Tegretol in the Treatment of Diabetic Neuropathy

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SUMMARY

Patients suffering from peripheral neuropathy caused by diabetes mellitus were admitted to a double-blind trial comparing the efficacy of Tegretol (carbamazepine) and placebo. Objective and subjective parameters were measured to assess the effect of the treatment.

Significant relief of pain was obtained, often within a few days, on a dosage of 200 mg Tegretol *t.d.s.* No interference with diabetic control was observed.

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Pathologically, diabetic neuropathy is a segmental degeneration of the peripheral nerve. In some cases it is related to vessel narrowing or occlusion, while in other instances no apparent cause can be demonstrated. The resulting functional loss involves both motor and sensory fibres of the peripheral nerve, and usually the lower limb exhibits more severe disease than the upper.

Clinically, the condition is heralded by the onset of paraesthesia of limbs, fingers and toes; burning sensation of hands and feet; cramps and pains in the legs and muscles. Very often there is a characteristic diurnal variation, being worse at night and causing sleeplessness. In some instances, the disease is so severe that patients cannot endure blankets on their feet, even in midwinter.

It is a disease of great frequency—perhaps greater than is generally appreciated. The Natalspruit Hospital Diabetic Clinic has just completed a survey of the incidence of diabetic neuropathy, and at this stage the estimate is in the vicinity of 30% of cases (results to be published).

PATIENTS AND METHODS

The Trial

Forty patients were selected for a double-blind, within-patient cross-over trial comparing Tegretol and a placebo. Most of these patients had previously been treated for diabetic neuropathy and the usual treatments employed had met with little or no success.

The dosage used was Tegretol 200 mg *t.d.s.* and an identical placebo dosage. The trial was over a 4-week period. At day 0, following a wash-out period of 2 weeks, the patients were admitted, assessed and put onto either Tegretol or placebo, according to a prerandomised balanced sequence. At day 7 patients were crossed over from Tegretol to placebo or *vice versa*.

The patients were asked to evaluate their own symptoms using an analogue scale, and independent assessments were made by the investigator. At the end of the treatment period a preference statement was made independently by the patients and the investigator. Observations were carried out on days 0, 3, 7, 10 and 14, with full neurological examinations on each occasion.

The Patients

Forty patients were studied and with 1 exception, a Coloured woman, all were Black. All patients at time of admission were stabilised in terms of their respective diabetic treatments. All the patients completed the trial and the following information is pertinent.

The mean age of patients participating in the trial was 56,4 years (range 28 - 70 years). The sex ratio was identical for both groups, 75% (30) of the sample being female. The two treatment subsamples were homogeneous with respect to height and mass.

An arbitrary period of 3 months was a qualifying condition in terms of neuropathic symptomatology. Seventeen of the patients had symptoms which were present for one-and-a-half years or more, and in 8 patients for longer than 2 years. Thirty patients complained of intermittent symptoms and 10 suffered constant symptomatology. This percentage is identical for both groups. The most constant complaint was a burning pain of the feet and hands.

None of the patients appeared malnourished. None had an alcoholic history and in no instance was alcoholism suspected. With one exception, the patients were considered reliable witnesses. Two patients had hypertension. Three patients were insulin-dependent diabetics. In all cases environment was not considered to be a contributory factor in the aetiology of the neuropathy.

Parameters Measured

The parameters measured were both objective and subjective.

Subjective parameters included pain; numbness; agitation; ability to sleep; depression and anxiety.

Objective parameters included assessment of pain appreciation—pinprick; assessment of light touch; assessment of thermal appreciation; assessment of vibration sense in upper and lower limbs; assessment of position sense; reflexes; trophic changes; shininess of the skin; ulcers; ability to walk; hyperhidrosis; blood pressure; urine analysis; and fasting blood sugars.

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RESULTS

Relief of Pain

Pain was measured by the patients on a 10-cm analogue scale. The means and standard errors are given in Table I. Probabilities are given in brackets whenever the difference is statistically significant (tested by means of Student's *t*-test).

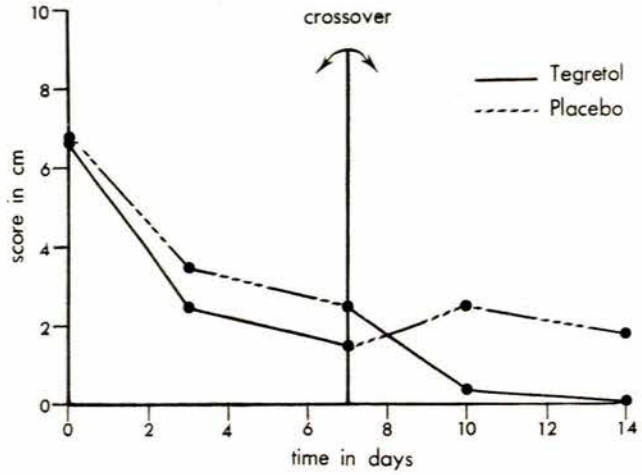

Fig. 1. Drug profile—pain.

