Efficacy and Safety of Mexiletine in the Treatment of Painful Diabetic Neuropathy

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OBJECTIVE — To investigate the efficacy and safety of mexiletine in the treatment of painful diabetic neuropathy.

RESEARCH DESIGN AND METHODS — A total of 126 insulin-treated diabetes patients with painful diabetic neuropathy were randomly allocated to three dosages of mexiletine or placebo. The Visual Analog Scale (VAS) for pain/discomfort was scored each day during daytime and nighttime, and sleeping disturbances were also recorded by the patients. Plasma levels of mexiletine and 24-h electrocardiogram (ECG) mapping were assessed before and during the 3-week study period.

RESULTS — A significant reduction in sleep disturbances and pain during nighttime was observed in the group of patients taking the highest dosage (675 mg/day) of mexiletine compared with the other groups. No significant correlation was found between plasma concentration of mexiletine and the therapeutic effect or adverse events. No serious adverse events were seen. The 24-h ECG mapping did not disclose onset of significant arrhythmias in any patient.

CONCLUSIONS — Mexiletine in a dosage of 675 mg daily can reduce pain caused by diabetic neuropathy, and the effect of this drug appears to have a rapid onset.

Management of painful neuropathy in clinical practice is difficult because traditional pain-reducing therapy is often not effective and because the evaluation of different therapeutic attempts is hampered by the lack of objective measurements. Furthermore, since spontaneous fluctuations appear, the effectiveness of a given agent is difficult to evaluate (1–3).

It is generally agreed upon that the basic therapy of sensory neuropathy in diabetic patients includes optimal glucose control for which purpose there is often a need of insulin treatment (4). Regular analgesics are certainly essential, but it remains a common clinical experience that such therapy frequently fails in relieving pain. Other classes of medications have also been tried here, and some have been found to be helpful. These include antidepressants (5–7), as well as anticonvulsant (8,9). Capsaicin (10) and lidocain (11) may also be helpful.

It has previously been observed that mexiletine, a structural analog of lidocain, may reduce the pain in diabetic peripheral neuropathy (12,13). Thus Dejgard et al. (12) randomized 16 diabetic patients with chronic painful diabetic neuropathy to receive mexiletine daily for 26 weeks in a double-blind, crossover, placebo-controlled trial. Subjective scoring showed a significant decrease in pain by mexiletine. Stracke et al. (13) compared the efficacy of mexiletine in 95 patients with painful diabetic neuropathy in a 5-week randomized, double-blind, placebo-controlled trial. Global assessment of symptomatology showed no significant effect of mexiletine, while a subanalysis suggested that patients with such symptoms as stabbing and burning benefited from mexiletine.

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Abbreviations: ECG, electrocardiogram; VAS, Visual Analog Scale; VE, ventricular ectopic.

The aim of our study was to further elucidate the pain-reducing efficacy and safety of mexiletine in patients with painful diabetic neuropathy and also to evaluate the optimal dose of the drug in this respect.

RESEARCH DESIGN AND METHODS

The study protocol was approved by the ethics committees of all involved hospitals, and all patients gave written informed consent before they entered the study. The study was conducted according to the principles of the Declaration of Helsinki revised in Hong Kong 1989.

Ambulatory patients with painful diabetic neuropathy attending the diabetes outpatient unit of the participating clinics were evaluated for inclusion in the study. The major criteria for eligibility included type 1 or 2 diabetes with painful diabetic neuropathy for more than 4 weeks; an age of 18 to 75 years; vibration threshold measurements or loss of Achilles tendon reflexes indicating neuropathy; and informed consent. Exclusion criteria were pregnancy; neuropathy of other origin; severe limb ischemia; renal insufficiency (s-creatinine >200 μmol/l); severe liver disease; heart failure stages II-IV according to New York Heart Association (NYHA). Continuous 24-h electrocardiogram (ECG) mapping was undertaken before inclusion, and patients exhibiting the following arrhythmias were excluded: sinus-bradycardia (<50 beats/ min), permanent AV-block I, left bundle branch block, >100 ventricular ectopic (VE) beats per 24 h (VE/24 h) in patients below age 50 years, >200 VE/24 h in patients over age 50 years, R on T VE or a Qtc interval exceeding 0.44 s. Patients with ongoing treatment with rifampicin, beta-blockers, quinidine, propafenon, flecainide or theophylline were not allowed to enter into the study.

