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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

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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]

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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®.

Results

Patient population

The study population consisted of 202 patients, including equal proportions of both sexes and covering all age groups, from teenagers to the very old (range: 17—83 years). The patient population also covered a very broad range of durations of disease (from 1 to 67 years) and of seizure frequencies (from 0 to 90 seizures per month). Most patients were suffering from symptomatic or cryptogenic epilepsy (47% and 49%, respectively); more than half of the patients had complex partial seizures (52%) and/or secondarily generalized partial seizures (53%). Eleven patients were suffering from generalized tonic-clonic seizures and were removed from the analysis (Table 1).

Another four patients discontinued OXC treatment because of inefficacy, so the efficacy population amounted to 187 patients.

A total of 25 patients (12.5%) discontinued OXC treatment during the first phase of the study. The main reason for discontinuing treatment was undesirable effects (n = 10—5%), mainly involving the central nervous system (dizziness, ataxia, headache). Other reasons were poor compliance (n = 6), inefficacy (n = 5), undesirable effects and inefficacy (n = 4).

Another 17 patients (12.5%) discontinued OXC treatment during follow-up, mainly because of personal reasons or clinical decisions independent of tolerability: inefficacy (3.1%), persistence of undesirable effects (1.9%), poor compliance (1.9%), lost to follow-up (5.6%).

Thus, 160 patients completed the 1-year follow-up period.

Treatment

Two-thirds of the patients included in the efficacy population were given OXC alone; more than half of these patients had not responded to or had not

Table 1 Main characteristics of the patient population

Characteristic	N = 202
Sex, n (%)	
Males	96 (47.5)
Females	106 (52.5)
Age (years)	
Mean ± S.D.	47.5 ± 16.7
Range	17—83
Duration of epilepsy (years)	
Mean ± S.D.	16.0 ± 15.9
Range	1—67
Mean monthly seizure frequency in the last 3 months before introduction of OXC, range	8.5 (0—90)
Etiology, n (%)	
Idiopathic	8 (4)
Symptomatic	95 (47)
Cryptogenic	99 (49)
Type of seizure, n (%)	
Partial seizures	191 (94.5)
Simple	29 (14.4)
Complex	105 (52)
Secondary generalization	107 (53)
Generalized tonic-clonic seizures	11 (5.5)

Table 2 Antiepileptic treatment

OXC usage (% patients)	
Monotherapy	129 (69%)
Newly diagnosed	54 (28.9%)
Refractory to other AED/ Other AED not tolerated	75 (40.1%)
Adjunctive therapy	58 (31%)
Mean number of combined AEDs, range	2.7 (2—5)
Most commonly combined AEDs (n patients %)	
Phenobarbital	45.3%
Valproate	25.0%
Lamotrigine	23.4%
Levetiracetam	14.7%
Topiramate	12.5%
Clonazepam	10.9%
Phenytoin	10.9%
Carbamazepine	9.4%
Clobazam	6.2%
Gabapentin, Vigabatrin, Diazepam, Barbesaclone, each	1.6%
OXC dosage (mg)	
Mean—all patients	1174
Mean—monotherapy	1049
Mean—adjunctive therapy	1405
Range	300—3000
N—Percentage of patients given	
<1000 mg	87—43.1%
1000—1500 mg	79—39.1%
>1500 mg	36—17.8%
b.i.d. regimen	76.5%
t.i.d. regimen	23.5%
Duration of treatment (days)—mean ± S.D.	307 ± 212
Percentage of patients treated for	
<6 months	58 (28.8%)
6—12 months	74 (36.6%)
>12 months	70 (34.6%)

tolerated another AED. The remaining third were given combinations of 2—5 AEDs. The AED that was most commonly combined with OXC was phenobarbital (45.3% of patients); nevertheless, modern AEDs were given to more than half of the patients (53.8%) (Table 2).

The dosage of OXC varied considerably from 300 to 3000 mg daily, being on average slightly higher when OXC was given as adjunctive therapy (1400 mg versus 1050 mg daily). Most of the patients were given low dosages below 1000 mg daily (43.1%), but the proportion of patient given high dosages above 1500 mg daily was not negligible (17.8%) (Table 2).

Mean duration of treatment was 10 months.

