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Symptomatic Treatment of Peripheral Diabetic Neuropathy with Carbamazepine (Tegretol®): Double Blind Crossover Trial

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Summary. A double blind crossover study with placebo and carbamazepine was done in 30 diabetic patients who presented diverse clinical types of peripheral diabetic neuropathy. The active drug offered symptomatic relief of all sensory manifestations in 28 cases. No effort was made to assess the action of carbamazepine upon motor or visceral manifestations of neuropathy. There were two complete failures. Untoward effects were frequent but usually mild and transient; two patients presented a rash that required discontinuation of the drug.

Traitement symptomatique de la neuropathie diabétique périphérique avec la carbamazépine (Tégrétol®) : Essai double aveugle en cross over

Résumé. Une étude de cross over double aveugle avec placebo et carbamazépine a été effectuée chez 30 patients diabétiques présentant divers types cliniques de neuropathie diabétique périphérique. La drogue active apportait un soulagement symptomatique de toutes les manifestations sensorielles dans 28 cas. Aucun effort n'a été fait pour évaluer l'action de la carbamazépine sur les manifestations motrices ou viscérales de la neuropathie. Il y eut deux échecs complets. Les effets secondaires étaient fréquents, mais en général légers et temporaires. Deux patients présentèrent une éruption qui nécessita l'arrêt du traitement.

Symptomatische Behandlung der peripheren diabetischen Neuropathie mit Carbamazepin (Tegretol) : Doppel-Blind-Austausch-Untersuchung

Zusammenfassung. An 30 Diabetikern, die unterschiedliche Formen einer peripheren diabetischen Neuropathie aufwiesen, wurde eine Doppel-Blind-Austausch-Untersuchung mit Carbamazepin und einem Plazebo-Präparat durchgeführt. Bei 28 der Patienten führt die aktive Droge zu einer symptomatischen Besserung sämtlicher Symptome von Seiten des sensiblen Nevensystems. Die Wirkung von Carbamazepin auf die motorischen und visceralen Erscheinungsformen der Neuropathie wurde nicht geprüft. Es traten zwei komplette Therapie-Versager auf. Nebenwirkungen waren häufig festzustellen; sie waren jedoch gewöhnlich leicht und klangen schnell ab. Bei zwei Patienten zwang das Auftreten eines Exanthems zum Absetzen des Präparates.

Key-words: Diabetic neuropathy, peripheral diabetic neuropathy, carbamazepine, Tegretol, treatment of peripheral diabetic neuropathy.

To date there is no specific therapy for the pain and paresthesia of peripheral diabetic neuropathy, and present symptomatic treatment is usually of little efficacy.

Recently, Carbamazepine (Tegretol®) has been found to be useful in the relief of neuralgia of diverse aetiologies [2, 8, 3, 7, 1]. This prompted us to investigate its possible usefulness in diabetic neuropathy.

Material and Methods

Thirty diabetic patients (Table 1) with well established subjective sensory manifestations of somatic neuropathy were studied.

The differential diagnosis including neurologic examination was carefully established in every case, but no attempt was made to evaluate changes in motor disorders or manifestations of visceral neuropathy. Initial complaints were chiefly pain and paresthesia. These included burning, numbness, tingling and cutaneous hyperalgesia (Table 2). All cases were of more than one month's duration, and most were moderate or severe in intensity. The characteristics of the patient population studied suggested (Table 1), that this was a mixed group with several types of diabetic peripheral neuropathy. In some cases, sensory symptoms were only related to varying degrees of hyperglycaemia

Table 1. *Clinical characteristics of the patients*

Sex		Age		Weight	
Men	9	Mean	54.2 years	Ideal	12
Women	21	Range	21—81 years	5—10 kg > Ideal	3
				5—10 kg < Ideal	15

Duration of diabetes		Retinal changes		Degree of control		Treatment	
Mean	10.9 years	Angiopathy	14	Good	11	Diet alone	2
Range	3—24 years	Retinopathy	14	Fair	5	Insulin	10
		No change	2	Poor	14	Oral hypoglycaemic agents	18

("hyperglycaemic neuralgia"); in others, pain and paresthesia were part of the more complex forms of diabetic neuropathy associated with vascular lesions ("atherosclerotic neuropathy") or with pure neurological changes ("somatic neuropathy"). Each patient was asked to describe his symptoms in his own words, and the terms employed were used throughout the study to assess the changes in intensity, extension and duration of complaints at each subsequent visit.

Table 2. *Symptoms of diabetic neuropathy in the studied group*

"Muscular" pains	26	86.6%
"Shooting" pains	23	76.6%
"Burning"	19	63.3%
Numbness	19	63.3%
Cutaneous hyperalgesia	15	50.0%
Cramps	10	33.3%
Tingling	5	16.6%

Duration: 1 to 36 months

During the double blind crossover trial, patients were given both carbamazepine (code letter A) and a placebo (code letter B). On a random basis, 14 individuals were assigned an A-B-A sequence of treatment and 16 were placed on a B-A-B sequence. Both the drug and the placebo tablets were identical and given in the same number to each patient. Carbamazepine tablets contained 200 mg each, and in most instances the daily dose was 600 mg. Each period of administration, A and B, had a two week duration.

