Mexiletine in the Treatment of Diabetic Neuropathy

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OBJECTIVE — To prove the efficacy of mexiletine in painful diabetic neuropathy.

RESEARCH DESIGN AND METHODS — Treatment was provided in three dosages. For pain measurements, a VAS and McGill's verbal rating scale were chosen. Ninety-five patients were included in the study.

RESULTS — A global assessment of the VAS among patients showed no differences between mexiletine treatment and placebo. The total evaluation (PRIT) of the McGill scale fell just below the level of significance. More specific exploratory evaluations of subclasses of the McGill scale, representing different degrees of pain, gave remarkable differences between mexiletine and placebo in sensory and miscellaneous items. In special subgroups, which were formed according to types and courses of complaints compiled at the beginning of this evaluation, the substantial advantages of the mexiletine treatment were shown with both the VAS and the McGill scale.

CONCLUSIONS — Evidence strongly indicates that, in particular, those patients with stabbing or burning pain, heat sensations, or formication will benefit most by mexiletine therapy. Concerning the dosage, a medium regimen of 450 mg/day seems to be appropriate. With an increase in the antiarryhthmic dosage level, the efficacy does not rise proportionally. Mexiletine proved to be a safe therapy with negligible side effects at the medium dose range, even less than placebo; and remarkably, no cardiovascular side effects were noted. Further studies should avoid global assessments and pay more attention to the variety of complaints and quality of life.

Various biochemical mechanisms play a role in the pathogenesis of diabetic neuropathy. One of these may be disturbances of the ionic equilibrium at the neuronal membranes caused by decrements in the activity of the Na^+/K^+-ATPase (1,2). In general, either small, thinly myelinated or unmyelinated nerve fibers are involved. Irregular bursts of spontaneous discharges arise from the membranes' electrical instability and induce the symptoms that bring on the various complaints (3).

Obviously, the great discrepancy between the request for treatment on one hand and polypragmatism on the other in the management of these patients clearly points to the need for an effective treatment. So far, no effective standard therapy has been established (4). Attempts have been made, although with little success, to alleviate the patients' complaints and improve their quality of life, with various classes of drugs in accordance with individual experience. The rationale for this study resides in the fact that membrane-stabilizing, Na^+-antagonistic antiarrhythmics of class 1 (Vaughan Williams) possess, to a variable extent, local anaesthetic properties; and some of them actually were found to be useful in treating various types of pain (5).

In patients suffering from diabetic neuropathy, pain reduction was already observed under lidocaine (6). A clinical study of mexiletine, a lidocaine analogue, was conducted in Denmark with 16 patients (7). In that study, mexiletine reduced pain significantly more than placebo, according to both the VAS index of pain and a clinical score based on five symptoms.

The aim of this study was to assess the pain-reducing effects of mexiletine in a large number of patients with symptomatic diabetic polyneuropathy, and to demonstrate the efficacy of the substance in this indication.

RESEARCH DESIGN AND METHODS

— This study was conducted between April 1989 and October 1990. Seven centers enrolled 100 patients in the double-blind, randomized placebo-controlled trial. Patients were informed by the attending physicians about the nature, significance, and risks of the clinical study. The participants gave written or oral consent in the presence of an independent witness in accor-

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VAS, VISUAL ANALOGUE SCALE; PRIT, PAIN-RATING INDEX TOTAL; PPI, PAIN PERCEPTION INDEX.

Table 1—*Inclusion and exclusion criteria of patients*

INCLUSION CRITERIA
MEN AND WOMEN
18–65 YR OF AGE
THE PAIN OR MALAISE CAUSED BY DIABETIC NEUROPATHY MUST CLEARLY IMPAIR THE PATIENT'S LIFE AND REQUIRE TREATMENT; THE INTENSITY OF PAIN MUST BE 25% ON THE VAS.
DURATION OF SYMPTOMS AT START OF STUDY AT LEAST 4 MO, MAXIMUM 5 YR
INFORMED CONSENT
EXCLUSION CRITERIA
POSSIBILITY OF A PREGNANCY
NEUROPATHY OF OTHER ORIGIN
ALCOHOL OR DRUG ABUSE
VITAMIN B_{12} DEFICIENCY
DIABETICS WITH RENAL INSUFFICIENCY (CREATININE THRESHOLD VALUE 1.5 MG/DL)
CIRRHOSIS OF THE LIVER
HEPATITIS
SEVERE CHRONIC DAMAGE TO THE LIVER
MANIFEST CARDIAC INSUFFICIENCY
MYOCARDIAL INFARCTION <3 MO BEFORE
CARDIAC ARRHYTHMIA, PREVIOUSLY KNOW SICK-SINUS SYNDROME; UNCLARIFIED SYNCOPES; AV BLOCK 2ND AND 3RD DEGREE.
OCCLUSIVE ARTERIAL DISEASE, STAGE II ONWARDS

dance with §§ 40/41 AMG (German drug laws). The study plan was approved by the ethical committee at the Medical Clinics of the Justus-Liebig University at Giessen.

