

# Oxcarbazepine: a new drug in the management of intractable trigeminal neuralgia

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**SUMMARY** The efficacy and tolerability of oxcarbazepine, a keto derivative of carbamazepine, has been assessed in six patients (two males, four females; mean age 61 years, range 42-77), with trigeminal neuralgia refractory to carbamazepine therapy, over a period of 6 months. An excellent therapeutic response to oxcarbazepine was seen in all patients with pain control correlating well with serum drug concentrations of oxcarbazepine and its primary active metabolite 10-OH-carbazepine. Onset of the effect was observed within 24 hours in all cases. An overall serum therapeutic concentration range, in the six patients, of 50-110  $\mu\text{mol/l}$  of 10-OH-carbazepine corresponding to a daily effective dose range of 1200-2400 mg (14.6-35.6 mg/kg body weight) oxcarbazepine, was observed. There was a significant correlation between oxcarbazepine dose and serum oxcarbazepine ( $r = 0.695$ ,  $p < 0.05$ ) and 10-OH-carbazepine ( $r = 0.957$ ,  $p < 0.001$ ) concentrations. Oxcarbazepine was well tolerated and no significant side effects were identified, though a mild hyponatraemia was observed during high doses ( $> 28$  and  $> 35$  mg/kg/day) in two patients. It is concluded that oxcarbazepine has potent antineuralgic properties in the absence of significant side effects and therefore may be useful in the management of intractable trigeminal neuralgia.

Carbamazepine is currently the drug of choice in the management of trigeminal neuralgia with an onset of action within 24 hours.<sup>1-4</sup> It is efficacious in only 70-80% of patients, and can be associated with toxicity manifested by drowsiness, confusion, nausea, ataxia, nystagmus and hypersensitivity necessitating discontinuation of medication.<sup>5,6</sup> Twenty per cent of patients responding initially to treatment may subsequently become refractory to carbamazepine.<sup>7</sup>

Oxcarbazepine (10,11-dihydro-10-oxo-5H-dibenz-(b,f)azepine-5-carboxamide), a keto derivative of carbamazepine, has been shown to have equal efficacy to carbamazepine in the management of epilepsy but with less side effects and greater tolerance.<sup>8-10</sup> Oxcarbazepine is rapidly absorbed after oral ingestion<sup>11,12</sup> and is metabolised to two major metabolites, 10,11-dihydro-10-hydroxycarbamazepine (10-OH-carbazepine) and trans-10, 11-dihydro-10, 11-dihydroxy-

carbamazepine. 10-OH-carbazepine is the primary metabolite and is active pharmacologically as an anticonvulsant drug.<sup>13</sup> Additionally, oxcarbazepine has been found useful in the management of affective disorders<sup>14</sup> and spasticity.<sup>15</sup> Recently, Farago (1987)<sup>16</sup> in a series of 13 patients with trigeminal neuralgia has reported that oxcarbazepine has antineuralgic properties in the absence of significant side effects.

The present evaluation was designed to assess the efficacy and tolerability of oxcarbazepine in the management of trigeminal neuralgia in 6 patients refractory to carbamazepine therapy over a period of 6 months and to determine systematically individual therapeutic doses of oxcarbazepine and therapeutic serum concentration ranges for 10-OH-carbazepine, the primary active metabolite of oxcarbazepine.

## Patients and methods

All six patients had classical idiopathic trigeminal neuralgia as indicated by the following criteria: (1) pain in the distribution of the trigeminal nerve; (2) pain of "electric shock", shooting or stabbing character of short duration; (3) pain provoked by innocuous stimuli such as light touch or vibration; (4) paroxysmal pain with episodes of complete

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Received 14 June 1988 and in revised form 24 September 1988.  
Accepted 8 November 1988

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remission; (5) complete abolition of pain could be achieved by a local anaesthetic injection into the trigger zone or by a regional block.

