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Intravenous Lidocaine Relieves Spinal Cord Injury Pain

A Randomized Controlled Trial

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Background: **Neuropathic pain in spinal cord injury is a common challenging therapeutic condition. The current study examines the analgesic effect of the sodium channel blocker lidocaine on neuropathic pain in patients with spinal cord injury and the predictive role of concomitant evoked pain on pain relief with lidocaine.**

Methods: **Twenty-four spinal cord injury patients with neuropathic pain at or below the level of injury were randomized and completed a double-blind crossover trial of 5 mg/kg lidocaine and placebo infused over 30 min. Twelve patients reported evoked pain, and 12 patients had no evoked pain. Spontaneous and evoked pains were assessed using a visual analog scale and quantitative sensory testing.**

Results: **Lidocaine significantly reduced spontaneous pain in all patients ($P < 0.01$) and in each of the two groups with ($P < 0.01$) and without ($P = 0.048$) evoked pain, with no difference in number of responders (pain reduction ≥ 33%) between the patients with (n = 6) and without (n = 5) evoked pain. Lidocaine significantly relieved both at-level and below-level neuropathic pain and decreased brush-evoked dysesthesia but not cold allodynia, pinprick hyperalgesia, or pain evoked by repetitive pinprick.**

Conclusions: **Lidocaine reduced neuropathic pain at and below the level of injury irrespective of the presence or absence of evoked pain. Results are consistent with a central-acting effect of sodium channel blockers acting on neuronal hyperexcitability. Agents (such as anticonvulsants or antiarrhythmics) with sodium channel–blocking properties may be a treatment option for spinal cord injury pain.**

NEUROPATHIC pain following spinal cord injury (SCI) is divided into neuropathic pain at the level of injury and neuropathic pain below the level of injury.[1] The exact mechanisms underlying SCI neuropathic pain are not known and may be different for at-level and below-level pain.[2] Below-level neuropathic pain is considered secondary to a central nervous system lesion, whereas at-level pain may be a consequence of either a spinal cord lesion or a segmental peripheral injury.[1] Recent studies have suggested a pain "generator" located in the vicinity of the spinal cord lesion to be involved in both at-level and below-level neuropathic pain. For example, experimental studies in rats by Vierck and Light[3] showed that anterolateral white matter lesions resulted in pain behavior caudal to the spinal lesion only when accompanied by gray matter damage. Based on this observation, it was suggested that excitatory input from around the gray matter zone play a role for central pain.[4] Similarly, in humans, based on sequential magnetic resonance imaging sections of the spinal cord, it has been found that patients with pain below lesion level have larger gray matter lesions at the rostral end of the lesion than pain-free patients.[5] Taken together, these findings suggest that gray matter lesions may give rise to a neuronal hyperexcitability that expresses itself as sensory hypersensitivity at the level of injury and plays a role for the pain felt below an injury. Ablation of spontaneous and evoked activity in the dorsal root entry zone rostral to a spinal cord injury with relief of below-level pain lends further support to the notion of a spinal pain generator.[6,7]

Interest has been directed at the molecular mechanisms underlying potential pain generators.[8–11] Among these, increased and abnormal sodium channels are known to be a source of neuronal hyperexcitability.[12] Recently, an experimental study demonstrated expression of abnormal sodium channels on dorsal horn neurons close to a spinal cord lesion, which was functionally linked to neuronal hyperexcitability and central pain behaviors.[13] A role for such sodium channels and neuronal hyperexcitability in central pain in humans can be tested pharmacologically using sodium channel blockers such as lidocaine.[14,15] In a previous study, it was suggested that sodium channel blockers may be more effective in patients with evoked pain.[16] Lamotrigine, acting on voltage-sensitive sodium channels and inhibiting sodium influx–mediated pathologic release of glutamate, was suggested to have a pain-relieving effect in patients with incomplete spinal lesion exhibiting clinical signs of allodynia.

This study tested the effect of lidocaine in SCI pain, and, based on the observation that clinical signs of neuronal hyperexcitability in spinal cord injury could play a role for neuropathic pain, we specifically raised the question whether the lidocaine response is different in spinal cord injury with and without evoked pain.