The experimental design provided for a 1-wk run-in phase in which any medication used to treat diabetic neuropathy was discontinued and replaced by placebo (t.i.d.). Patients were allowed, however, to take at most 5 × 500 mg paracetamol tablets to alleviate their neuropathic pain, if necessary. To ensure the inclusion only of patients who were distinctly handicapped by their complaints, their pain score on the VAS had to reach ≥25% at the beginning of the run-in period. After completing that phase, all patients were reevaluated with respect to the inclusion or exclusion criteria (Table 1), before they finally were included. Five patients were excluded, because their pain score on the VAS had been clearly >25%. Thus, 95 patients were treated.

Thereafter, the patients received 75 mg mexiletine 3 times/day or the corresponding placebos labeled low dose for 1 wk. This dosage could be raised stepwise in weekly intervals to 150 and 225 mg mexiletine or corresponding placebos, each administered 3 times/day. The total duration of the treatments lasted 5 wk, so that the patients received a fixed dosage for at least 3 wk (Fig. 1). During the entire study, paracetamol was allowed as an analgesic medication when required.

Examinations were made at weekly intervals. They consisted of an assessment of the neurological status, ECG, and blood glucose determinations. Laboratory parameters were recorded at the beginning and end of the study. A VAS was used to quantify pain 2 times/day. The verbal pain score according to McGill was filled in at weekly intervals. At each examination, the patients were asked to voice any undesirable drug effects, and their answers were documented. The patients' demographic data are listed in Table 2.

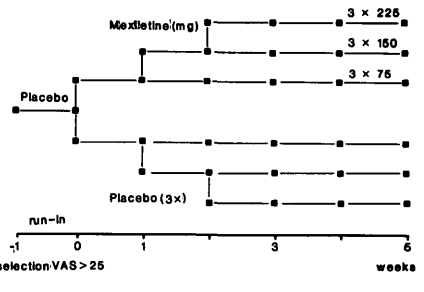

Figure 1—*Time course and alternative dosage regimens.*

Of the patients treated with mexiletine, 47% previously had been given thioctic acid, analgesic/antirheumatic agents, vitamins, or carbamazepine; this also applied to 56% of the placebo control subjects. Insulin was the antidiabetic medication for 66% of the cases in the mexiletine group and in 71% of the patients randomized to placebo, whereas oral antidiabetic agents were taken by 45 and 33%, respectively.

As primary end points were considered, the pain score based on the rating in the McGill questionnaire, the subjective pain perception according to the VAS, and the paracetamol consumption were observed. McGill's verbal pain questionnaire is an internationally recognized instrument that was developed primarily for evaluating carcinoma pain. A detailed description is given in the literature (8). The adjectives describing the sensations are divided into 20 groups, which may be classified as describing 4 main qualities: sensory qualities, affective qualities, a description of the individual life situation, and finally miscellaneous qualities. In addition, the questionnaire provides for an overall PPI ranging from 0 = no pain to 5 = excruciating pain. McGill's score allows a more differentiated judgment than the global rating from a VAS, where the patient marks the intensity of his pain perception along a 10-cm line. The VAS also was used by Dejgard in the Danish trial (7). Furthermore, heart rate and blood pressure were determined, and a resting ECG was recorded at the weekly examinations. The blood pressure was determined 3 times/

Table 2—*Patient characteristics*

	Patient groups	
	Mexiletine	Placebo
N	47	48
Sex W/M (%)	25 (53)/22 (47)	17 (35)/31 (65)
Age (yr)	56.0 (31–74)	57.0 (43–75)
Insulin dependent (%)	31 (66)	34 (71)
Oral antidiabetic agents (%)	21 (45)	16 (33)

day. At the beginning and end of the study, a blood cell count, serum electrolytes, transaminases, urea, and creatinine were assayed, as were HbA_1 and HbA_{1c} for evaluation of diabetes status.

Statistical evaluation

To evaluate the McGill and VAS scores, the differences between the beginning and end of therapy were tested by analysis of variance, allowing for interactions by centers. The Wilcoxon/Mann-Whitney test was used to check the changes in the PPI scores. All evaluations were done by means of the intent-to-treat principle; i.e., all patients randomized were analyzed (minor deviations from protocol, which have been observed in 8 patients, were not considered).