The six patients (four females and two males) aged 42–77 years (mean 61) had been diagnosed as having trigeminal neuralgia for 6 months to 16 years (mean 7.4). Details of the individual patients and their medication regimens just prior to oxcarbazepine treatment are shown in table 1. Two patients had a proven allergy to carbamazepine<sup>5</sup> and four patients had failed to gain pain control with carbamazepine or phenytoin due to the development of side effects.

At the time of entry into the assessment all patients had been suffering from painful paroxysms for at least 4 weeks. Each patient had a history of good drug compliance and was capable of assessing the severity of his/her pain. Informed written consent was obtained from all patients and oxcarbazepine was prescribed on a named patient basis. Patients were free to withdraw from the assessment at any time.

*Assessment protocol design*

Patients were clinically evaluated as out-patients and oxcarbazepine administered orally in the form of 300 mg tablets 2–4 times a day (Ciba Geigy Pharmaceuticals, UK). Prior medication was either withdrawn immediately (2 patients) or withdrawn over a period of 2 days (4 patients). Patients were examined weekly and oxcarbazepine adjusted until pain control was achieved, and then followed up at 2–4 weekly intervals. At the end of a pain free 2-week period, patients were considered optimally managed on oxcarbazepine and dosage decreased by one dose/week (300 mg). If patients relapsed dosage was re-titrated. In four patients depression and anxiety was assessed by the use of the Hospital Anxiety and Depression Scale<sup>17</sup> before the start of oxcarbazepine and after 6 months of treatment.

Biochemical and haematological screens were carried out prior to treatment with oxcarbazepine and at intervals during the assessment period. Blood samples for the determination of steady state serum oxcarbazepine and 10-OH-carbazepine concentrations were collected between 3 and 4 hours after the morning dose. Serum samples were stored frozen at -20°C until analysis.

*Pain registration*

All patients kept a weekly pain and activity diary where self-registration of pain was recorded. The diary was divided into 3 hour periods for the recording of diurnal pain severity and drug related side effects. This type of pain assessment in trigeminal neuralgia has been used previously with success<sup>18</sup> and allows for the rapid establishment of dose and serum drug concentration/response correlates. The severity of the pain paroxysm was assessed as nil—0, mild—1, moderate—2, severe—3, most severe—4.

*Analysis of oxcarbazepine and 10-OH-carbazepine*

Oxcarbazepine and its primary metabolite 10-OH-carbazepine were analysed by a recently developed microassay technique using high pressure liquid chromatography.<sup>19</sup> Briefly, to 300 µl of serum was added 4 µg of 10-methoxycarbamazepine as internal standard, 300 µl of 0.2 M NaOH and 1 ml dichloromethane. After shaking for 15 min and centrifuging for a further 5 min, the aqueous layer was aspirated and the dichloromethane layer transferred to a clean 2.0 ml microcentrifuge tube (Sarstedt Ltd) and evaporated to dryness using oxygen free nitrogen. Each sample was then reconstituted in 15 µl acetonitrile and 10 µl injected into a Spectra Physics SP8000 liquid chromatograph. LiChrosorb RP8 10 µ column (Hichrom Ltd) and an acetonitrile:water (35:65) mobile phase (flow rate 1.8 ml/min) resulted in retention times for 10-OH-carbazepine, oxcarbazepine and 10-methoxycarbamazepine of 3.5, 5.0 and 8.5 min, respectively. The Schoeffel S 770 UV detector was set at 215 nm.