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Materials and Methods

Patients

Patients were recruited for the study from September 2002 to August 2003 from the two spinal cord units in Denmark and the Pain Clinic at Aarhus University. The study was approved by the local ethical committee for the county of Aarhus, Aarhus, Denmark (No. 20020119); the Danish Data Protection Agency, Copenhagen, Denmark (No. 2002412065); and the Danish Medicines Agency, Copenhagen, Denmark (No. 2612–2018). The study was performed in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and monitored by the Good Clinical Practice unit of Aarhus University, and all patients gave informed written consent. Patients aged 18 yr or older with neuropathic pain due to trauma or disease of the spinal cord or cauda equina with a median pain intensity of 3 or more on a 0- to 10-point numeric rating scale during a 1-week baseline period were eligible for the study. Other reasons for pain were either excluded or considered highly unlikely. Patients were excluded for any of the following reasons: known concomitant cerebral damage or dementia (total score on the Mini-Mental State Examination a.m. Folstein below 26), pregnancy or lactation, alcohol or substance abuse, mental disease, hypersensitivity to lidocaine, cardiac or circulatory disease, or severe nephropathy (glomerular filtration rate below 35 ml/min). Patients taking sodium channel blockers and antidepressants were slowly tapered off during a prestudy period of at least 1 week before the baseline period. Concomitant treatment with spasmolytics (baclofen and tizanidine), gabapentin, opioids, and simple analgesics (nonsteroidal antiinflammatory drugs, paracetamol, or acetylsalicylic acid) for pain was allowed in a constant and unchanged dose during the trial. On the day of examinations, patients were asked not to take any of the above-mentioned drugs, although they were allowed provided they took the same dose on the two treatment sessions.

Group Assignment

Patients were assigned to one of two groups: a group with and a group without evoked pain based on the presence or absence of brush-evoked allodynia, cold allodynia, or pinprick hyperalgesia. Brush-evoked allodynia was defined as pain evoked by stroking the skin twice with a small brush at a rate of 1–2 cm/s, cold allodynia was defined as pain evoked by a thermal roll of 20°C and a cold pain threshold below 20°C using the Somedic Thermotest (Somedic AB, Hörby, Sweden), and pinprick hyperalgesia was defined as more pain than above the injury level evoked by bending a von Frey hair (No. 5.88, bending force 75.9 g/745 mN; Semmes-Weinstein monofilaments, Stoelting, IL).[17]

Study Design

The study was designed as a randomized, double-blind, placebo-controlled, crossover trial. Before drug treatment, a medical history and a full neurologic and physical examination using quantitative sensory testing were obtained. Pain patients completed the Danish version of the McGill Pain Questionnaire.[18,19] Spinal lesions were classified according to the American Spinal Injury Association's standards for classification of SCI.[20] Spasticity was assessed by the investigator as a combined score of muscle tone (in hip, knee, and ankle joints) using the Ashworth scale[21] and a clinical grading of tendon reflexes (patellar and Achilles tendon).[22]

A 1-week baseline period was followed by two treatment sessions separated by at least 6 days and followed by a 1-week period. Identical 250-ml infusions of lidocaine (5 mg/kg) or saline (0.9% NaCl) were administered intravenously over a 30-min period. Blood pressure and an electrocardiogram were monitored throughout the experiment.

Randomization and Blinding Procedure

Assignment to treatment sequence was random *via* a computer-generated randomization list with a block size of four and consecutive allocation of patients as they entered the study. One randomization list was prepared for each of the two groups (with and without evoked pain). One investigator (N. B. F.) was provided with sealed code envelopes, one for each patient, containing information on the treatment given, and envelopes were returned unopened to the monitor after study termination.

The primary outcome measure and pain relief was evaluated by an investigator (A. J. T.) unaware of symptomatology, group assignment, and possible adverse effects. While the primary investigator (N. B. F.) left the room, A. J. T. entered and asked the patient about spontaneous pain, and the patient was told not to report anything else (such as adverse effects) to A. J. T. In performing the clinical examination, quantitative sensory testing, and evaluation of adverse effects, N. B. F. did not discuss changes in spontaneous pain with the patient.

