

Predictive Value of Lidocaine for Treatment Success of Oxcarbazepine in Patients with Neuropathic Pain Syndrome

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ABSTRACT

Introduction: Pharmacotherapy in patients with neuropathic pain syndromes (NPS) can be associated with long periods of trial and error before reaching satisfactory analgesia. The aim of this study was to investigate whether a short intravenous (i.v.) infusion of lidocaine may have a predictive value for the efficacy of oxcarbazepine.

Methods: In total, 16 consecutive patients with NPS were studied in a prospective, uncontrolled, open-label study design. Each patient received i.v. lidocaine (5 mg/kg) within 30 min followed by a long-term oral oxcarbazepine treatment (900–1,500 mg/day). During an observation period of 28 days, treatment response was documented by a questionnaire including the average daily pain score documented on a numeric rating scale (NRS).

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Results: A total of 6 out of 16 patients (38%) were lidocaine responders (defined as pain reduction >50% during the infusion), and 4 of 16 (25%) were oxcarbazepine responders. In total, 6 out of 16 participants (38%) discontinued oxcarbazepine treatment due to side effects. In an interim analysis predictive value of the lidocaine infusion was low with a Kendall's tau correlation coefficient of 0.29 and coefficient of determination R^2 of 0.119 (95% confidence interval -0.29 to 0.72). As a consequence of this low correlation, the study was discontinued for ethical reasons.

Conclusion: In conclusion, lidocaine infusion has a low predictive value for effectiveness of oxcarbazepine—if at all.

Keywords: Lidocaine; Neuropathic pain; Oxcarbazepine; Predictive value; Treatment response

INTRODUCTION

Treatment of neuropathic pain syndrome (NPS) constitutes a big challenge for the patient, for the physician, and for the whole public health system [1]. A multitude of drugs are recommended in the treatment of NPS [2]. Although there are a number of recommendations for the treatment of NPS [3–5], no clear criteria exist as to what drug should be used to initiate therapy in a certain patient.

Sodium channel inhibitors such as lidocaine and oxcarbazepine are used in the treatment of neuropathic pain [6, 7]. Studies that have looked at the role of systemic lidocaine for predicting subsequent response to mexiletine showed a weak predictive value [8, 9]. In contrast to mexiletine, which is a class IB antiarrhythmic drug and not licenced in Switzerland,

oxcarbazepine is a sodium channel blocker which does not have the potential for significant cardiac side effects. Carbamazepine and oxcarbazepine are mostly considered third-line drugs for the treatment of NPS [6]. Compared to carbamazepine, oxcarbazepine has less side effects and is better tolerated [10]. Oxcarbazepine was therefore considered the best choice to be used in the setting of this study. The aim of this study was to investigate whether the response to lidocaine may predict the therapeutic efficacy of oxcarbazepine.

METHODS

Subjects and Study Design

A prospective and uncontrolled open-label study design was used. The study was approved by the local ethical authorities. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study. Based on the published data of Galer et al. [8], a power analysis was performed that planned to include 30 patients. Participants were recruited from outpatients at the Department of Neurology and the Pain Clinic of the Institute of Anaesthesiology, University Hospital Zurich. The diagnosis of NPS was made either by a certified neurologist and confirmed by a certified anesthetist, or the other way round. Each participant was diagnosed by clear clinical criteria, including suggestive history, pain presentation in a certain body area, and the coexistence of positive symptoms (namely paresthesias, dysesthesias, spontaneous pain, allodynia, and hyperalgesia), and negative symptoms (namely hypoesthesia, hypoalgesia,

and thermhypesthesia). All patients had NPS of mainly peripheral origin; these patients are known to be more responsive to treatment than patients with NPS of mainly central origin. Each participant filled in a questionnaire, supplying information about the NPS. Inclusion criteria were clinical diagnosis of NPS, age >18 years, and an average intensity of pain score of at least 5 according to an 11-point numeric rating scale (NRS; 0 = no pain; 10 = maximum pain imaginable) [11]. Exclusion criteria were intellectually or mentally impaired subjects, medical contraindication to lidocaine or oxcarbazepine, pregnancy, and/or antineuropathic comedication.