The investigation was performed as a prospective, double-blind, double-dummy, randomized, placebo-controlled study with parallel groups for 3 weeks. Three different doses of mexiletine (225, 450, and 675 mg/day) were compared.

Altogether, 127 white patients were enrolled in the study. Clinical and demographic characteristics of the patients

Table 1—*Baseline characteristics*

	Treatment group			
	I	II	III	IV
Daily dose of mexiletine (mg)	225	450	675	Placebo
n	31	33	31	31
Sex (F/M)	20/11	24/9	22/9	24/7
Age (years)	57 ± 11	55 ± 10	51 ± 14	57 ± 9
Height (cm)	173 ± 8	174 ± 9	173 ± 9	174 ± 7
Weight (kg)	79 ± 13	76 ± 16	76 ± 18	79 ± 15
Duration of diabetes (years)	14 (1–40)	12 (0.5–28)	18 (1–67)	14 (1–51)
Mean duration of neuropathy (weeks)	126	133	162	143
Duration of neuropathy (months)	12–500	5–500	10–780	6–520
Mean blood pressure (systolic/diastolic) (mmHg)	145/83	142/83	141/83	142/88
HbA_{1c} (%)*	8.27 ± 1.7	7.93 ± 1.7	8.47 ± 1.7	7.81 ± 1.7
S-creatinine (μmol/l)*	86 ± 15	92 ± 14	94 ± 24	94 ± 16
ECG (normal/abnormal)	30/1	29/4	31/0	29/2

Data are means ± SD or *n* (range), unless otherwise specified.

before the start of the study were similar in the four groups (Table 1). All patients underwent clinical examination, with special reference to the neuropathy just before the start of the study and after 3 weeks of treatment. Visual Analog Scale (VAS) score was assessed by the patients and recorded daily 1 week before the start of the study and during the whole study.

Because of protocol violation, one patient was excluded. Thus 126 patients were entered into the study. A total of 95 patients were randomly allocated to mexiletine; 225 mg daily final dose (group I, *n* = 31, 450 mg daily final dose (group II, *n* = 33), and 675 mg daily final dose (group III, *n* = 31). All treatment groups received 75 mg three times daily at start, whereafter the dose was modified so that all patients received the final fixed dosage during the last 2 weeks of the investigation. Of the patients, 31 were randomly allocated to placebo treatment (group IV). All the daily doses were divided in equal parts and taken orally three times per day for three weeks. All the capsules containing mexiletine or placebo were of identical size and shape and packed in blister charts. All medication taken during the study was listed. Plasma for the determination of mexiletine levels was collected and frozen on day 0, 3, 7, and 21. All blood samples were analyzed simultaneously, and 24-h ECG mapping was performed before start of therapy on day 3 and day 21, respectively.

Data from 10 patients were excluded from the explanatory analyses. A total of nine of these patients received mexiletine: four patients in group I, two in group II, three in group III. The reasons for exclusion were as follows: allergic reaction, tachycardia, enteritis, and breast cancer for group I; thrombosis in the lower limb, tiredness, and dizziness for group II; no compliance and diarrhea for group III; and chest pain for group IV.

The efficacy of mexiletine was evaluated by estimating the reduction of pain as assessed by each patient on a horizontal VAS of 10 cm.

The statistical analysis of patient/physician opinion on efficacy and tolerance was performed by the Kruskal-Wallis nonparametric test. Analysis of variance according to a general linear model was used for the VAS score.

RESULTS— The pain during nighttime as estimated by the VAS score in the four groups is shown in Fig. 1. A significant reduction was observed in group III (675 mg) compared with the placebo group (P = 0.029). Sleep disturbances during nighttime are shown in Fig. 2. A significant reduction was again observed in group III (675 mg) compared with the placebo group (P = 0.046).