RESULTS

McGill pain questionnaire

Mexiletine had no statistically significant advantage regarding the overall evaluation criteria of the McGill scale.

Pain-rating indexes

The evaluation refers mainly to the PRIT. The test for differences between treatments was conducted by comparing the results at the end of wk 5 with those at the end of the run-in period. Mean values and SDs for PRIT are given in Table 3 according to the final dosage reached and for the pooled data. The test on treatment differences with the pooled data yielded $P = 0.0580$, which is just short of the significance level of 0.05. No differences were indicated between individual centers or interactions between centers and treatments. However, if the PRIT were used specifically on those complaints compiled during the run-in, certain aspects could be well differentiated. The anamnestically compiled complaints were of cutting or stabbing sensations; sensations of coldness, heat, burning, tingling, or tugging; formicaton; and hyposensitivity.

In exploratory analyses of the subgroups formed according to the type of complaints, mexiletine could be shown to be especially effective (*P* value in test on treatment differences ≤0.1) in patients describing their complaints as sensations of stabbing, heat, and/or burning or formication. The PRIT differences for these groups are given in Figs. 2–5). It is interesting to see that the difference between mexiletine and placebo was more pronounced in patients who had ≥2 of the special symptoms (Table 4).

We already mentioned that the McGill pain questionnaire may be divided into four classes, each representing different qualities of pain experience or perception. Associated to these classes are different pain-rating indexes: sen-

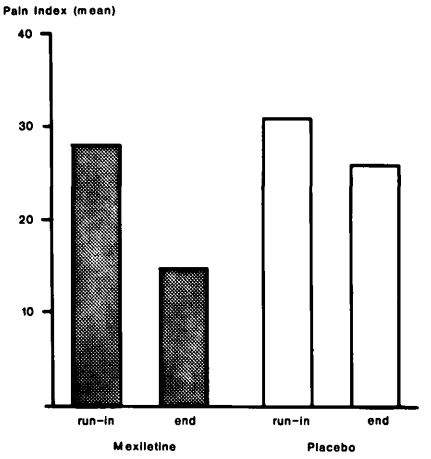

Figure 2—*PRIT in patients who experienced stabbing sensations at run-in (Mexiletene = 27, Placebo = 25 patients, P = 0.02).*

Table 3—*PRIT for different dosages and pooled data*

	Mexiletine				Placebo			
	N	Beginning	End	Difference	*N*	Beginning	End	Difference
Dosages								
Low	7	17.7 ± 7.0	8.4 ± 9.9	−9.3 ± 6.8	1	13	0	−13
Medium	18	24.3 ± 12.6	12.2 ± 10.0	−12.1 ± 9.7	12	28.2 ± 11.0	19.8 ± 14.0	−8.3 ± 8.2
High	21	29.1 ± 13.3	20.4 ± 18.7	−8.7 ± 14.0	35	26.1 ± 12.7	21.3 ± 13.7	−4.8 ± 10.5
Pooled data	46*	25.5 ± 12.7	15.4 ± 15.2	−10.1 ± 11.5	48	26.3 ± 12.3	20.5 ± 13.8	−5.9 ± 10.0

Values are means ± SD.

* One patient refused to fill in the McGill Pain Questionnaire.

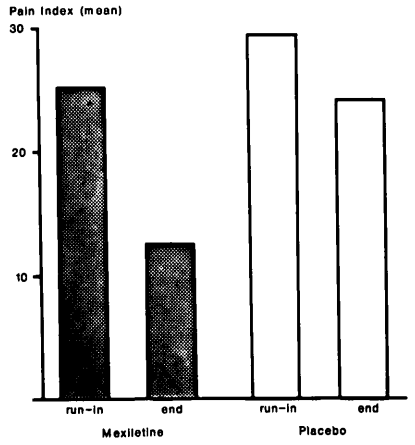

Figure 3—*PRIT in patients who experienced sensations of heat at run-in (Mexiletene = 13, Placebo = 14 patients, P = 0.10).*

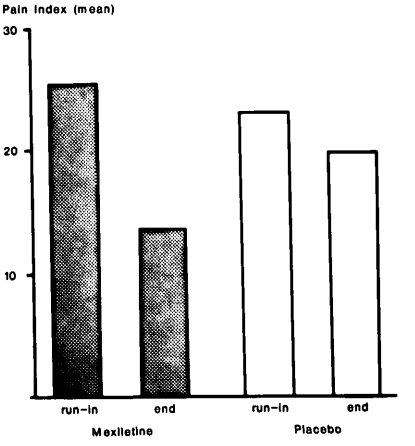

Figure 5—*PRIT in patients who experienced formication at run-in (Mexiletene = 18, Placebo = 18 patients, P = 0.04)).*

sory, affective, evaluation of life situation, and miscellaneous qualities. Our results gave no differences between the two study groups in the affective parts of the questionnaire, and with regard to the evaluation of the life situation. However, the advantages for mexiletine were marked in the groups of sensory and miscellaneous qualities ($P = 0.004$ and 0.001).