Outcome Measures

Figure 1 shows the sequence of tests conducted. The patients scored their current spontaneous pain on a visual analog scale of 0–100 before and 25 and 35 min after the start of the infusion. The time for maximal effect of lidocaine infusion was unknown; therefore, the predefined primary outcome measures were (1) the change in pain score from baseline to the end of the infusion using the lowest of the two scores (at 25 and 35 min) calculated for the whole group and for each subgroup and (2) the difference in number of responders (patients with at least 33% pain reduction) between the two groups. Predefined secondary outcome measures were (1) pain relief for overall,

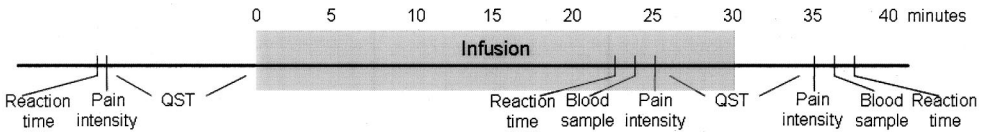

Fig. 1. Timetable. Pain intensity was measured as spontaneous ongoing pain on a visual analog scale (0–100 mm). Quantitative sensory testing (QST) performed in all 24 patients includes cold detection threshold measured at the cheek, evoked sensations to brush, single and repetitive pinprick, and cold pain threshold measured at and below injury level.

at-level, and below-level spontaneous pain (complete, good, moderate, slight, none, or worse); (2) median of daily pain on days between treatments and the first week after final treatment rated on a numeric rating scale of 0–10 using a pain diary; (3) effect on brush-evoked allodynia (pain) or dysesthesia (unpleasantness), cold allodynia, pinprick hyperalgesia, and pain to repetitive pinprick (with a 125.9-g von Frey hair at a rate of 2 Hz for 30 s) measured on a visual analog scale of 0–100 at and below injury level; and (4) effect on cold detection threshold measured at the cheek using the Thermotest. Reaction time to a light and sound stimulus was measured with a self-constructed reaction time detector as the mean of three measurements.[23] Adverse events were assessed using open-ended questions during and after infusions and by presenting patients a list of possible adverse events after infusion. Blinding was assessed by asking patients which intravenous drug treatment they believed they had and the reason for this.

Lidocaine Plasma Concentrations

Plasma concentration of lidocaine was examined from peripheral venous blood samples drawn at the end of each treatment period (at 24 min and approximately 37 min after the start of the infusion; fig. 1). All samples were stored at −20°C until they were analyzed by Ulf Bondesson, Prof., Ph.D., M.Sc. Pharm. (Department of Chemistry, National Veterinary Institute, Uppsala, Sweden). The quality-control samples for lidocaine analysis at 1,057 ng/0.5 ml (n = 5) gave a precision of 6.8%, and the limit of quantification was greater than 1.0 ng/ml.

Statistical Analysis

Differences in baseline data between groups were tested using the *t* test or the Mann–Whitney U test. The Fisher exact test was used to compare dichotomized data. Analyses were made on patients who achieved two treatments corresponding to at least 4.17 mg/kg (25 min) of lidocaine or the full dose of 5 mg/kg within 40 min and without major protocol violation. Missing data were not replaced. A responder was defined as a patient with a pain reduction of 33%.[24] Differences between treatments were evaluated by Kock's adaptation of the Wilcoxon signed rank test for paired data and the Mainland-Gart test for dichotomized data. The Hodges-Lehmann estimator was used for providing a point estimate with 95% confidence interval for the treatment effect. All *P* values given are two tailed. $P < 0.05$ was considered statistically significant for the primary outcome measure, and $P < 0.005$ was considered statistically significant for evoked pain (n = 10) according to a Bonferroni correction. Numbers needed to treat are given for 50% pain relief.[25] Considering a difference in spontaneous pain of at least 15 points on the 0- to 100-mm visual analog scale between the lidocaine and placebo treatments as clinically relevant and an SD of 18,[16] 12 patients were expected to be sufficient to obtain a statistical power greater than 80% ($\alpha = 0.05$).

Results

Patients

Twenty-six patients were enrolled, and 24 completed the trial (study population; fig. 2). Two patients dropped out before any treatment: one dropped out for personal reasons, and one was excluded because of a low pulse before the first treatment. Twelve patients similar in terms of age; American Spinal Injury Association classification; Functional Independence Measure[26]; spasticity score; duration, location, and description of pain; McGill Pain Questionnaire; and treatment (table 1) were included and treated in each group, with no withdrawals. Eight patients with evoked pain had a cervical or trigeminal neurologic level, and the group without evoked pain had nine patients with a thoracic level ($P = 0.01$, Fisher exact test), and the intensity of spontaneous pain was