**Results**

Oxcarbazepine dosage ranged from 600 mg to 2400 mg/day. Steady state serum oxcarbazepine and 10-OH-carbazepine concentrations at 3–4 hours after the morning dose ranged from 0.0–11.4 µmol/l and 42–150 µmol/l respectively. Both oxcarbazepine and 10-OH-carbazepine serum concentrations correlated significantly,  $r = 0.957$  ( $p < 0.001$ ) and  $r = 0.695$  ( $p <$

Table 1 *Clinical evaluation of the six patients with trigeminal neuralgia*

Patient	Sex	Age (yr)	Duration of trigeminal neuralgia (yr)	Location of neuralgia	Medication just prior to oxcarbazepine (dose, mg/d)	Duration of last treatment therapy (mths)	Steady state serum concentration (µmol/l)	Reason for initiation of oxcarbazepine
1	M	77	3.0	L-V <sub>b</sub>	Phenytoin (300)	3.0	—	Refractory to management with phenytoin. Hypersensitized to carbamazepine
2	F	42	5.0	R-V <sub>b</sub>	Phenytoin (600)	2.0	119	Phenytoin induced side effect eg drowsiness. Hypersensitized to carbamazepine
3	F	72	10.0	R-V <sub>b</sub>	Phenytoin (300)	1.0	36	Suffered nausea and headaches. Low white cell count
4	F	58	0.5	R-V <sub>c</sub>	Carbamazepine (400)	5.0	13	Refractory to treatment.
				L-V <sub>c</sub>	Phenytoin (300)		44	
5	M	69	16.0	R-V <sub>a</sub>	Carbamazepine (600)	8.0	21	Nausea and drowsiness
				R-V <sub>b</sub>	Carbamazepine (800)		47	
6	F	47	10.0	R-V <sub>a</sub>	Phenytoin (300)	8.0	36	Refractory to treatment.
				R-V <sub>c</sub>	Carbamazepine (1600)		34	

L=left, R=right, V<sub>a</sub>=Ophthalmic division trigeminal nerve, V<sub>b</sub>=Maxillary division trigeminal nerve, V<sub>c</sub>=Mandibular division trigeminal nerve.

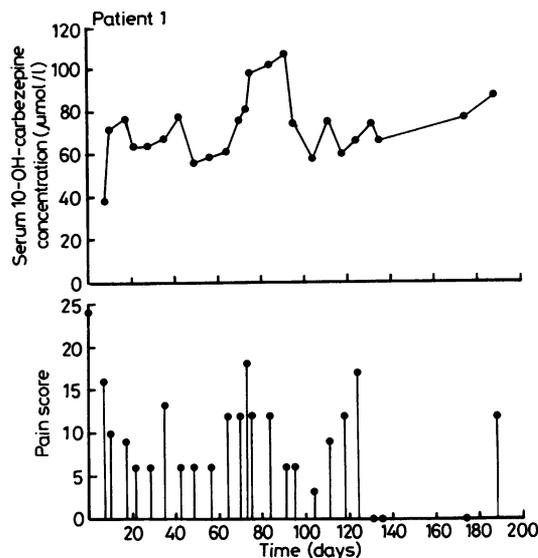


Fig 1 Steady state serum 10-OH-carbazepine concentrations (upper panel) and corresponding daily pain scores (lower panel) during 6 months of oxcarbazepine treatment (patient 1).

0.05) respectively, with oxcarbazepine dose. Additionally, serum concentrations of oxcarbazepine, which were 15–30 fold lower than those of 10-OH-carbazepine, and 10-OH-carbazepine correlated significantly ( $r = 0.810$ ,  $p < 0.001$ ).

A longitudinal comparison of total daily pain score and serum 10-OH-carbazepine concentrations in two

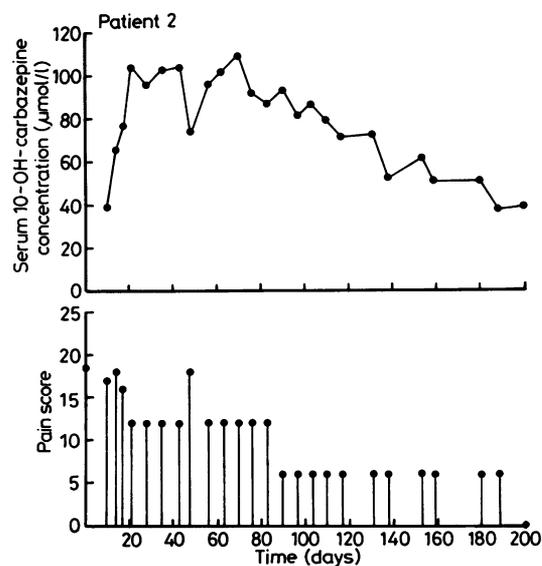


Fig 2 Drug concentrations and pain scores in patient 2.