VAS

The global evaluation of the VAS indicated no difference between the treatments, i.e., neither when all centers were combined nor when considered separately. When examining the VAS results with regard to the degree of impairment of the patients—as previously done with the McGill questionnaire—it seemed obvious that the greater a patient's handicap, the more the patient benefitted from mexiletine therapy. When the type of pain a patient was suffering was evaluated separately—as done for the McGill scales—mexiletine proved clearly superior to placebo, especially in patients with stabbing or burning sensations.

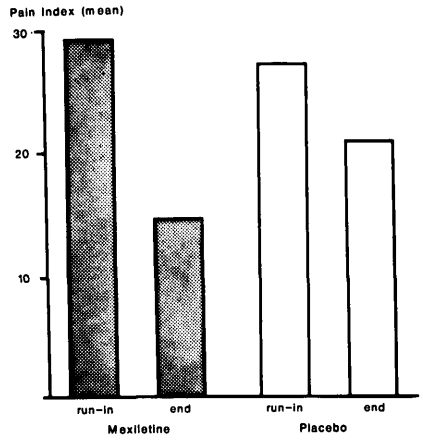

Figure 4—*PRIT in patients who experienced burning sensations at run-in (Mexiletene = 15, Placebo = 24 patients, P = 0.01)).*

Evaluation of the secondary parameters

Of the patients, 37 did not take additional paracetamol. Hence, this parameter constituted a secondary end point only, with no significant difference between treatments. No differences were found in the neurological status nor in the vibratory sensibility. The metabolic situation improved in both groups after the run-in phase; another slight amelioration was observed at the end of the study.

The final overall assessment of tolerance indicated, as expected, that placebo was tolerated slightly better, because 40 patients in the mexiletine group (85%) and 46 patients under placebo (95%) rated the tolerance as being good. Of the patient groups, 4 in the mexiletine group and 1 in the placebo group found the tolerance unsatisfactory. With respect to the therapeutically effective dose, no difference was found between the low mexiletine dose of 225 mg/day and placebo. At the intermediate range, which was 450 mg/day, mexiletine had a clearly favorable effect when assessed by the PRIT index of the McGill scale, but not by the VAS. A further increase of the dose to 675 mg/day showed little improvement.

Undesirable side effects were observed in 11 mexiletine-treated patients and 6 placebo-treated patients. The side effects occurring with mexiletine depended on the dosage and conspiciously were only at the 675-mg level, where types and frequencies of complaints turned out to be the typical side effects of mexiletine in its antiarrhythmic indication.

In contrast, with the intermediate dosage, the frequency of adverse reactions was strikingly lower than with placebo (see Fig. 6). Regarding the type of side effects experienced, essentially gastrointestinal and CNS symptoms, which are typical for mexiletine, were observed. The majority of the side effects also was seen under placebo. No effects on the cardiovascular parameters were investigated, and, in particular, no effects on ECG intervals.

The laboratory parameters did not change under either therapy. In the mexiletine group, the HbA_1 was reduced from 10.1 to 9.2%, and the HbA_{1c} from 9.0 to 7.5%; the corresponding reductions under placebo were 9.6 to 8.9%, respectively, and 8.9 to 7.8%. Thus, metabolism was improved in both groups. No differences were observed in the subgroups formed according to the four special symptoms mentioned above with respect to metabolic conditions.

CONCLUSIONS — In accordance with the complexity and diversity of the clin-

Table 4—*Data for patients who have 1 of the 4 special symptoms (sensations of stabbing, burning, heat or formication)*

	Mexiletine				Placebo				
	N	Beginning	End	Difference	*N*	Beginning	End	Difference	*P*
At least									
One symptom	40	26.2 ± 13.0	15.0 ± 16.1	−11.2 ± 11.3	40	27.5 ± 12.9	22.2 ± 14.1	−5.3 ± 10.5	0.0172
Two symptoms	22	26.6 ± 11.2	13.0 ± 12.9	−13.6 ± 10.5	25	27.0 ± 15.2	21.7 ± 14.8	−5.3 ± 10.7	0.0099
Three symptoms	8	31.5 ± 11.4	13.5 ± 16.1	−18.0 ± 11.4	11	32.4 ± 13.1	28.4 ± 14.8	−4.0 ± 13.2	0.0248

Values are means ± SD.

ical features, similarly differentiated criteria must be chosen for the therapeutic success, as can be inferred from the results. Whenever global criteria were used to evaluate patients' complaints, the results of our study turned out to be irrelevant. This was true with both the VAS and the global score for general pain, the PPI, of the McGill scale. A separate evaluation of individual subgroups in the McGill questionnaire gave significant results that favored mexiletine over placebo for the sensory and miscellaneous pain qualities.