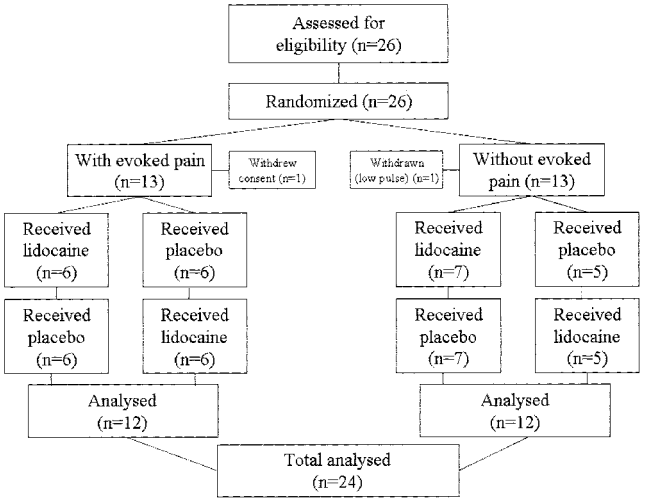

Fig. 2. Flowchart showing recruitment of spinal cord injury patients for the study.

Table 1. Clinical Characteristics of the Study Population

	Study Population		
	Patients with Evoked Pain	Patients without Evoked Pain	*P* Value
Number	12	12	1
Age, yr	51.5 (32–61)	54.5 (28–66)	0.79*
Sex, M/F	10/2	7/5	0.37†
Mechanism of spinal injury			
Traumatic (vehicle accident, fall, shooting)	8	7	1†
Disease (myelopathy, infection, AV malformation, abscess, metastasis)	4	5	
Neurologic level			
Cervical	8 (2 trigeminal)	1	0.01†
Thoracic	3	9	
Lumbosacral	1	2	
ASIA impairment scale			
A	0	5	0.08†
B	2	1	
C	2	1	
D	8	5	
Functional Independence Measure	120 (105–124)	117 (58–124)	0.19*
Spasticity score (0–64)	19.5 (12–48)	19 (0–34)	0.50*
Duration of pain, yr	4.5 (1–13)	6.5 (2–12)	0.48*
Pain intensity (numeric rating scale 0–10)	5.5 (3–9)	8 (4–10)	0.04*
Location of pain			
At level pain	11	6	0.07†
Below level pain	10	10	1
McGill Pain Questionnaire			
PRI (R), mean (SD)	37 (18–59)	29 (20–49)	0.52*
NWC, mean (SD)	16.5 (10–20)	14 (8–19)	0.07*
Pain descriptor			
Burning, scalding	12	11	1†
Tiring	10	12	0.48†
Pricking, tingling	10	9	1†
Shooting	8	5	0.41†
Treatment			
Spasmolytics	8	4	0.22†
Pain treatment	11	7	0.16†
Gabapentin	6	4	0.68†
Opioids, tramadol	8	3	0.10†
Simple analgesics	8	5	0.41†

Data are presented as number or median (range). Neurologic level: the most caudal segment of the spinal cord with normal sensory and motor function on both sides of the body.

* Mann–Whitney U test. † Fisher exact test.

ASIA = American Spinal Injury Association (A = complete, no sensory or motor function is preserved in the sacral segments S4–S5; B = incomplete, sensory but not motor function is preserved below the neurologic level and includes the sacral segments S4–S5; C = incomplete, motor function is preserved below the neurologic level and more than half of key muscles below the neurological level have a muscle grade of less than 3; D = incomplete, motor function is preserved below the neurologic level and at least half of key muscles below the neurologic level have a muscle grade of 3 or greater); AV = arteriovenous; NWC = total number of words chosen; PRI (R) = pain rating index (rank value).

significant higher in the group without evoked pain ($P = 0.04$, Mann–Whitney U test). Two patients were tapered off tricyclic antidepressants before the baseline week, whereas 22 patients continued their usual medication. Before entering the study, 14 patients had tried antidepressants, 13 patients had tried sodium channel blockers (lamotrigine, oxcarbazepine), 11 patients has tried opioids, and 6 patients had tried gabapentin but had stopped because of either lack of effect or adverse effects.

Twenty-three patients received the full dose of 5 mg/kg lidocaine in 30 min, and one patient (patient 18) received only 4.75 ml/kg in 28.5 min because of adverse effects.

