Long-term treatment of trigeminal neuralgia with carbamazepine

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Summary
The results of treating 143 patients with trigeminal neuralgia with carbamazepine (CBZ) over a 16-year period have been reviewed. The drug was effective initially with few mild side effects in 99 patients (69%). Of these, 19 developed resistance later, i.e. between 2 months and 10 years after commencing treatment, and required alternative measures. Of the remaining 80 (56%), the drug was effective in 49 for 1-4 years and in 31 for 5-16 years. Thirty-six patients (25%) failed to respond to CBZ initially and required alternative measures, as did 8 (6%) who were intolerant of the drug. One patient developed CBZ-induced water intoxication with hyponatraemia. Subsequently hyponatraemia was excluded in 17 patients who had been taking CBZ for between 4 months and 7 years. This study has thus confirmed the efficacy of CBZ in the treatment of trigeminal neuralgia and shown that it may continue to be effective for many years.

Introduction
Since Blom's preliminary report (1962) of the relief of trigeminal neuralgia (TN) with carbamazepine (CBZ), this drug has become almost universally accepted as the first line of treatment for this condition. However, there have been few reports of long-term treatment (Marotta, 1969; Lloyd-Smith and Sachdev, 1969; Petit and Christiaens, 1970; Bonduelle, 1976). The object of this paper is to report the results of long-term treatment with CBZ in the patients with TN, who have attended the Regional Department since 1962 when CBZ was first supplied in the U.K. as G32883.

Following the discovery of CBZ-induced hyponatraemia and water intoxication in one of the patients (Stephens et al., 1977), this complication was looked for specifically in other patients who were still taking the drug.

Patients and methods
This review includes 143 patients with classical TN who have attended the Regional Department of Neurosurgery and Neurology at the Derbyshire Infirmary and the Nottingham General Hospital since 1962, and had treatment with CBZ. Others, with notes or details missing, and those with multiple sclerosis, tumours, trigeminal neuropathy and other facial pains were excluded.

There were 56 males and 87 females. The age of onset of TN ranged between 24 and 78 (mean 54) years. The neuralgia was right-sided in 83, left-sided in 59 and bilateral in one.

The starting dose of CBZ was 100 or 200 mg 3 or 4 times per day, and was increased until the pain was well controlled or side effects developed. Patients were advised to continue the minimum dose to prevent the pain, and to stop the drug during remissions. Those who did not respond adequately to CBZ or who developed intolerable side effects were treated with other drugs, alcohol injection or surgical procedures.

In order to check on the occurrence of hyponatraemia, 17 patients who were still taking CBZ during 1977 were reviewed and blood samples were taken for estimation of plasma electrolytes and urea and serum CBZ.

Results
Of the 143 patients, 46 (32%) were completely well controlled by CBZ, and 53 (37%) partially but acceptably controlled. Treatment with CBZ was therefore satisfactory initially in 99 (69%) of these patients. In 10 of these patients, mild transient side effects occurred but did not necessitate cessation of treatment. Some of the patients whose pain was only partially controlled with CBZ were also taking other...
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of the 99 patients who had a good initial response, 19 developed late resistance in that the pain recurred and did not then respond to CBZ. In these cases, resistance developed 2 months to 10 years (mean 4 years) after commencing treatment.

Sixty-three of the 143 patients (44%) required alternative treatment. These comprised 36 who failed to respond to CBZ initially, 8 who were intolerant of CBZ and the 19 who had responded initially but developed late resistance. Of the 80 patients who obtained satisfactory relief from CBZ without requiring other measures, 31 took the drug for periods ranging from 5 to 16 years (Fig. 1). Thirteen of these patients died (aged 59–96 years) from various coincidental causes during the period of follow-up.

Some patients required and tolerated 200 mg 5 to 8 times per day during severe bouts; others found that 100 mg 2 or 3 hourly was the best regime to control pain without side effects. Many patients could tell whether the pain was liable to recur because, at certain times, touching the face or eating still tended to trigger the pain. Relatively small maintenance doses of CBZ (100 to 200 mg twice daily or less frequently) was sometimes sufficient, but the commonest dosage was 200 mg thrice daily.

Of the 8 patients who developed side effects necessitating cessation of CBZ, 6 had a rash. One patient had to stop treatment owing to nausea and thirst on a dose of 300 mg daily, and in 1976 another patient developed CBZ-induced water intoxication (Stephens et al., 1977). Subsequently, 17 of the patients who were still taking CBZ attended for review and the results of estimation of their plasma electrolytes and urea, and serum CBZ are shown in Table 1. Their age range and average age (61–2 years) were comparable to that of the group as a whole. None had symptoms of water intoxication nor plasma sodium lower than 137 mmol/l, and the blood urea of each patient was also normal, ranging from 3·0 to 7·4 mmol/l (mean 5·2 mmol/l). The serum CBZ levels in these patients ranged from 2·5 to 8·5 mg/ml.

Discussion

When CBZ under the guise of G32883 was initially reported as relieving TN (Blom, 1962), a new era in the treatment of this condition started. The first reports of its use in the U.K. (Taylor, 1963; Spillane, 1964; Graham and Zilkha, 1966) confirmed its efficacy and CBZ is now generally regarded as the drug of choice for the treatment of TN. The present

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**Table 1. Details of 17 patients with trigeminal neuralgia; dosage and serum levels of carbamazepine, plasma sodium and blood urea**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years) and sex</th>
<th>Duration (years)</th>
<th>Dose (mg/day)</th>
<th>Serum level (µg/ml)</th>
<th>Plasma sodium (mmol/l)</th>
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results support this, pain being satisfactorily controlled by CBZ initially in 69% of the patients.

With regard to the long-term results, in 56% CBZ remained effective, often in relatively small doses taken continuously or intermittently for many years. However, 25% had no relief of pain from CBZ, 13% became resistant after responding initially, and 6% were intolerant of the drug, so that alcohol injection or other measures were necessary in 44%.

The majority of patients, however, could tolerate CBZ. Although one patient developed water intoxication, no evidence of hyponatraemia was discovered in the remainder who were still taking the drug. It is now established that CBZ has water-retaining properties and Stephens, Coe and Baylis (1978) have suggested that this anti-diuretic action is a physiological effect of the drug, mediated by increased renal sensitivity to normal plasma concentrations of arginine vasopressin (AVP) and resetting of osmo-receptors. In 2 other reports of patients with CBZ-induced water intoxication (Ashton et al., 1977; Smith, Esprit and Baylis, 1977), the plasma AVP concentrations were inappropriately high and returned to normal when the drug dosage was reduced, consistent with disturbed auto-regulation. Special care should thus be exercised when treating TN with CBZ in elderly patients and those with cardiovascular disease. If symptoms consistent with water intoxication occur, the plasma sodium and osmolality should be checked. If hyponatraemia develops, CBZ should be reduced or stopped. However, this is a rare complication and long-term treatment with CBZ which proved successful in more than 50% of the present patients with TN should now have an established place in the management of this condition.

Acknowledgments
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References