The McGill scale and the VAS concurred in patients suffering from stabbing and heat sensations. In these cases, mexiletine was definitely more effective than placebo. The same held true when patients were describing their complaints at the beginning of the study as changing over the course of the day or as being paroxysmal. In these cases, too, the VAS and McGill scale consistently indicated an improvement under mexiletine. Moreover, the results of this study indicate that patients benefit most by mexiletine therapy if they have ≤2 of the above mentioned symptoms (sensations of stabbing, heat, and burning; and formication). As these results are of exploratory nature, further study will be necessary to confirm these findings.

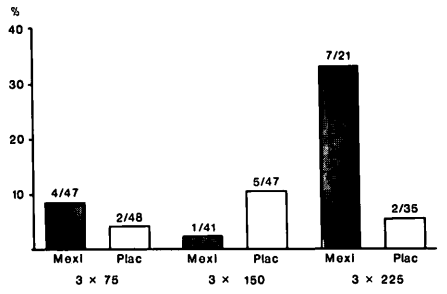

Figure 6—*Percentage and number of patients with adverse events in each of the alternative dosage regimens (mg).*

Parallel to our experience, positive results for local anesthetics in patients complaining of stabbing pain were described (9). Reflections on the pathogenesis of the clinical symptoms indicate conformance of our results with the basics of physiology. The most frequently diagnosed and the most painful symptoms in diabetic polyneuropathy originate from lesions of small, thinly myelinated or unmyelinated protopathic nerves called small fibers (3,10). And these frequent disorders are described mainly as stabbing and/or heat sensations, or sometimes as formication.

The hyperaesthetic symptoms are caused by high-frequency bursts of neural activity. Familiar from the class 1 B-substances in tachycardias is their action principle of use-dependence. It describes their fast-binding kinetics to receptors at the Na^+-channels that yields an unblocked channel in advance of the next activation. The mean binding time for this group of drugs is <1 s. Therefore, members of the class 1 B antiarrhythmics develop their highest effectiveness at higher frequencies. The same use-dependence also exists at the membranes of the nerve cells, which can explain why especially hyperactive or spontaneously active neurons respond to local anesthetis (3,14–16).

Therefore, it is not surprising that no changes could be detected on the vibratory sensitivity in this study or in the Danish study by Dejgard (7), because vibratory sensitivity measurements are specific for the functions of thicker nerve fibers and their type of conduction. In addition, one would be unable to observe changes in nerve-conductance velocities when the lesions are composed only of small protopathic fibers (11).

In summary, it can be said that using the VAS and the McGill global scales, irrelevant or virtually undiscerable differences in treatments could be demonstrated. However, when considering single components, i.e., when types and course of complaints are differentiated, one may observe prominent differences favoring mexiletine. It should be the aim of future studies on the therapeutic efficacy of drugs in diabetic neuropathy to use reliable and validated instruments for assessing the quality of life, that is, those proven useful in this syn drome (12,13).

Because our study was conducted with three different dosages, a statement on the dosage in this indication was to be expected. The results demonstrated that the medium range of 450 mg/day was effective, and contrasts to the dose recommended for antiarrhythmic therapy with mexiletine, which amounts to 600–800 mg/day.

In any clinical study, the safety of

the test drug is of particular interest. The frequency of side effects of mexiletine appeared to be dose-dependent. For the medium dosage, i.e., the effective dose, the frequency of side effects was negligible (1 of 41 patients). However, when the dose was increased from 450 to 675 mg, the side effects rose from 2.4 to 33.3%. Moreover, to cover the safety aspect completely, ECG parameters were recorded, and laboratory investigations conducted. None of the ECG intervals or laboratory parameters was affected during the study. Hence, the safety of mexiletine in diabetic neuropathy seems to be confirmed by the fact that its effective dose is clearly lower than the dose recommended for antiarrhythmic therapy, and that the frequency of side effects with this dosage is lower than with placebo. Therefore, further studies should be conducted in the range of 450 mg mexiletine and also should include parameters adequately adapted to measure the patients' quality of life.

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