patients during 6 months of oxcarbazepine therapy is shown in figs 1 and 2. For clarity and because serum oxcarbazepine was not detectable at the lower oxcarbazepine doses, serum oxcarbazepine concentrations have been omitted from the figures. The daily pain scores shown (maximum score = 24) are those of the 24 hour period prior to the morning serum 10-OH-carbazepine concentration. There was a wide inter-individual range both prior to oxcarbazepine treatment (day 0) and during the six month assessment period and this is a reflection to some extent, of the clinical condition with spontaneous fluctuations in the severity of the pain. Additional variation can probably be attributed to inter-individual differences in pain estimation, consequently each patient acted as his/her own control. Pain scores of 7 and above were associated with a decline in ability to eat and talk.

The response to oxcarbazepine treatment was dramatic in all patients with the onset of effect occurring in all cases within 24 hours. This is particularly well illustrated by patient 2 (fig 2) who had been unable to maintain good oral hygiene prior to commencement of oxcarbazepine therapy (fig 3). 10-OH-carbazepine concentration ranges were determined for each patient and these data are shown in table 2. Pain control correlated well with serum 10-OH-carbazepine concentration with excellent overall pain alleviation in our 6 patients when serum 10-OH-carbazepine concentrations were in the range 50–110 µmol/l. Large changes in serum 10-OH-carbazepine concentrations were associated with pronounced and almost immediate alteration in pain score (for example fig 2, day 49). Anxiety and depression scores in three of the four patients assessed were reduced by an average of 43% and 59% respectively. The continuing depression seen in the fourth patient can be attributed to a cardiac condition and his anaesthesia dolorosa.

No clinical side effects were observed although a mild hyponatraemia ( $\text{Na} = 123\text{--}131$  mmol/l) was seen in two patients taking high doses ( $> 28$  mg/kg/d and  $> 35$  mg/kg/d) of oxcarbazepine. One of these patients had an associated 1 kg weight gain. All other haematological and biochemical parameters were normal.

## Discussion

Oxcarbazepine has been used to treat systematically six patients with intractable trigeminal neuralgia over a period of 6 months and good therapeutic responses have been observed. The associated reduction in the anxiety and depression score in three of the four patients tested, reflected the very clear improvement in the patients' quality of life.

Since oxcarbazepine is rapidly metabolised to 10-OH-carbazepine it is difficult to ascertain which

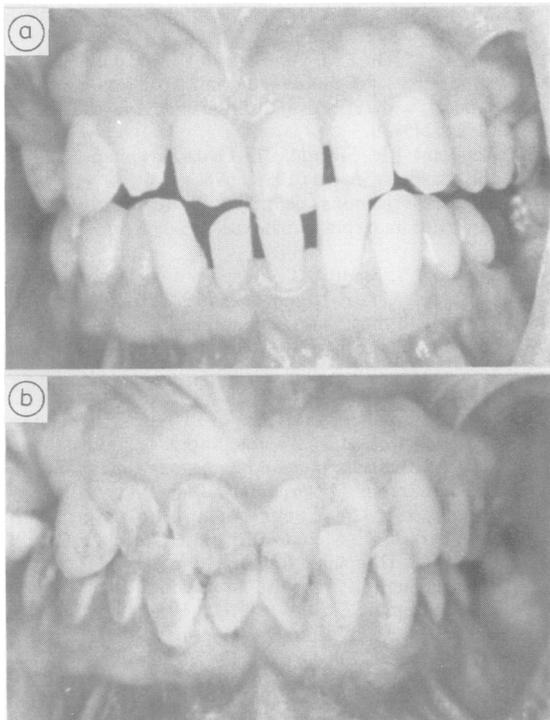


Fig 3 Oral hygiene before (a) and 2 months after (b) treatment with oxcarbazepine (patient 2). The maintenance of good oral hygiene after oxcarbazepine treatment is clearly visible.