Inspection of Table I and the drug profile shown in Fig. 1 indicates a number of important features:

The decrease in score for day 0 to day 3 is statistically significant ($P<0,01$) for both Tegretol and placebo. No difference was found between the treatment on day 0 or day 3. The two factors discussed above could indicate either a high placebo response or a disease fluctuation.

From day 3 to day 7, a further fall in the pain score was observed, and although Tegretol tended to decrease the pain score at a faster rate than placebo, this difference was not statistically significant.

From day 7 to day 10 (when crossover took place) the pain scores of placebo-treated patients increased, whereas the scores of the Tegretol patients decreased significantly ($P<0,01$).

On days 10 and 14 differences between the treatments were significant ($P<0,05$) in favour of Tegretol.

The results of this detailed analysis indicate that Tegretol is effective in controlling pain in diabetic neuropathy.

Pain was measured by the observer on a 4-point scale where 0 = absent, 1 = mild, 2 = moderate and 3 = severe. The results are tabulated and analysed by the Kruskal-Wallis H-test. No significant difference was found between the two subsamples on day 0. On days 3 and 7 a tendency towards significance in favour of Tegretol was observed (H = 2,88 and 3,09 respectively, $P<0,10$). On days 10 and 14 a statistically significant difference (H = 4,39, $P<0,05$ and H = 5,55, $P<0,01$) in favour of Tegretol was observed.

Numbness

Numbness significantly ($P<0,05$) decreased from day 0 to day 3 for the Tegretol-treated patients (Table II).

Numbness was also measured on a 4-point scale (0 = absent, 1 = mild, 2 = moderate and 3 = severe) by the observer at all 5 assessments. Three patients in the Tegretol/placebo treatment subsample and 1 in the placebo/Tegretol subsample were dropped from the analysis, since they had scores of '0' throughout the treatment period.

TABLE I. PAIN (10-CM ANALOGUE SCALE)

Pretreatment	Day 3	Day 7	Day 10	Day 14
	Tegretol		Placebo	
	($P<0,001$)		2,57 ± 0,76	1,78 ± 0,67
6,69 ± 0,75	2,54 ± 0,75	1,54 ± 0,56	($P<0,05$)	($P<0,05$)
	($P<0,01$)	($P<0,01$)		
6,74 ± 0,75	3,46 ± 0,62	2,48 ± 0,60	0,35 ± 0,24	0,02 ± 0,01
Pretreatment	Placebo		Tegretol	

TABLE II. NUMBNESS (10-CM ANALOGUE SCALE)

Pretreatment	Day 3	Day 7	Day 10	Day 14
	Tegretol		Placebo	
	($P<0,05$)			
4,62 ± 0,88	1,96 ± 0,66	2,18 ± 0,78	1,84 ± 0,66	1,21 ± 0,65
5,92 ± 0,76	3,93 ± 0,74	2,01 ± 0,63	0,74 ± 0,54	0,17 ± 0,16
Pretreatment	Placebo		Tegretol	

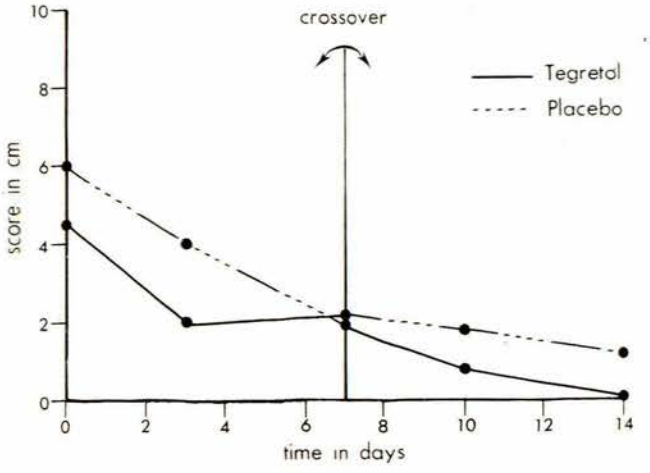

Fig. 2. Drug profile—numbness.

