Seizure (2006) **15**, 150—155

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Oxcarbazepine reduces seizure frequency in a high proportion of patients with both newly diagnosed and refractory partial seizures in clinical practice

G. Pauletto *, **P. Bergonzi**

On behalf of the Triveneto Epilepsy Study Group

Department of Neurology, DPMSC, University of Udine, Italy

Received 22 November 2005; accepted 16 December 2005

KEYWORDS
Oxcarbazepine;
Partial epilepsy;
Treatment;
Observational;
Clinical practice;
Seizures

Summary The antiepileptic efficacy and tolerability of oxcarbazepine, used both as monotherapy and adjunctive therapy, were observed for 1 year in 202 adult patients, aged 17—83 years, with newly diagnosed or refractory partial epilepsy in clinical practice in Italy. At first observation, the seizure free rate was 72.2% in newly diagnosed patients given monotherapy, 40% in patients in whom oxcarbazepine replaced another monotherapy and 10.3% in patients given oxcarbazepine as adjunctive therapy. At least 50% reduction in seizure frequency was achieved in 90.7, 72 and 57%, respectively. Efficacy increased with the duration of treatment ($p < 0.0001$). In the 160 completers the seizure free rate was 61.3% with monotherapy and 28% with adjunctive therapy. 16.3% of patients reported adverse effects, mainly sedation and sleepiness; 5% discontinued oxcarbazepine because of adverse events. OXC is an effective and well-tolerated antiepileptic agent for the long-term treatment of partial epilepsy in adults.

Introduction

Oxcarbazepine (OXC) is a new antiepileptic drug (AED) approved for the treatment of both simple and complex partial seizures with or without secondary generalization, either alone or in combination, in newly diagnosed patients and in non-responders to alternative agents. It was developed through structural changes to carbamazepine (CBZ) with the intention of achieving a more favourable pharmacokinetic profile associated with fewer undesirable effects. It has proved to be a distinctly different drug to CBZ, characterized by minimal cytochrome P-450 metabolization, calcium channel modulation in addition to sodium current blockade and better tolerability. It has also proved to be effective as add-on or replacement treatment in patients in whom CBZ has not achieved sufficient seizure control.[1]

* Correspondence to: Department of Neurology, DPMSC, Ospedale S. Maria della Misericordia, Padiglione Specialità, IV piano, Piazzale S. Maria della Misericordia, 33100 Udine, Italy.
Tel.: +39 0432 552720; fax: +39 0432 552719.
E-mail address: giada.pauletto@libero.it (G. Pauletto).

1059-1311/$ — see front matter
doi:10.1016/j.seizure.2005.12.008

The compound has been extensively evaluated within the context of randomised, controlled, double blind clinical trials both as monotherapy and as adjunct therapy.[2,3] OXC monotherapy has been compared to monotherapy with the main traditional AEDs, including valproate, phenytoin, and CBZ in newly diagnosed patients. Antiepileptic efficacy was similar, the overall seizure-free rate with OXC being 60%.[4–12]

Double-blind studies in surgery candidates with refractory epilepsy have shown that rapid OXC titration (2400 mg in one day) is well tolerated and that one-third of patients become seizure-free after two days of treatment.[13,14]

However, experience has shown that compounds that yield very promising results in ''gold standard'' clinical trials may be of little use in clinical practice on account of unforeseen developments in the uncontrolled conditions of clinical practice, where patients do not meet the rigid eligibility criteria of a clinical trial and usage is not monitored according to a rigorous experimental plan.[15,16]

Moreover, little is known about the natural history of epilepsy. Remissions may occur spontaneously, independently of therapy. This phenomenon, which is very difficult to quantify, needs to be taken into account for the evaluation of long-term efficacy.

Observational post-marketing surveillance studies performed in the setting of clinical practice have been devised to overcome the shortcomings of clinical trials.

The purpose of this study was to record the antiepileptic efficacy and tolerability of OXC, used both as monotherapy and adjunctive therapy, in a population of adult patients with newly diagnosed or refractory partial epilepsy in clinical practice in Triveneto (North of Italy).

Materials and methods

This was a prospective, multicenter, observational trial involving 18 centres in Triveneto (Italy), which are members of the Triveneto Epilepsy Study Group.

Co-operative patients with a clinical diagnosis of partial epilepsy attending the out-patient clinics of the centres were included, provided that they were at least 17 years old and were not affected by haematological diseases and/or conditions associated with electrolyte imbalance (serum Na+ $<$130 mEq/l at baseline). Also pregnancy, lactation, major psychiatric diseases, a history of abuse and a history of hypersensitivity to CBZ or other components of OXC tablets were exclusion criteria.

Demographic information and a detailed medical history related to epilepsy were collected, specifying its category according to the International League against Epilepsy (ILAE) classification and whether it was symptomatic, idiopathic or cryptogenic in order to make the clinical definition of the various diagnoses more homogeneous; age at onset of epilepsy and seizure frequency in the last 3 months were also noted. Any available neuroimages were evaluated. Information on OXC treatment included date of introduction, dosage regimen, duration of treatment, usage as monotherapy or as adjunctive therapy; in the event of use as adjunctive therapy, the additional AEDs used. Investigators titrated the drug according to their standard clinical practice, using uncoated 300 mg tablets.[a]

Physical examination findings and the results of routine laboratory tests (CBC + differential, electrolytes, serum creatinine, blood urea nitrogen, transaminases, GGT) and of EEG were collected. Upon completion of this first phase of study, the patients were asked whether they were willing to enter the second phase of the study, a 1-year observation period. If they were, they were given a diary to fill in, where they wrote down the number and type of seizures, any contributing factors, such as lack of sleep, alcohol intake, menses, etc., dosage of OXC and other AEDs, undesirable effects and changes in concomitant treatment. During the 1-year observation period they attended the centre for a physical examination and blood sampling for routine laboratory tests every 3 months.

The therapeutic response was evaluated using a 6-item semi-quantitative rating scale expressing the reduction in seizure frequency: $<$50%, $\geq$50%, $\geq$75%, seizure-free (SF), no change, worse.

The evaluation of tolerability was based on elicited adverse events (AE) during visits, neurological examination findings and routine laboratory tests. AE were considered to be severe when they required medical intervention and/or caused reduction in OXC dosage and/or its discontinuation.

Efficacy data were analysed using the test of Wilcoxon–Mann–Whitney and the test of Jonckeree-Terpestra, according to duration of treatment and the type of seizures and/or epileptic syndrome.

Patients who no longer met the eligibility criteria during the trial (e.g. appearance of generalized epilepsy not diagnosed previously) were considered violators and excluded from the statistical analysis.

[a] Tolep®.