The mean pain during daytime changed from 5.27 to 4.13 (baseline to days 9–21) in group I, from 4.43 to 3.71 in group II, from 4.35 to 2.72 in group III, and from 4.95 to 3.80 in the placebo group. The results were in agreement with the differences shown for nocturnal pain and sleeping disturbances, but the differences in effect between the groups were not statistically significant (P = 0.15).

The global assessment of efficacy (good-moderate-sufficient) was rated 69% in group I, 63% in group II, 75% in group III, and 66% in the placebo group. No significant differences between the groups were observed.

The plasma levels of mexiletine on day 21 in group I were investigated in 17 patients and found to be below 1.5 μmol/l in all but one patient (2.5 μmol/l, a level within the therapeutic range of 2–9 μmol/l for the treatment of cardiac arrhythmias). The plasma level in group II (*n* = 15) on day 21 was below 2.0 μmol/l in 47%, between 2.0 and 3.5 μmol/l in 47%, and 3.7 μmol/l in one patient. The corresponding levels in group III (*n* = 21) were 24% below 2 μmol/l, 33% between 2.0 and 3.5 μmol/l, and 43% above 3.5 μmol/l, with the highest level being 6.6 μmol/l.

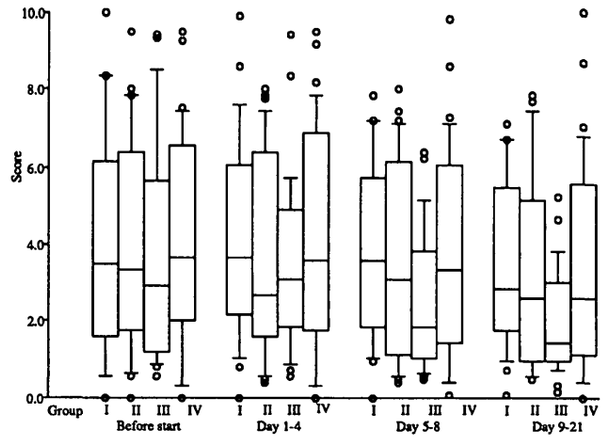

Figure 1—*Nocturnal pain as revealed by VAS score.*

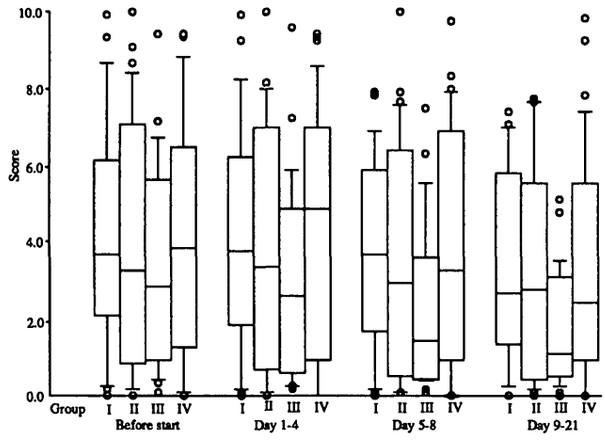

Figure 2—*Sleeping disturbances as revealed by VAS score.*

No significant correlation was found between the plasma concentration of mexiletine and its therapeutic effect as well as adverse events. No significant change in consumption of analgesics was registered during the study, and hence no significant correlation was found between the pain relief and the consumption of analgesics.

No significant change in HbA_{1c} was observed during the study, and no significant correlation between HbA_{1c} and intensity of pain was found.

No death or serious adverse events were reported in the study. Adverse events reported by patients were one event with an allergic reaction, one with tachycardia, and two with diarrhea in group I; one event with dry mouth, one with thrombosis in the lower limb, and one with tiredness and dizziness in group II; and three events with nausea, one with diarrhea, one with gastric pain, one with stomach pain, one with sleeping disturbances, and one with shakiness in group III. One event with dizziness and one with chest pain appeared in the placebo group. Of the 17 patients who reported adverse events, 6 patients reported more than one.

The 24-h ECG mapping did not disclose onset of significant arrhythmias in any of the patients. No patient was withdrawn from the study because of the results from ECG mapping.