compound is responsible for the observed effects in our patients. Farago<sup>16</sup> has, however, administered 10-OH-carbazepine to 11 patients with trigeminal neuralgia who responded very well and suggests that perhaps oxcarbazepine's therapeutic role may be that of a pro-drug. The significant correlation between dose and serum concentrations of oxcarbazepine and 10-OH-carbazepine is in agreement with Farago<sup>16</sup> and suggests that first order kinetics operate at serum concen-

Table 2 Oxcarbazepine therapeutic dose and serum 10-OH-carbazepine ranges in six patients

Patient	Dose needed to achieve optimal pain control		Serum 10-OH-carbazepine therapeutic range $\mu\text{mol/l}$
	mg/d	mg/kg/d	
1	1200	14.6	70-80
2	2400	21.3	90-110
3	1200	21.0	60-80
4	2100	32.8	60-80
5	1500	18.0	50-70
6	2100	35.6	70-90
Overall patient range:	1200-2400	14.6-35.6	50-110

trations observed in this assessment ( $< 152 \mu\text{mol/l}$ , 10-OH-carbazepine;  $< 22.5 \mu\text{mol/l}$  oxcarbazepine).

A placebo effect in trigeminal neuralgia is negligible,<sup>3</sup> therefore the significant correlation between serum oxcarbazepine and 10-OH-carbazepine concentrations and pain control suggests that the measurement of either would be a good index of therapeutic efficacy. However, the fact that serum 10-OH-carbazepine concentrations are 15-30 fold higher than that of oxcarbazepine, and that pharmacologically 10-OH-carbazepine may be more important, indicates that the measurement of serum 10-OH-carbazepine is perhaps more appropriate.

The optimal serum therapeutic range, in our patients, for 10-OH-carbazepine was 50-110  $\mu\text{mol/l}$  and compares well with that previously reported (35-100  $\mu\text{mol/l}$ ).<sup>16</sup> No adverse side effects were reported by our patients and the allergic skin reaction, present in two patients which were hypersensitive to carbamazepine, completely cleared during oxcarbazepine therapy. The hyponatraemia that has been associated with oxcarbazepine therapy<sup>20,21</sup> was only observed at the high doses ( $> 28$  and  $> 35 \text{ mg/kg/day}$  in two different patients), was mild and essentially clinically asymptomatic.

It is concluded from the present study that oxcarbazepine has potent antineuralgic properties in the absence of significant side effects and therefore may be useful in the management of intractable trigeminal neuralgia.

We are grateful to Dr F F Nally and Mr D G T Thomas for referring their patients. We thank Ms J Wilson and Mr A A Elyas for technical assistance, Mrs Marina Shaw for her excellent secretarial assistance and Ciba Geigy Pharmaceuticals (UK) for the supply of oxcarbazepine. Generous financial support from the Welton Foundation to JMZ and CSO Valuations to PNP is gratefully acknowledged.