Fasting blood sugars, body weights and 24 h urinary glucose losses were determined initially, and before every change of medication. Whenever possible, fluctuations in control and modifications in diet or hypoglycaemic treatment were avoided during the six weeks of trial. At each visit, the patient was asked to give a subjective evaluation of changes in intensity, distribution and duration of the symptomatology that he had originally described. The presence of untoward effects was systematically investigated.

Results were tabulated by one of the authors who had not followed the patients clinically and did not know the code. They were graded from 0 (no change) to 5↓ (disappearance) or 5↑ (maximal increase). This grading procedure was applied to each symptom, and the overall results of each patient at the end of every two week period were obtained by summing algebraically all positive and negative changes.

Results

There were no major changes in body weight or diabetic control during the trial (Table 3).

Individual results at the end of each period of carbamazepine and placebo are presented in Table 4. The group placed on the A-B-A sequence (carbamazepine-placebo-carbamazepine) shows a definite decrease in intensity, extension and duration of symptoms after the first period of carbamazepine administration. Improvement persisted in some patients when changed to placebo, whereas in others there was a relapse. In contrast, resumption of carbamazepine was followed by a new general decrease in complaints.

Patients on the B-A-B sequence (placebo-carbamazepine-placebo) demonstrated a different pattern. At

Table 3. *Changes in body weight, blood sugar and glycosuria during the trial period*

	Weight	Blood Sugar	Glycosuria
No changes	26	20	18
Fluctuation	0	6	10
Increase	2	3	0
Decrease	2	1	2

Table 4. *Individual results after each one of the carbamazepine and placebo-periods*

Case	A	B	A	Case	B	A	B
2	↓↓↓	↓↓↓	↓↓↓	1	↓	↓↓↓↓	
3	↓↓↓	↓↓↓	↓↓↓↓	4	↓a↓↓	↓↓↓↓↓	↑
7	↓	↓	↓	5	↓a↓↓	↓↓↓	↓
10	↓↓↓↓	↑	↓↓↓↓	6	↑	↓↓	↓↓↓↓↓
12	↓↓	↑		8	↑	↓	↓
14	↓↓↓	↑↑a↑↑↑	↓↓↓	9	0	0	↓
17	↓↓↓	↑	↓↓↓↓	11	↓	↓↓↓↓	↑↑↑
19	↓	↓	↓	13	0	↓↓	↑
20	↓↓	↓	↓↓↓↓	15	↑	↓↓↓	↓↓↓
21	↓↓↓↓	↑a↑↑		16	↓	↓↓↓↓	↓↓
23	↓↓	↑↑	0—↑	18	↑↑	↓↓↓	↓
25	↓↓↓	↓	↓↓↓↓	22	0	↓a↓↓	↓
27	↓	↓	↓↓↓	24	↓	↓↓↓↓	↓↓↓
30	↓	↓	↓↓	26	↑↑	↓	↑
				28	0	↓↓↓↓	↓↓↓↓↓
				29	↓	↓↓↓↓	↓↓

A: Carbamazepine. B: placebo.
Results for each period represent algebraic sum of changes in each initially referred symptom graded from 5↓ (disappearance) to 5↑ (maximal increase)

the end of the first B period, few or no changes were reported. On beginning therapy with carbamazepine (period A), a general decrease in symptomatology was the distinctive feature. After the second placebo period, most patients relapsed, although a certain degree of improvement persisted in some.

Overall results are summarized in Table 5. A marked decrease in complaints at the end of every carbamazepine period can be observed in both groups, with minor improvement, no change or exacerbation following placebo administration. This lack of generalized response was specially noticeable after the first B period of the B-A-B sequence. Two patients in the first group did not complete the last carbamazepine period because of untoward effects; one of the second group did not attend to the last visit.

Table 5. *Overall results for each carbamazepine and placebo period*

Changes in symptoms	A	B	A	B	A	B
Disappearance (5↓)	1	0	0	0	1	2
Improvement (3↓ to 4↓)	6	2	8	0	9	2
Improvement (1↓ to 2↓)	7	6	3	7	5	7
No change	0	0	1	4	1	0
Increase (↑ to 5↑)	0	6	0	5	0	4
Not recorded			2			1

Table 6. *Type and frequency of untoward effects*

Somnolence	16	53.3%
Dizziness	12	40.0%
Gait changes	4	13.3%
Urticaria	2	6.6%
Nausea	2	6.6%
Vomiting	1	3.3%

Untoward effects (Table 6) were frequent but usually mild and transient. They appeared during the carbamazepine periods or in the first few days of placebo following carbamazepine administration. Mild somnolence and dizziness were the chief complaints, and they tended to subside after the first week of treatment. Two patients presented a cutaneous rash which required discontinuation of the drug.