CONCLUSIONS— Mexiletine is an orally active class Ib anti-arrhythmic drug, which has been in routine use for many years in cardiac patients in doses of 200 and 300 mg three times daily, and its dose-related adverse effects such as gastrointestinal disturbances and neurological side effects are well known (14). In our study, much emphasis was put on assessments of the safety of the drug with respect to its potential pro-arrhythmic effect and hence, 24-h ECG mapping was undertaken before and during mexiletine treatment. These recordings did not disclose onset of significant arrhythmias in any of our patients. The side effects occurring with mexiletine were mainly at the 675-mg level, and the complaints turned out to be the typical side effects of mexiletine.

The present study demonstrates that oral mexiletine relieves the symptoms of painful diabetic neuropathy, which supports the observations by Dejgard et al. (12) in their study on a small group of patients. Stracke et al. (13) failed to demonstrate an overall positive effect in their study; however, the patients with such symptoms of neuropathy as stabbing and burning benefited from oral mexiletine. Because these three studies assessed efficacy by pain relief as reported by the patient on a VAS score, it is likely that the somewhat divergent findings cannot be attributed to the methodology for assessment of pain. It appears most likely that the patients being investigated were essentially comparable from a clinical point of view. Unlike Stracke et al., we did not include the McGill verbal pain questionnaire in our investigation and, therefore, we were not able to perform a subanalysis to qualify subjective pain. Our study population had a female predominance in contrast to the two other studies. Since the findings of Dejgard et al. are very much in line with ours, a sex specificity appears quite unlikely. The study designs of these three investigations differed basically regarding the study periods used, with our study comprising only 3 weeks, Stracke et al. using 6 weeks for evaluation, and Dejgard et al. studying patients up to 26 weeks. Considering these differences, it has to be noted however that it has been demonstrated by Kastrup et al. (11) that lignocaine, a similar drug, exerts a symptom-relieving effect after a single intravenous injection, and that this effect may last for 3–21 days (11).

It is well known that tight glycemic control benefits pain in diabetic neuropathy and that intensive treatment also may reverse other manifestations of diabetic neuropathy. Dejgard et al., who monitored glucose control by HbA_{1c} during their relatively prolonged study, did not register any improvement of this parameter with time, and they could not establish a relation between pain relief and HbA_{1c} within the relatively small group of patients that they studied (12). We did not find a significant change in HbA_{1c} over time, and HbA_{1c} did not correlate significantly with pain as assessed by the VAS scores. Somewhat in contrast, the patients studied by Stracke et al. (13) exhibited marked improvements of glucose control with time, with no significant differences being observed between the groups analyzed. Against this background, it has to be speculated upon whether such an improvement of metabolism as obtained by Stracke et al. might have concealed an intrinsic effect of mexiletine on pain.

In the present study, efforts were made to analyze the dose-dependency of the effect of mexiletine on painful neuropathy and to ascertain whether differences in the metabolism of mexiletine, as assessed by its levels in plasma, could be of value in understanding the responsiveness of individual patients. Taken together, our analyses suggested that mexiletine exerted a clinically relevant effect when given in the dose of 675 mg/day and that the plasma levels obtained did not correlate significantly with the effect of the drug.

The cause of sensory diabetic neuropathy and related pain is not well understood, but most likely involves several factors. Hypotheses have mainly focused on metabolic mechanisms and nerve injury, both being consequences of insulin deficiency and/or prolonged hyperglycemia (1). The mechanism by which mexiletine decreases the symptoms of pain is also unknown. Its structural similarity to lidocain indicates a

possible common mechanism for the two drugs. To be in favor of a central rather than a peripheral mode of action says that no changes in neurological tests, vibration threshold levels, or autonomic nervous function tests were found during mexiletine treatment by Dejgard et al. (12). However, because mexiletine has a sodium-channel blocking effect that is important to nerve function, the pain-relieving effect may also be due to inhibition of the spontaneous activity in regenerating nerve fibers.

In summary, we have found that mexiletine, a drug that has long been used in the treatment of cardiac arrhythmias, reduces pain caused by diabetic neuropathy when delivered in a dose that corresponds well to the therapeutic dose-interval of its antiarrhythmic effect. The effect of mexiletine appears to have a rapid onset, which is certainly helpful for the clinician in evaluating its efficacy in a patient.

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