus time of infusion. There was appreciable variation in the lidocaine concentrations in whole blood at each time point. (SD bars are shown.) The coefficients of variation at each time point are, respectively, 0.0, 0.38, 0.27, 0.27, 0.31, 0.28, 0.35.

52.7%–77.4%). Both ranges of protein binding are consistent with previously published norms for lidocaine over the concentration range of the samples (10). There was little interpatient variability in the degree of protein binding at initial onset of analgesia and when complete analgesia was achieved (both CV = 0.10). The difference in the degree of protein binding between the two time points was statistically significant ($P < 0.04$), coinciding with the usual increase in the free lidocaine concentration as higher drug concentrations are achieved (10).

Scoring of the McGill Pain Questionnaire before and after receiving an infusion of IV lidocaine demonstrated an analgesic effect (Table 3) ($P < 0.008$). However, a significant analgesic effect was not seen at 1 and 2 wk postinfusion. The effect of analgesia upon performance of activities of daily living was measured by the Multidimensional Pain Inventory. No significant effect was found upon performance of activities of daily living at 1 and 2 wk postinfusion.

One patient exhibited vertical nystagmus after 20 min of infusion ($[\text{lidocaine}]_{\text{whole blood}} = 1.20\ \mu g/mL$). No other abnormality was noted in any of the neurologic examinations.

With respect to subjective responses, 6 of 13 patients reported light-headedness at some time during the infusion. The range of lidocaine concentrations in whole blood was 0.95 $\mu g/mL$ to 3.08 $\mu g/mL$. Light-headedness resolved spontaneously in two patients. Two patients complained they felt "drunk" (whole blood lidocaine concentrations = 1.50 $\mu g/mL$ and 4.01 $\mu g/mL$), although appearing to be alert and oriented. Two patients appeared somewhat sedated (whole blood lidocaine concentrations = 2.34 $\mu g/mL$ and 4.01

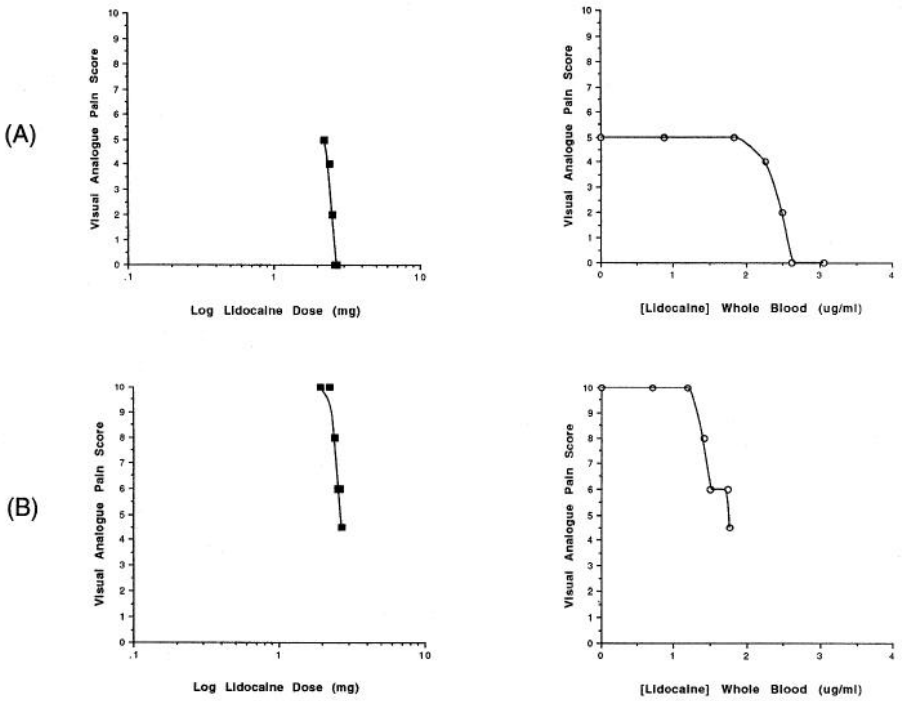

Figure 4. Graded dose-response and concentration-effect curves for two representative patients (A and B). (Lines in the figure represent computer-modeled interpolation, not regression analyses.) The slopes of both types of plots were steep for all individual patients, irrespective of the attainment of complete analgesia.

Table 2. Blood and Serum Concentrations, and Temporal and Dosage Characteristics of the Analgesic Response

	n	Mean (μg/mL) (unless otherwise specified)	Coefficient of variation	Range (μg/mL) (unless otherwise specified)
$[Serum]_{onset}$	13	2.43 ± 1.01	0.42	0.97–3.79
$[Serum]_{complete\ analgesia}$	10	3.79 ± 1.00	0.26	1.60–5.27
$[Serum]_{complete\ analgesia} - [Serum]_{onset}$	10	1.32 ± 0.69	0.52	0.41–2.65
$[Free]_{onset}$	13	0.67 ± 0.26	0.40	0.30–1.11
$[Free]_{complete\ analgesia}$	10	1.28 ± 0.35	0.28	0.70–1.69
$[Free]_{complete\ analgesia} - [Free]_{onset}$	10	0.60 ± 0.34	0.57	0.0–0.95
$Time_{onset}$	13	14.8 min ± 6.6	0.40	5–25 min
$Time_{complete\ analgesia}$	10	45.0 min ± 8.6	0.20	23–53 min
$Dose_{onset}$	13	123.0 mg ± 0.55	0.45	41.7–441.5 mg
$Dose_{complete\ analgesia}$	10	374.9 mg ± 22.7	0.19	191.6–441.4 mg

μg/mL). At no time was it necessary to adjust patients' rate of infusion because of subjective complaints of toxicity.