Discussion

The original therapeutic use of carbamazepine was as an anticonvulsant [9, 4]. Further clinical experience showed that the new drug was capable of relieving paroxysmal crisis of neuralgia in a wide variety of disorders [2, 8, 3, 7, 1]. In some, like in trigeminal neuralgia, a central aetiological component has been implied, and it was suggested as the explanation for the therapeutic results obtained with this anticonvulsant. In others, such as tabetic crisis, the problem is spinal or peripheral and a different explanation for the antineuralgic action is required. In this relation, it has recently been shown that carbamazepine has a selective depressant effect upon the neurons involved in the central transmission of trigeminal pain impulses, and a similar mechanism might be responsible for its antineuralgic action in other types of pain [5].

Since this therapeutic effect seems to be non-specific and limited to the blocking of sensory impulses, no attempt was made to investigate the overall action of carbamazepine on diabetic neuropathy, especially as regards motor and visceral manifestations.

However, a central cortical effect, manifested through psychological changes, cannot be discarded. Carbamazepine is a drug closely related in structure to imipramine, which is a well known anti-depressant drug, and some studies have implied that it has at least a thalamic action. Furthermore, we have now some individual observations indicating that imipramine offers some symptomatic relief in diabetic neuropathy. Nevertheless, no systematic effort was made to evaluate a central psychological effect of carbamazepine, because it was thought that such an addition to the experimental design was out of the scope of this study.

Thus, with the purpose of studying the action of the drug on as many sensory symptoms of diabetic neuropathy as possible, we selected a mixed group of patients that included several clinical types of peripheral neuropathy. Classifications of diabetic neuropathy are usually incomplete and often confusing, and it was found that Plum's [6] division of peripheral neurologic diabetic disorders into hyperglycaemic neuralgia, arteriosclerotic peripheral neuropathy and "true" diabetic neuropathy was well suited for this clinical evaluation. The types described by Plum are purely clinical, and they include the following neurologic manifestations: hyperglycaemic neuralgia covers the diffuse muscular pain and paresthesia that frequently accompany early untreated diabetes and subside with treatment, usually no direct objective evidence of neural involvement can be found; peripheral neuropathy accompanying arteriosclerosis is characterized by paresthesia and symmetrical loss of sensation with lesser degrees of motor impairment, associated with other signs of circulatory involvement; lastly, "true" diabetic neuropathy gives a full-blown neurological picture with pain, dysesthesia, sensory loss, autonomic disturbances and moderate motor changes, and it can be seen in younger patients without gross findings of arteriosclerosis. All types were evenly represented in the group studied.

Relief of symptoms, in our patients, can be attributed only to drug action, placebo effect or spontaneous fluctuations, since changes in clinical management, body weight and metabolic control were carefully avoided. Nevertheless, it must be admitted that this study is subject to the limitations imposed by the fact that it was based on subjective evaluations made by each patient. Furthermore, the complete efficacy of the double blind system can be questioned, since the frequency of secondary effects may serve as an identifying clue to both the patient and the treating physi-

cian. Finally, the two week periods provend to be too short, and there was considerable residual action of the drug during the placebo administration, but unfortunately this was realized only after completion of the study.

Although we are well aware of these shortcomings, we feel that they are inherent in any clinical evaluation of relief of sensory symptoms. In spite of them, it appears unlikely that modifications in symptomatology could have been random spontaneous fluctuations, in view of the contrasting results obtained with the two different therapeutic sequences.

Thus, it appears that the overall results, as seen in Table 5, indicate a marked "blocking" action of carbamazepine upon the sensory manifestations of all clinical types of diabetic neuropathy. Some cases showed moderate improvement during placebo administration, but this was mainly so when the placebo was given following a period of carbamazepine, and it could be explained through residual action of the active drug.

Moreover, the moderate relief of symptoms seen in 25% of the patients during the first placebo period in the B-A-B sequence, is to be expected in any clinical trial including a placebo, and it contrasts sharply with the more marked and generalized improvement produced by carbamazepine. Decrease of pain occurred sooner than relief of paresthesia, but there was usually improvement of both, with remarkable amelioration in some cases. Two patients failed to show any response. Whenever present, motor, trophic and visceral symptoms remained unchanged.

The frequency of untoward effects was disturbing, but the side reactions were usually mild and transient and no instance of serious toxicity was observed.

From these results, it can be concluded that carbamazepine provides good, sometimes remarkable, symptomatic relief of sensory manifestations of peripheral diabetic neuropathy, and that, although they are very frequent, secondary effects are usually well tolerated. This therapeutic action of carbamazepine is very likely non-specific.

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