Primary Outcome Measures

Types of evoked responses and pain scores of individual patients are presented in table 2. Lidocaine significantly reduced pain compared with placebo in the total sample of SCI patients ($P < 0.01$, Kock's adaptation of the Wilcoxon signed rank test) and in the groups with ($P < 0.01$) and without ($P = 0.048$) evoked pain (fig. 3). The median difference in pain reduction (95% confidence interval) between lidocaine and placebo was 36% (18–50%) in the total group of 24 patients, 40% (13–58%) in the group with evoked pain, and 35% (9–59%) in the group without evoked pain. In the total group, nine patients obtained 50% pain relief during lidocaine, and one obtained 50% pain relief during placebo, *i.e.*, number needed to treat for 50% pain relief is 3 (CI, 1.8–8.1); in the group with evoked pain, five responded to lidocaine and none responded to placebo, giving a number needed to treat of 2.4 (CI, 1.4–7.3); and in the group without evoked pain, four responded to lidocaine and one responded to placebo, giving a number needed to treat of 4 (CI, 1.8–∞). Significantly more patients were responders (with at least 33% pain reduction) to lidocaine (n = 11) than to placebo (n = 2) ($P = 0.008$, Mainland-Gart test; fig. 4). There was no difference in number of responders between the group with (six patients) and without (five patients) evoked pain ($P = 1.0$, Fisher exact test; fig. 4).

Secondary Outcome Measures

Nineteen patients reported pain relief during lidocaine treatment, and 4 reported pain relief during placebo ($P < 0.01$, Mainland-Gart test; fig. 5). Twelve patients obtained relief of their at-level pain during lidocaine compared with none during placebo ($P < 0.01$, Mainland-Gart test), and 12 patients obtained relief of their below-level pain during lidocaine compared with 4 during placebo ($P = 0.018$, Mainland-Gart test; fig. 5). Ten patients presented with below-level pain and no allodynia, and of these, 7 obtained relief of their below-level pain during lidocaine compared with 3 during placebo, a nonsignificant difference ($P = 0.5$, Mainland-Gart test).

There was no difference in median pain intensity the week after each treatment ($P = 0.45$, Kock's adaptation of the Wilcoxon signed rank test; data available for 19 patients).

Lidocaine significantly reduced brush-evoked dysesthesia at the level of injury ($P = 0.002$, Kock's adaptation of the Wilcoxon signed rank test), whereas reduction of

Table 2. Evoked Sensations and Intensity of Spontaneous Pain during Lidocaine and Placebo

	Evoked Sensations				Lidocaine VAS (0–100 mm)		Placebo VAS (0–100 mm)	
Patient No.	Brush	Pinprick	Repetitive Pinprick	Cold	Baseline	Lowest at the End of Infusion	Baseline	Lowest at the End of Infusion
Patients with evoked pain								
1	dys	+	+	−	77	69	74	70
2	dys	+	−	+	46	20	81	81
3	dys	+	+	−	32	21	18	7
4	+	+	−	−	84	74	89	91
5	dys	+		−	18	11	18	13
6	dys	+	+	+	100	96	99	100
7	+	+	+	+	24	5	65	51
8	+	−	+	−	24	12	6	8
9	dys	+	+	+	49	36	49	49
10	−	−	−	+	56	11	100	100
11	+	+	+	+	36	34	27	26
12	dys	+	+	+	45	35	30	46
Patients without evoked pain								
13	−	−	−	−	97	16	97	73
14	−	−	−	−	57	0	49	46
15	−	−	−	−	34	14	29	34
16	−	−	−	−	48	15	40	42
17	−	−	−	−	51	40	58	58
18	−	−	−	−	47	37	43	44
19	−	−	−	−	100	80	65	83
20	−	−	−	−	81	83	74	75
21	−	−	−	−	78	51	93	45
22	−	−	−	−	70	72	92	91
23	−	−	−	−	72	73	67	72
24	−	−	−	−	44	31	51	50

dys = dysaesthesia; VAS = visual analog scale; + = present; − = absent.

evoked pains tested did not reach significance (after Bonferroni correction, n = 10). We could not demonstrate a correlation between effects on brush-evoked dysesthesia at the level of injury and effects on spontaneous pain below injury level, but only seven patients presented with both symptoms during lidocaine infusion. There was no difference in cold detection threshold ($P = 0.83$, Kock's adaptation of the Wilcoxon signed rank test).