#### References

- Campbell FG, Graham JG, Zilkha KJ. Clinical trial of carbamazepine (Tegretol) in trigeminal neuralgia. *J Neurol Neurosurg Psychiatry* 1966;**29**:265-7.
- Rasmussen P, Rushede J. Facial pain treated with carbamazepine (Tegretol). *Acta Neurol Scand* 1970;**46**:385-408.
- Rockliff BW, Davies EH. Controlled sequential trials of carbamazepine in trigeminal neuralgia. *Arch Neurol* 1966;**15**:129-36.
- Tomson T, Tybring G, Bertilsson L, Ekblom K, Rane A. Carbamazepine therapy in trigeminal neuralgia. Clinical effects in relation to plasma concentration. *Arch Neurol* 1980;**37**:699-703.
- Zakrzewska JM, Ivanyi L. In vitro lymphocyte proliferation by carbamazepine, carbamazepine-10, 11-epoxide and oxcarbazepine in the diagnosis of drug induced

- hypersensitivity. *J Allergy Clin Immunol* 1988;**82**:110–5.
- 6 Sillanpaa M. Carbamazepine pharmacology and clinical use. *Acta Neurol Scand* 1981;**64**(suppl 88):115–6.
  - 7 Taylor JC, Brauer S, Espir MLE. Long term treatment of trigeminal neuralgia with carbamazepine. *Postgrad Med J* 1981;**57**:16–8.
  - 8 Rai PV. Clinical trial for the estimation of anticonvulsant properties and side reactions of a new drug keto-carbamazepine. In: Wada JA, Penry JK, eds. *Advances in Epileptology: Xth Epilepsy International Symposium*. New York: Raven Press, 1980:357.
  - 9 Philbert A, Dam M, Jackobsen K. Oxcarbazepine in the treatment of epilepsy—a usable alternative to carbamazepine? *Irish J Med Sci* 1986;**155**:297.
  - 10 Reinikainen KJ, Keranen T, Halonen T, Komulainen H, Riekkinen PJ. Comparison of oxcarbazepine and carbamazepine: a double blind study. *Epilepsy Res* 1987;**1**:284–9.
  - 11 Schutz H, Feldman KF, Faigle JW, Kriemler HP, Winkler T. The metabolism of <sup>14</sup>C-oxcarbazepine in man. *Xenobiotica* 1986;**16**:769–78.
  - 12 Theisohn M, Heimann G. Disposition of the antiepileptic oxcarbazepine and its metabolites in healthy volunteers. *Eur J Pharmacol* 1982;**22**:545–51.
  - 13 Baltzer V, Schmutz M. Experimental anticonvulsive properties of GP 47680 and GP 47779, its main human metabolite; compounds related to carbamazepine. In: Meinardi H, Rowan AJ, eds. *Advances in Epileptology*. Amsterdam and Lisse: Swetz and Zeitlinger, 1977: 295–9.
  - 14 Emrich HM, Dose M, von Zerssen D. The use of sodium valporate, carbamazepine and oxcarbazepine in patients with affective disorders. *J Affective Disord* 1985;**8**:243–50.
  - 15 Bittencourt PR, Silvado CE. Oxcarbazepine, GP 4779 and spasticity. *Lancet* 1985;**i**:676.
  - 16 Farago F. Trigeminal neuralgia: its treatment with two new carbamazepine analogues. *Eur Neurol* 1987;**26**: 73–83.
  - 17 Zigmond AS, Snaith RP. Hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361–70.
  - 18 Tomson T, Tybring G, Bertilsson L, Ekbon K, Rane A. Carbamazepine therapy in trigeminal neuralgia: clinical effects in relation to plasma concentration. *Arch Neurol* 1980;**37**:699–703.
  - 19 Elyas AA, Goldberg VD, Patsalos PN. A microanalytical high pressure liquid chromatographic technique for the assay of oxcarbazepine and its primary metabolite 10-OH-carbazepine. *J Chromatogr* 1988; (in press).
  - 20 Houtkooper MA, Lammertsma A, Meyer JWA, Goedhart DM, Meinardi H, van Oorschot CEAH, Blom GF, Hoppener RJE, Hulsman JARJ. Oxcarbamazepine (GP 47.680): a possible alternative to carbamazepine. *Epilepsia* 1987;**28**:693–8.
  - 21 Johannessen AC, Nielsen OA. Hyponatremia induced by oxcarbazepine. *Epilepsy Res* 1987;**1**:155–6.