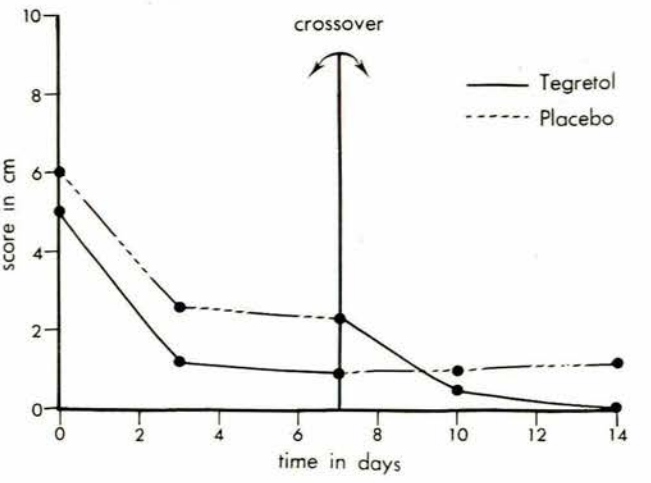

Fig. 3. Drug profile—ability to sleep.

The results of the Kruskal-Wallis H-test on this data showed that there was no significant difference between the two treatment subsamples on day 0, or between the treatments on days 3, 7, 10 and 14. With time the numbness improved to a greater extent with Tegretol treatment than with placebo.

Ability to Sleep

The patients measured their ability to sleep on a 10-cm analogue scale. The means and standard errors are given in Table III. The differences were tested by means of the Student's *t*-test and, where significant, the probabilities are given in brackets. One patient with a score of '0' throughout the period was dropped from the analysis.

Both Tegretol and placebo significantly ($P<0,01$) decreased the score from day 0 to day 3. On days 0, 3, 7 and 10 there is no significant difference between the two treatment subsamples. On day 14 the differences between the two treatments just failed ($P<0,1$) to reach significance in favour of Tegretol (Table III and Fig. 3).

Patient's Preference Statement

At the end of the trial period the patient was asked which treatment was preferred. This preference statement was scored either as 'week 1', 'week 2' or 'no difference'. Twenty-four patients preferred the active drug Tegretol, 14 preferred placebo and 2 were indifferent.

Investigator's Preference Statement

Twenty-eight patients improved on the active drug Tegretol, 9 patients improved on placebo, and 2 were indifferent. One patient was considered unreliable and omitted from the analysis.

The other parameters showed no significant difference. While it is not possible to include a detailed breakdown of all other parameters which were measured, this information is available. In most instances no improvement was anticipated in terms of areflexia, diminished sensation, diminished thermal appreciation, etc.

Side-Effects

Twenty-five of the 40 patients on Tegretol reported side-effects, and only 2 on the placebo. Side-effects were in most instances mild, transient, and of 2 - 3 days' duration. In view of the dosage regimen side-effects were not wholly unexpected and did not interfere with treatment.

TABLE III. ABILITY TO SLEEP (10-CM ANALOGUE SCALE)

Pretreatment	Day 3	Day 7	Day 14	Day 21
	Tegretol		Placebo	
	($P<0,01$)			
4,98 ± 0,82	1,22 ± 0,46	0,91 ± 0,59	2,44 ± 0,86	1,13 ± 0,62
	($P<0,01$)			($P<0,10$)
6,00 ± 0,79	2,64 ± 0,62	2,32 ± 0,76	0,94 ± 0,47	0,02 ± 0,00
Pretreatment	Placebo		Tegretol	

TABLE IV. SIDE-EFFECTS

	Total	Mild	Moderate	Severe
Tegretol				
Dizziness	21	14	3	4
Drowsiness	3	3		
Vomiting (1 day each)	4	1	1	2
Diarrhoea	1	1		
Paraesthesia left side of face (2 days)	1	1		
Anorexia	1	1		
*	31	21	4	6
Placebo				
Dizziness	2	2	0	0

* Some patients reported more than one symptom or side-effect.

DISCUSSION

Forty patients entered this within-patient trial to compare the efficacy and tolerability of Tegretol against placebo in the treatment of symptoms due to peripheral neuropathy caused by diabetes mellitus. Pretreatment homogeneity indicated the subsample Tegretol as the first drug and placebo as the second drug, and *vice versa*, to be completely homogeneous with respect to age, sex, race, mass, height, duration of illness, nature of symptoms, spontaneous daily fluctuation, previous therapy and concomitant medication.

Tegretol significantly improved pain (both patient and observer assessment) compared with placebo. A carry-over effect appears to be present in a number of cases. No serious side-effects were encountered in this trial, and there was no interference with diabetic control.

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 physician.

The results achieved are clinically remarkable if one considers the severity, chronicity, resistance to therapy and duration of the disease process.

It is the experience of this clinic that the incidence of diabetic neuropathy far outstrips that of neurosis, and that in the past many of us have glossed over the patients' symptomatology because of the difficulty in offering an effective therapy. Tegretol is a useful tool in the treatment of diabetic neuropathy.

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