Other Measurements

There was no difference in number of responders to lidocaine between patients with complete (n = 5) and incomplete (n = 19) SCI ($P = 1.0$, Fisher exact test). There was a statistically significant increase in reaction time from baseline to 25 min from the start of the

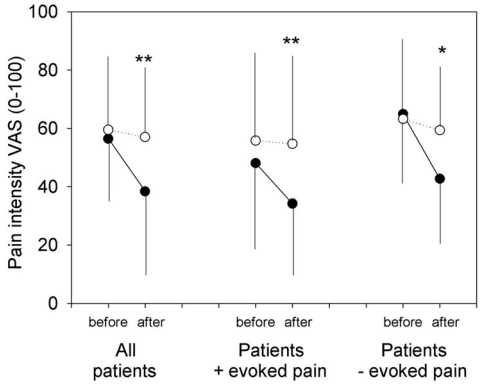

Fig. 3. Intensity of spontaneous ongoing pain (visual analog scale [VAS], 0–100) before and by the end of (after) the 30-min lidocaine (*closed circles*) and placebo (*open circles*) infusion. Presented for all patients (n = 24) and for the subgroups of patients with (n = 12) and without (n = 12) evoked pain and expressed as mean ± SD. * $P < 0.05$, ** $P < 0.01$, change during lidocaine compared with change during placebo, Kock's adaptation of the Wilcoxon signed rank test.

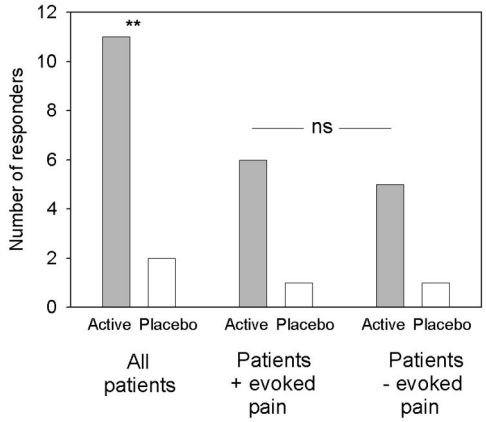

Fig. 4. Number of responders (patients with at least a 33% pain reduction from baseline to end of treatment) for all patients (n = 24) and for the subgroups of patients with (n = 12) and without (n = 12) evoked pain. ** $P < 0.01$, Mainland-Gart test, Fisher exact test. ns = nonsignificant.

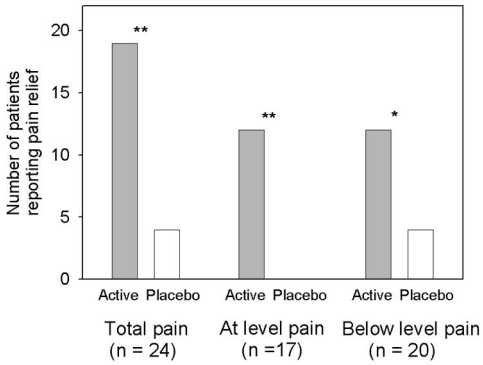

Fig. 5. Number of patients reporting pain relief of their total pain, at-level pain, and below-level pain during lidocaine (*closed bars*) and placebo (*open bars*). *$P < 0.05$, ** $P < 0.01$, Mainland-Gart test.

infusion (change [median (range)]), from 0.24 s (0.18–0.46 s) to 0.26 s (0.20–0.42 s) during lidocaine compared with 0.24 s (0.17–0.39 s) to 0.24 s (0.17–0.35 s) during placebo ($P = 0.007$, Kock's adaptation of the Wilcoxon signed rank test), but not to 35 min, from 0.24 s (0.18–0.46 s) to 0.25 s (0.18–0.39 s) during lidocaine and from 0.24 s (0.17–0.39 s) to 0.24 s (0.17–0.40 s) during placebo ($P = 0.07$).

Adverse Events

Nineteen patients during lidocaine and one during placebo experienced adverse effects (table 3). Forty-nine adverse effects were rated as only mild, and three were rated as moderate. All five patients without adverse effects to lidocaine were nonresponders. There was a significant increase in blood pressure (from mean 129/77 [95% CI, 121–137/73–80] to 139/85 [130–148/82–89] during lidocaine and 127/77 [120–133/73–82] to 130/77 [122–136/73–81] during placebo) and pulse (from 68 [64–72] to 71 [67–75] during lidocaine and 66 [63–70] to 66 [63–69] during placebo) during lidocaine infusion ($P < 0.05$, paired t test).