According to a standard protocol, the lidocaine infusion was given over 30 min at a dosage of 5 mg/kg body weight [12]. Pain measure (NRS) and reported side effects were documented, and minimal pain score reached during infusion time was used for statistical outcome. Subjects were started on oxcarbazepine, initially administered with a fixed scheme (day 1 and 2: 60 mg/day; day 3 and 4: 120 mg/day; day 5 and 6: 240 mg/day; day 7 and 8: 300 mg/day; day 9 and 10: 450 mg/day; day 11–14: 600 mg/day). Thereafter, the titration was individual according to efficacy and tolerability; the average maintenance dosage was between 900 and 1,500 mg oxcarbazepine per day. The observation period was 28 days, during which NRS and side effects were documented daily by the patients on a standardized form. For statistical outcome, the minimal daily NRS reached by the patient during the observation period was used.

Clinical Measures and Statistical Analysis

Treatment success (responders) was defined as a reduction of NRS of 50% or more and treatment failure (nonresponders) as a pain reduction of

less than 50% [13]. Treatment efficacy was measured by post/pre-ratio. The correlation was calculated using Kendall's rank test and Fisher's z-transformation for 95% confidence interval (CI). Kendall's tau correlation coefficient and the coefficient of determination were used to express the predictive value of the lidocaine test, with the latter test in a version with few predictions and therefore allowing for negative values.

Noticing the high dropout rate of oxcarbazepine treatment due to adverse effects, ethical questions about the continuation of the study were raised amongst the authors. Therefore, an unplanned interim analysis of the data and a post hoc power analysis were performed to estimate the sample size needed to find conclusive answers in the patient population based on the data set. Using χ^2 test of equal proportions based on the data from the 16 included patients and to get a power of 80% with a test significance level of 0.05 with a one-sided test, a sample size of 51 would have been necessary.

RESULTS

According to the adjusted sample size calculation based on the study sample, which required 51 subjects to obtain adequate power to prove a negative result, the study was stopped due to ethical reasons. To this point, a total of 19 patients had been enrolled in the study. Three participants were excluded: one because of an asthma attack during lidocaine infusion, and two because of incomplete documentation forms during the observation period, resulting in 16 participants that could be analyzed. The male:female ratio was 12:4, median age was 51 ± 16 years, and median duration of symptoms was 4.0 ± 2.8 years. For characteristics of patients and pain profiles, see Table 1.

Table 1 Demographics and clinical characteristics of the 16 included patients

Proband	Age	Sex	Disease	Pain location	Allodynia (Y/N)	Lancinating (Y/N)	Paraesthesia (Y/N)	Hypaesthesia (Y/N)
1	60	F	Polynuropathy of unknown origin	Sole of right foot and Dig I and II of left foot	Y	Y	N	Y
2	39	M	Combined phantom- and neuropathic pain after toe amputation	Dig I and V of right foot	N	Y	Y	Y
3	33	M	Polynuropathy with suspicion for mitochondrial metabolism deficiency	Both feet and hands	N	N	Y	Y
4	30	F	CRPS type II	Right knee	Y	Y	Y	Y
5	38	M	Postoperative neuropathy (thoracotomy)	Dermatome Th3, dorsal	Y	N	Y	N
6	32	F	Postoperative neuropathy (patellar luxation)	Right leg	Y	Y	Y	Y
7	38	M	Polynuropathy of unknown origin	Right foot Dig III to V, left foot Dig II	N	N	Y	Y
8	68	M	Polynuropathy of unknown origin	Both feet and lower legs	Y	Y	N	Y
9	55	M	Polynuropathy of unknown origin	Both feet	Y	Y	Y	Y
10	70	M	Alcohol neuropathy	Both feet and both hands	Y	N	N	Y
11	75	M	Polynuropathy of unknown origin	All toes	Y	N	N	N
12	54	M	Polynuropathy, probably HIV-associated, DD alcoholic neuropathy	All toes and fingers	Y	Y	Y	Y
13	24	F	Postoperative neuropathy (inguinal hernia)	Inguinal left	Y	Y	N	N
14	69	M	Polynuropathy of unknown origin	Toes and soles of both feet	Y	Y	Y	N
15	48	M	Diabetic polyneuropathy	Both feet and lower legs	Y	N	Y	Y
16	58	M	Diabetic polyneuropathy	Both feet	N	N	N	Y