Discussion

The results of this study demonstrate that the analgesic response to IV lidocaine in the treatment of neuropathic pain is characterized by large increases in pain relief for very minimal increases in dosage and blood concentration. The slopes of both the graded dose-response curve (entire group; Fig. 1) and quantal dose-response curve (linear portion; Fig. 2) were very steep. The slope of the linear portion of the quantal dose-response curve was almost reminiscent of an "all-or-none" phenomenon. The difference between the ED_{50} (372.0 mg) and the ED_{90} (416.5 mg) was 44.5 mg of lidocaine (5.3 min of infusion). The concentration-effect relationship was also steep with pain scores abruptly decreasing over a range of 0.62 μg/mL of lidocaine (Fig. 1).

Free drug concentration is generally regarded as a more accurate reflection of the active concentration (5). In the present study, the free concentration of lidocaine had no better correlation with the onset of analgesia or the attainment of complete analgesia than

Table 3. Psychometric Test Scores

Psychometric test	Preinfusion	Postinfusion	1 wk postinfusion	2 wk postinfusion
Short-form McGill Pain Questionnaire	1.33 (0.13–2.40)	0 (0–1.2)	1.07 (0.7–2.07)	1.2 (0.13–2.33)
Multidimensional Pain Inventory	1.54 (0.00–4.00)	Not performed	1.81 (0.00–3.53)	1.68 (0.00–2.93)

Values are presented as median with range.

the serum concentration of lidocaine (see respective CVs, Table 2). This suggests that the mechanism of analgesia to IV lidocaine may not be based upon a conventional concentration-effect relationship. It is worthy of note that the lack of correlation between plasma concentrations and the symptomatic effect of oral mexiletine (a lidocaine cogener) previously was discounted as a false-negative result (11). Yet, the work of Brose and Cousins (12) suggests that target blood concentrations may be important in achieving analgesia with continuous subcutaneous infusions of lidocaine, though free lidocaine concentrations were not measured.

Steady-state concentrations were not achieved in the present study because of the use of a fixed-rate infusion, which allowed definition of dose-response relationships and examination of concentration-effect relationships over a range of lidocaine concentrations. However, the relationship of free drug concentration, as a more accurate reflection of the active concentration, should have held, irrespective of the attainment of steady-state concentrations, as lidocaine concentrations were increasing relatively slowly, particularly at the time of attainment of complete analgesia.

Several authors have documented the production of protracted analgesia (days to weeks) with administration of IV lidocaine (2,4,13) which also suggests the presence of an unconventional pharmacodynamic response to blood or serum concentrations of lidocaine as the half-life of lidocaine is only 1.6 h (5). In the present study, the production of protracted analgesia was examined by administration of the short-form McGill Pain Questionnaire, and any concomitant increase in functional activity was assessed using the Multidimensional Pain Inventory. There was no evidence of protracted analgesia or an increase in functional activity when measured at 1 and 2 wk postinfusion. This is in contrast to the study of Edwards et al. (2) where 33% of patients responding to IV lidocaine had pain relief of greater than 1 wk duration. The reasons for this discrepancy are obscure, but are perhaps related to the smaller number of patients ($n = 13$) in this preliminary study examining blood concentrations as compared to the larger descriptive study of Edwards et al. (2) ($n = 211$).

Similar to the findings of Edwards et al. (2), Galer et al. (14), and Rowbotham et al. (15), certain patients did not achieve complete analgesia. The reasons for their partial analgesic responses are also obscure. Would administration of greater quantities of lidocaine have achieved a complete response? Certainly, the partial analgesic responses cannot be attributed to higher initial intensities of pain (Table 1) or a preponderance of central or peripheral pathologies in these incomplete responders (Table 1). [Various authors have suggested the predominance of central (1,13,16) versus peripheral (17) analgesic mechanism(s) for IV lidocaine as its site of action is not clear. No conclusions regarding the predominance of one mechanistic site or another can be drawn from the present findings due to the small total number of patients and the preponderance of patients with a probable peripheral origin for their pain.]

A possible criticism of this preliminary study is the lack of methodology to exclude placebo responders. Patients included in this study were referred to the Pain Center specifically to receive infusions of IV lidocaine as it is a conventional therapy for the treatment of neuropathic pain. Regardless of a response to a placebo infusion, patients would have received IV lidocaine as therapy for their neuropathic pain. Thus we thought it unwise to include placebo infusions (18).

In summary, the results of this study suggest that large increases in analgesic response are achieved for very minimal increases in dosage when IV lidocaine is used for the treatment of neuropathic pain. The slopes of both the graded (entire group) and quantal (linear portion) dose-response curves were very steep. The slope of the linear portion (ED_{20} [330.0 mg] through ED_{90} [416.5 mg]) of the quantal dose-response curve was almost reminiscent of an "all-or-none" phenomenon (Fig. 2). The concentration-effect relationship was also steep, with pain scores abruptly decreasing over a range of 0.62 μg/mL of lidocaine (Fig. 1). The free concentration of lidocaine was no better correlated with the onset of analgesia or the attainment of complete analgesia than the serum concentration of lidocaine. This suggests that the pharmacodynamic response to IV lidocaine may not be predicated upon a conventional concentration-effect relationship. Corroboration of this hypothesis and elucidation of its implications are important topics for further research. In conclusion, the results of this study suggest that the analgesic response to IV lidocaine for the treatment of

neuropathic pain of varying etiology was best characterized by an abrupt "break in pain" over a narrow dosage and concentration range.

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