Plasma Concentration

There was no correlation between maximal plasma concentration and maximal pain relief or pain intensity, and the mean (range) maximal plasma concentration was 4.2 μg/ml (2.4–8.0 μg/ml) in nonresponders and 3.2 μg/ml (1.5–4.1 μg/ml) in responders ($P = 0.13$, t test).

Table 3. Adverse Effects during Lidocaine and Placebo Treatment

Adverse Effect	No. of Patients	
	Lidocaine	Placebo
Any adverse effect	19	1
Somnolence	11	1
Dizziness	7	0
Dysarthria	7	0
Lightheadedness	7	0
Blurred vision	3	1
Tremor	0	0
Other (*e.g.*, unpleasantness, light headache, warmth, dry mouth)	15	0

Assessment of Blinding

Twenty one patients (88%) correctly identified the period in which they were receiving active treatment, one identified the wrong period, and two were unable to choose one period over another. Among the 21 patients who identified the right treatment, the reason for choosing that period was pain relief in nine patients, adverse events in four, and both pain relief and adverse events in eight. The 12 patients who chose the right treatment because of adverse events had the same analgesic response as the other 12 patients (median difference in pain [range] was 11.5 [−2 to 45] *versus* 11.5 [−2 to 81]; $P = 0.79$, Mann–Whitney U test). The investigator (A. J. T.) correctly identified the right treatment based on adverse effects in only 1 of the 24 patients.

Discussion

This randomized, placebo-controlled, crossover trial of the sodium channel blocker lidocaine showed a statistically significant effect on spontaneous neuropathic pain in patients with spinal cord injury independent of the presence or absence of evoked pain. Furthermore, lidocaine relieved neuropathic pain both at and below the level of injury, suggesting that lidocaine has an effect on central pain–generating mechanisms.

Our previous study suggested that a sodium channel–blocking agent (lamotrigine) had an effect on spontaneous pain in patients with evoked pain but not in those without evoked pain.[16] This suggests that treatment and mechanisms of this pain condition are different in patients with and without pain. This is the first trial designed to study whether a sodium channel–blocking agent is more effective in patients with evoked pain. We chose intravenous lidocaine to test this hypothesis because it has relatively specific mechanisms of action. Although glycinergic actions or blocking of *N*-methyl-D-aspartate, substance P, and acetylcholine receptors have been suggested, the reversible sodium channel blockade is considered the major mechanism of analgesia.[27] The current study could not demonstrate a differential effect of sodium channel blockade on spontaneous pain depending on the presence or absence of evoked pain as suggested by studies with lamotrigine.[16] Pharmacologic actions of lamotrigine and lidocaine differ; it is possible that the effect of lamotrigine in spinal cord injury patients with neuropathic pain and evoked pain is due to the additional antiglutamatergic action of lamotrigine. In the current study with lidocaine, there was a tendency toward a better effect in the group with evoked pain,

and baseline pain intensity was higher in the group without evoked pain than in the group with evoked pain, which may mask a possible difference between the two groups. Therefore, although not supported by this study, the presence of mechanical allodynia has been suggested to be predictive of the response to intravenous lidocaine in patients with peripheral neuropathic pain,[28] and careful classification of pain and sensory disturbances in future trials are important to further evaluate this matter and to develop a mechanism-based classification.

High plasma concentrations of lidocaine have a high risk of causing adverse effects. We chose a dose of 5 mg/kg, which previously was found to relieve central pain in patients with brain and spinal cord injuries,[14] whereas 2.5 mg/kg had no effect on below-level pain in spinal cord injury patients.[15] Adverse effects may unblind the patient, thereby giving a false treatment effect, although an increase in pain relief would be expected to be similar in patients with and without evoked pain. An active placebo would help to blind the patient, but we chose not to use an active placebo because central pain mechanisms have not been fully elucidated. The introduction of an active placebo, such as γ-aminobutyric acid agonists, may therefore be problematic if the drug has analgesic effects, if used alone or as an add-on to the active drug used. However, we think that blindness of the study was retained. Efforts were made to blind the investigator (see Materials and Methods section). Most of the adverse effects were mild, including sedation, dizziness, and lightheadedness, and in some cases, the patients related these effects to just lying down. We assessed the success of blinding using a method previously described,[14] although other measures may be used (*e.g.*, by assessing how many could identify the right treatment). We compared the 12 patients who recognized the right treatment because of adverse effects or both adverse effects and pain relief to the 12 patients who did not identify the right treatment because of adverse effects. These two groups had the same analgesic response, suggesting that blinding was preserved. Also, there was no difference in cold detection threshold measured above the lesion level, which supports an analgesic effect of lidocaine because this measure includes a reaction from the patient.