CRPS complex regional pain syndrome, DD differential diagnoses, Dig digit, F female, M male, N no, Y yes

Table 2 Drug response of all patients

Study subject	Lidocaine				Oxcarbazepine				Side effects
	Pain before lidocaine (NRS)	Pain after lidocaine (NRS)	Pain reduction (%)	Response	Pain before oxcarbazepine (NRS)	Pain after oxcarbazepine (NRS)	Pain reduction (%)	Response	
1	6.0	1.5	75.0	R	8.0	6.0	25.0	NR	Stopped after 5 weeks due to: hyponatremia, headache, dizziness, concentration difficulties, abdominal discomfort, nausea, vomiting
2	5.5	5.0	10.0	NR	8.0	5.0	37.0	NR	None reported
3	8.0	1.0	87.5	R	8.0	3.0	63.0	R	None reported
4	7.0	5.0	29.0	NR	9.0	9.0	0.0	NR	Stopped after 3 weeks due to: vomiting
5	7.0	3.5	50.0	R	5.0	1.0	80.0	R	None reported
6	8.5	3.5	59.0	R	5.0	5.0	0.0	NR	Stopped after 3 weeks due to: depression, tremor
7	5.5	4.5	19.0	NR	5.0	4.0	20.0	NR	None reported
8	5.0	4.0	20.0	NR	7.0	5.0	29.0	NR	Stopped after 4 weeks due to: tiredness, nausea, blurred vision, dizziness
9	8.0	5.0	37.5	NR	6.0	3.0	50.0	R	None reported
10	5.0	5.0	0.0	NR	5.0	5.0	0.0	NR	None reported
11	10.0	7.0	30.0	NR	6.0	3.0	50.0	R	Dizziness
12	5.0	5.0	0.0	NR	6.0	6.0	0.0	NR	None reported
13	8.0	4.0	50.0	R	9.5	9.5	0.0	NR	Stopped after 6 weeks due to: liver enzyme changes
14	5.5	1.0	82.0	R	7.0	6.0	14.0	NR	Dizziness
15	7.0	5.0	29.0	NR	8.0	8.0	0.0	NR	Stopped after 3 weeks due to: no improvement
16	10.0	10.0	0.0	NR	10.0	10.0	0.0	NR	None reported

The table shows the response and side effects of each subject to either lidocaine or oxcarbazepine. Six patients discontinued the study because of side effects with oxcarbazepine. The two matched responders (R) are marked in *italics*, the eight matched nonresponders (NR) in **bold** NRS numeric rating scale (0 = no pain; 10 = maximum pain imaginable)

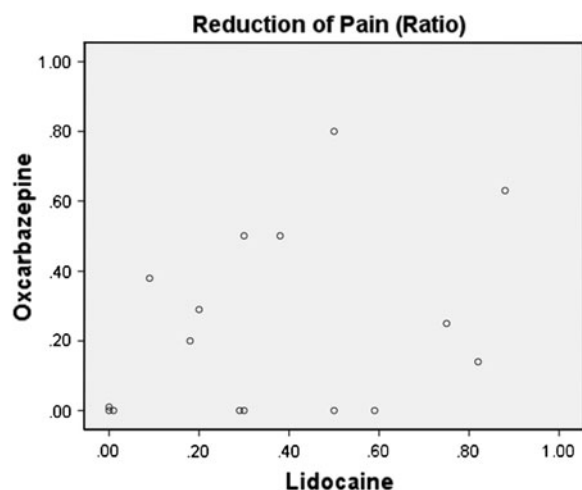


Fig. 1 Correlation of drug response. The figure shows that there was no correlation between the pain reduction to lidocaine and oxcarbazepine. Kendall's tau = 0.31, $R^2 = 0.119$, 95% confidence interval -0.29 to 0.72

In general, lidocaine infusion was well tolerated. During oxcarbazepine treatment, 8 out of 16 patients (50%) reported side effects; 6 of them stopped oxcarbazepine treatment due to side effects.

