Oxcarbazepine: Drug of the Future in the Treatment of Trigeminal Neuralgia

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ABSTRACT

**Background:** The aim of the study was to estimate the efficacy of oxcarbazepine in trigeminal neuralgia. Oxcarbazepine is a novel antiepileptic drug, and its effect on trigeminal neuralgia has not been studied extensively previously.

**Materials and methods:** Fifty-three patients with trigeminal neuralgia (34 men and 19 women) took a mean dose of 600 mg of oxcarbazepine for a period of three weeks. Pain intensity was measured by using visual analog scale.

**Results:** Of the 53 patients, 42 (79%) were completely or well controlled by OXC, and nine (17%) partially but acceptably controlled. Treatment with OXC was therefore satisfactory initially in 51 (96%) of the patients. In seven of these patients, mild transient side effects occurred but did not necessitate cessation of treatment.

**Conclusion:** OXC appears to be an effective substitute for carbamazepine in those patients intolerant of this agent, or experiencing significant side effects.

**Keywords:** Trigeminal neuralgia, Oxcarbazepine, Carbamazepine.

INTRODUCTION

Trigeminal neuralgia is a sudden, brief, sharp, stabbing, recurrent pain in the distribution of the trigeminal nerve. It usually presents after the age of 50, is unilateral and affects the sensory branches of the fifth cranial nerve. In most patients trigeminal neuralgia is caused by compression of the trigeminal nerve root, close to its entry into the pons, by an aberrant arterial or venous loop. Less than 10% of patients have symptomatic disease associated with an identifiable cause other than a vascular compressive lesion—usually a benign tumor or cyst.

Antiepileptic drugs are commonly used in the treatment of trigeminal neuralgia. Older antiepileptic drugs, like phenytoin, carbamazepine, valproate, phenobarbital and benzodiazepines have been used in epilepsy treatment for many years. Many newer antiepileptic drugs have been introduced since the early 1990s, including felbamate, gabapentin, lamotrigine, oxcarbazepine (OXC), topiramate, tiagabine, vigabatrin, zonisamide, pregabalin and levetiracetam. Compared to the pharmacokinetics of older antiepileptic drugs, these new drugs have progressed in terms of longer half-lives, permitting once- or twice-daily dosing, greatly reduced potential for drug interactions, thus increasing ease of treatment, and general lack of hepatic enzyme induction, which facilitates polytherapy as well as other aspects of treatment.

OXC is a novel AED that is chemically related to CBZ and is approved as an initial or add-on treatment for partial seizures. Oxcarbazepine follows a different metabolic pathway, resulting in several clinical advantages. Unlike carbamazepine, it is not metabolized to an epoxide metabolite (which is responsible for many of the toxic effects). The carbonyl group of the parent compound oxcarbazepine is reduced by presystemic 10-keto-reduction to form 10-monohydroxy derivate (MHD), which is the metabolite responsible for the pharmacological effect of oxcarbazepine in vivo. Minor amounts are oxidized to the pharmacologically inactive metabolite 10,11-dihydroxy derivative (DHD). Very low concentrations of the parent drug are found in patients taking therapeutic amounts of oxcarbazepine. Oxcarbazepine, MHD, and carbamazepine all share a principal mechanism of action, which is the blockade of voltage-gated sodium channels, thereby stabilizing hyperexcited neural membranes, inhibiting repetitive neuronal firing and diminishing the propagation of synaptic impulses. However, there are small differences in other mechanisms, mainly that MHD blocks N/P- and R-type calcium channels, while carbamazepine blocks L-type calcium channels.

Antiepileptic drugs can adversely affect cognitive function by suppressing neuronal excitability or enhancing inhibitory neurotransmission. The most common side effects of oxcarbazepine are dizziness, somnolence, headache, ataxia and abdominal complaints, whereas a more serious side effect is hyponatremia. Studies suggest that OXC does not affect cognitive function in epilepsy patients. It is probably not harmful after 1 year of medication.
As a result of its pharmacokinetic advantages, oxcarbazepine was selected for this study. Very limited research has been conducted in this area of medical field. Hence, the aim of the study was to compare the efficacy of oxcarbazepine in the treatment of trigeminal neuralgia.

MATERIALS AND METHODS

This study was carried out in the Department of Oral Medicine and Radiology, Sharad Pawar Dental College and Hospital, Wardha, and RKDF Dental College and Research Centre, Bhopal, India. Fifty-eight patients with classical trigeminal neuralgia were treated with OXC, with 53 completing the study including 34 men and 19 women. The patients ranged in age from 48 to 71 years. All the patients included in this study had classical idiopathic trigeminal neuralgia as indicated by the following criteria: (1) Intense, sharp, stabbing pain in the distribution of the trigeminal nerve; (2) paroxysmal attacks of pain lasting from a fraction of a second to 2 minutes; (3) pain provoked by innocuous stimuli such as light touch or vibration; (4) complete abolition of pain could be achieved by a local anesthetic injection into the trigger zone or by a regional block; (5) no neurological deficit is clinically evident; (6) not attributed to another disorder. Exclusion criteria included patients with hematological, hepatic disease, renal failure or with any systemic illness, pregnancy or breastfeeding mothers; and who were treated surgically for trigeminal neuralgia in the past. All patients were suffering from trigeminal neuralgia from 10 months to 7 years. Details of individual patients and their previous regimens are given in Table 1. This study was approved by the local ethical committee. Informed written consent was obtained from all patients. The patients were given 600 mg oxcarbazepine (Oxcarb 300, Cipla) for 3 weeks. As there is less need for therapeutic drug monitoring with the newer antiepileptic drugs, and due to short duration of therapy in the present study, therapeutic monitoring of OXC was not done. Pain intensity was measured by using visual analog scale. In it descriptive rating scales, e.g. no pain, mild, moderate and severe pain were used.