Lidocaine may exert its action both centrally and peripherally, and reduction of central pain, such as central poststroke pain[14] and spinal cord injury,[14] strongly supports the hypothesis that lidocaine produces its effect centrally. In the current study, we show that lidocaine has an equal effect on pain in those with and without allodynia. Based on the lidocaine effect in patients without allodynia together with the observation that lidocaine in a dose of 5 mg/kg does not affect peripheral conduction,[14,29] we suggest that the current analgesic effect is a central rather than a peripheral effect. The role of peripheral input on central neurons in below-level pain cannot be excluded, but the fact that lidocaine in the current study relieved below-level spontaneous pain favor the hypothesis that the effect is exerted centrally. A central effect of lidocaine and other local anesthetics is supported by experimental studies. These drugs have the ability to reduce spinal-mediated nociceptive withdrawal reflexes in animals[30] and humans,[29] to suppress dorsal horn wide-dynamic-range neurons in the spinal cord after peripheral nerve injury[31] and spinal injury,[32] to reduce *N*-methyl-D-aspartate and neurokinin receptor–mediated postsynaptic depolarization of spinal neurons,[33] and to attenuate allodynia in neuropathic rats when injected into the rostroventromedial medulla and the periaqueductal gray.[34]

At therapeutic concentrations, lidocaine affects hyperexcitable neurons without affecting normal nerve conduction. The high susceptibility of hyperexcitable neurons to lidocaine may be explained by their frequency dependency but also by the changed expression of sodium channels during nerve injury, which may render them subject to exaggerated blockade by lidocaine.[27] This supports the thoughts that the anatomical target of sodium channel blockers in central pain is related to suppression of ectopic discharges from injured neurons in the spino-thalamo-cortical pathway,[14,35] caused in part by altered expression of sodium channels. Whether lidocaine exerts its effect at the spinal or cerebral level cannot be determined from this study. A recent study demonstrated that the tetrodoxin-sensitive $Na_v1.3$-type sodium channel is up-regulated in dorsal horn sensory neurons in segments below a contusion SCI[13] and that $Na_v1.3$ functionally contributes to the hyperexcitability of dorsal horn sensory neurons after SCI and to mechanical allodynia and thermal hyperalgesia below the injury level. Therefore, one possible site of action of lidocaine is abnormal sodium channels at the dorsal horn.

Modality specific effects of lidocaine have previously been found.[14,36] In the current study, lidocaine alleviated brush-evoked dysesthesia but not brush-evoked pain (allodynia) and pain evoked by cold, single, or repetitive pinprick. The current study did not have the power to study differences in evoked pain, and the number of patients experiencing each of these may be too low to conclude that lidocaine is ineffective in relieving certain types of evoked pain.

A plasma concentration–dependent decrease in pain has previously been reported in peripheral nerve injury for lidocaine concentrations up to 2.5 μg/ml.[37] The lack of a positive correlation between pain relief and plasma concentration of lidocaine in the current study may be due to higher plasma concentrations, which may then be in a range where the dose–effect relation has reached a plateau. Consistent with this observation, in postherpetic neuralgia, lidocaine in doses of 5 mg/kg signifi-

cantly relieved pain without a correlation between relief and plasma concentrations.[38]

In conclusion, the current results demonstrate that sodium channel blockade can relieve spinal cord injury neuropathic pain independent of the presence or absence of evoked pain. Lidocaine relieved below-level neuropathic pain and at-level pain, suggesting a central action of the drug. Although long-term effects of intravenous lidocaine are reported,[39] lidocaine is usually not suited for long-term treatment, and mexiletine, the oral analog of lidocaine, does not seem to be effective in tolerated doses.[14,40,41] However, the study does suggest a role of agents with sodium channel blocker properties (such as anticonvulsants) in the treatment of this pain condition and also in patients without evoked pain. The development of subtype-specific sodium channel blockers with fewer adverse effects[12] represents a potential treatment option for spinal cord injury neuropathic pain.

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