Six patients (38%) were lidocaine responders, and 4 out of the 16 subjects (25%) responded to oxcarbazepine. Table 2 provides a summary of the results.

As shown in Fig. 1, there was no correlation between the change in pain while taking lidocaine and oxcarbazepine (Kendall's tau = 0.31, $R^2 = 0.119$, 95% CI -0.29 to 0.72).

DISCUSSION

The assumption that lidocaine infusion may reduce neuropathic pain but is ineffective in nonneuropathic pain was already made back in the 1980s [14]. Galer et al. [8] were the first to assume that if neuronal sodium channel inhibition was an important mechanism for relieving neuropathic pain, then different methods of producing this inhibition should

produce similar degrees of pain relief. They tested the predictive value of lidocaine infusions for the effectivity of mexiletine in a small study of nine patients with polyneuropathy of various etiologies [8]. They postulated a significant correlation between the efficacies of both drugs, proposing to use intravenous lidocaine as a predictive test for the efficacy of analogous oral substances. However, the correlation was rather low in this study (Kendall's tau = 0.58) as well as a subsequent study by Attal et al. [9], in which the correlation of lidocaine and mexiletine in their ability to reduce static mechanical allodynia was evaluated (Kendall's tau = 0.62).

This study aimed to investigate the predictive value of lidocaine infusion for the efficacy of oxcarbazepine choosing a substance which is widely used in Switzerland, both for the treatment of epilepsy and NPS. Investigating 16 consecutive patients, the responder rate to lidocaine infusions was 38% and the responder rate to oxcarbazepine was 25%. These results are, although low, within the range of efficacy reported in previous studies [12, 15]. However, 50% of patients experienced side effects due to oxcarbazepine, and the dropout rate was 38%. Therefore, we performed an interim analysis in which Kendall's tau correlation coefficient was low and by far not significant. These interim data were far less promising than the previously published data and raised serious concerns about (1) the benefit of the oral oxcarbazepine treatment in our patient population, and (2) the predictive value of lidocaine. An adjusted interim sample size calculation was computed, which revealed a total number of 51 subjects to reach the defined significance levels (one-sided statement) and therefore prove, with a false negative error (=power) of 0.8, that lidocaine has no predictive value for the response to

oxcarbazepine. Lacking a minimum number of 35 participants, and since the lidocaine test is an invasive procedure with potentially dangerous side-effects such as cardiac arrhythmias, with the benefit of oxcarbazepine in our patient group being very limited and hampered by significant side effects, the decision was made to discontinue the study for ethical reasons.

To balance patient interests against the need for acquiring evidence is sometimes difficult for researchers. Nonetheless, it is ethically correct and considered “state of the art” in clinical research to stop a study as soon as convincing evidence that a new tool is not beneficial becomes available [16].

As in all studies with a comparable design, we cannot entirely exclude that the present results may have been biased by a placebo effect of lidocaine (and oxcarbazepine) or a nocebo effect or an interaction between the two sessions. In contrast to Attal et al. [9] we had decided not to blind the lidocaine infusion, as we found that patients in the clinical setting had reported slight paresthesias and dizziness, which they described spontaneously, making blinding, in our view, far less valuable.

In conclusion, we could not confirm our hypothesis, that lidocaine infusion can be used as a predictive test for effectiveness of oxcarbazepine, and prematurely aborted the study for ethical reasons following an interim analysis and a post hoc power calculation which revealed a far larger sample size compared to the first power calculation.

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Dr. Sándor is the guarantor for this article, and takes responsibility for the integrity of the work as a whole.

Conflict of interest. Dr. Sándor declares he has no conflict of interest. Dr. Schipper declares he has no conflict of interest. Dr. Gantenbein declares he has no conflict of interest. Dr. Maurer declares he has no conflict of interest. Prof. Alon declares he has no conflict of interest.

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