RESULTS

Fifty-three patients had received treatment with this single antiepileptic drug. Out of 53, 19 patients had received treatment with carbamazepine in the past, three patients had received treatment with phenytoin, and four patients received a combined dose of carbamazepine and phenytoin. Most of the patients were refractory to treatment or suffered from adverse effects like drowsiness and skin rashes. The previous treatment was gradually stopped and new treatment with oxcarbazepine was started. All took a mean dose of 600 mg of oxcarbazepine for a period of 2 weeks. Further follow-up for next 1 week was done. Onset of effect was observed within 48 hours in most cases.

Of the 53 patients, 42 (79%) were completely or well controlled by OXC, and nine (17%) partially but acceptably controlled. Treatment with OXC was therefore satisfactory initially in 51 patients (96%). In seven of these patients, mild transient side effects occurred but did not necessitate cessation of treatment. No evidence of skin rashes was noted. Two patients who did not respond adequately to OXC were treated with alcohol injection or surgical procedures. Forty-two patients with ‘no pain’ were advised to continue with the same dose, while dose of OXC was increased to 900 mg in nine patients with ‘mild pain’ in the visual analog scale.

DISCUSSION

There is good evidence that certain anticonvulsants exhibit analgesic action in neuropathic pain. This is on the basis of their ability to reduce neuronal excitability. There are differences among agents with regard to the specific mechanisms. For example, gabapentin modulates neuronal calcium channels, and carbamazepine and lamotrigine act on sodium channels, while topiramate acts on both. The well-studied agents are gabapentin, pregabalin and carbamazepine; however, there is growing evidence for lamotrigine, topiramate and oxcarbazepine. In trigeminal neuralgia, oxcarbazepine monotherapy is as effective as carbamazepine with fewer side effects. The evidence suggests that carbamazepine is still the first line drug for medical management of trigeminal neuralgia, but this should be changed to oxcarbazepine if there is poor efficacy and an unacceptable side effect profile. Combination of carbamazepine with lamotrigine or baclofen is the second line treatment when monotherapy fails, but the evidence is weak.

Carbamazepine remains the drug of choice for trigeminal neuralgia; however, oxcarbazepine and lamotrigine are potential alternatives. Several studies had raised the need for large-scale randomised controlled trials on the efficacy of antiepileptic drugs in neuropathic pain in general, and in cancer-related neuropathic pain and neuropathic pain of central origin in particular. Oxcarbazepine is considered to be safer than carbamazepine in relation to the fact that it has no epoxide metabolite, has less hepatic induction and it does not depress white cell counts. The aplastic anemia and agranulocytosis that can be seen with carbamazepine may also not occur. Several double-blind, placebo-controlled trials have evaluated oxcarbazepine in painful diabetic neuropathy and trigeminal neuralgia. There is good evidence that oxcarbazepine is effective in relieving the pain associated with trigeminal neuralgia. Its efficacy in treating painful diabetic neuropathy is less clear; however, it seems to be useful when tolerated at doses of 1800 mg/day.

Several studies have shown the role of OXC in epilepsy. However its role in TN lacks enough evidence. Farago F20 tested the dihydroketo and dihydromonohydroxy analogs of carbamazepine against carbamazepine in patients suffering from trigeminal neuralgia. Both derivatives brought about freedom from symptoms or a marked reduction in the pain in all patients. For both analogs the effective dose was between 10 and 20 mg/kg body weight in most patients. There was a linear
relationship, with a correlation coefficient of 0.83 (n = 36; p less than 0.001), between the doses and the serum level. Farago F further stated that doses almost twice as high as those of carbamazepine are needed in order to achieve freedom from symptoms with the carbamazepine analogues. Since unwanted effects, in the form of dizziness and ataxia, occur much less frequently than with carbamazepine, the analogues can be administered in higher doses. A review found three randomized, controlled trials demonstrating an analgesic effect in trigeminal neuralgia, and one controlled trial found comparable analgesia between amitriptyline and oxcarbazepine in cancer-related neuropathic pain, with fewer adverse events in the oxcarbazepine group. There were no important changes in cognitive function testing during administration of OXC compared with placebo. Standard doses of OXC can be given as add-on therapy in epileptic patients receiving carbamazepine, valproic acid or phenytoin without producing a clinically relevant pharmacokinetic interaction.

Serum concentrations of unchanged OXC are very low and decline rapidly over the first 8 to 10 hours after drug intake. One study indicates that the kinetics of OXC and 10-OH-CZ are not influenced significantly by comedication with valproic acid, and are affected only moderately by comedication with phenobarbital. Patsalos PN et al reported oxcarbazepine to be less of a hepatic enzyme inducer than carbamazepine or carbamazepine and phenytoin in combination, however induction by OXC may be dose related. Thus, oxcarbazepine appears to be an effective substitute for carbamazepine in those patients intolerant of this agent, or experiencing significant side effects. OXC has no negative effect on cognition; it does not increase the risk of fractures or rash. Oxcarbazepine may be useful in the management of intractable trigeminal neuralgia, and should be called the drug of the future. Future studies should examine the effects of oxcarbazepine in monotherapy and in adjunct therapy with other anticonvulsants.

REFERENCES

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