Efficacy

Success rates in terms of reduction in monthly seizure frequency were highest in the subgroup of newly diagnosed patients given OXC monotherapy: nearly three patients out of four became seizure free. Fairly high success rates were achieved also in the subgroup of patients given OXC to replace another AED monotherapy (reduction in seizures by 50% in 72% and complete elimination of seizures in 40%) (Fig. 1). Even in patients given OXC as adjunctive therapy results were not negligible, as a reduction in seizure frequency by more than 50% was achieved in more than half the patients (56.9%); a reduction by more than 75% was achieved in just over one-third (34.5%) and 10.3% of patients became seizure-free.

Efficacy was greater when treatment had been continued for more than 6 months not only when OXC was given as monotherapy, but also when it was given as adjunct therapy (Figs. 2 and 3). The difference between success rates in patients

	>50%	>75%	100%
< 6 months	70	55	47,5
>=6 months	84,4	76,7	55,6

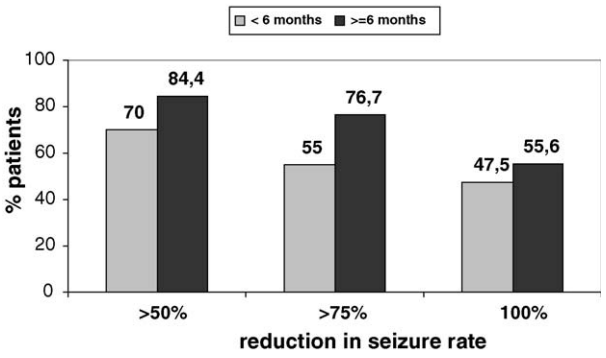

Figure 2 Effect of duration of therapy on the reduction in seizure rate achieved with OXC monotherapy.

treated for less than 6 months and those treated for 6 months or more was statistically significant ($p < 0.0001$). No significant difference in efficacy was found according to type of seizure or epileptic syndrome.

The success rates achieved during the first phase actually improved during the second phase, especially in the group of patients in whom OXC was used as adjunctive therapy (Fig. 4). Overall, 34 patients improved versus phase 1; out of these eight patients on adjunctive OXC therapy improved without any changes in concomitant AEDs. Moreover, OXC dosage was increased only in two patients by 300 mg daily.

Tolerability

A total of 33 patients (16.3%) reported undesirable effects in the first phase. Most of them involved the central nervous system: sedation ($n = 12$—5.9%),

	>50%	>75%	100%
newly diagnosed	90,7	85,2	72,2
replacement of other AED	72	58,7	40

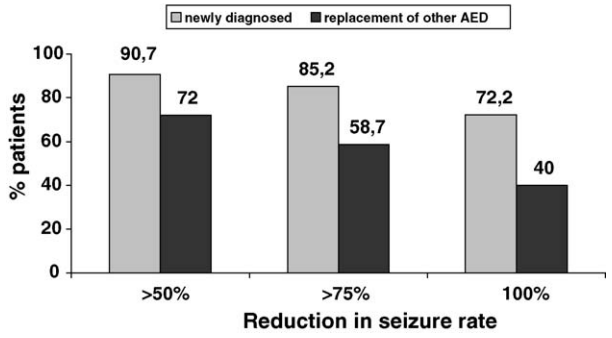

Figure 1 Reduction in seizure rate achieved by OXC monotherapy in newly diagnosed patients ($n = 54$) and following replacement of other AED ($n = 75$).

	> 50%	>75%	100%
<6 months	30	20	10
>=6 months	63,8	38,3	10,6

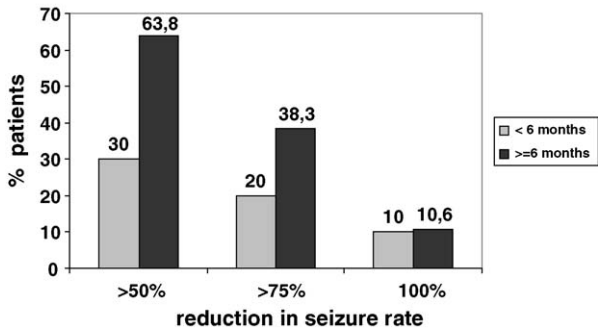

Figure 3 Effect of duration of therapy on the reduction in seizure rate achieved with combination therapy OXC + -other AED.

	>50%	>75%	100%
monotherapy	83,8	79,3	61,3
combination therapy	64	54	28

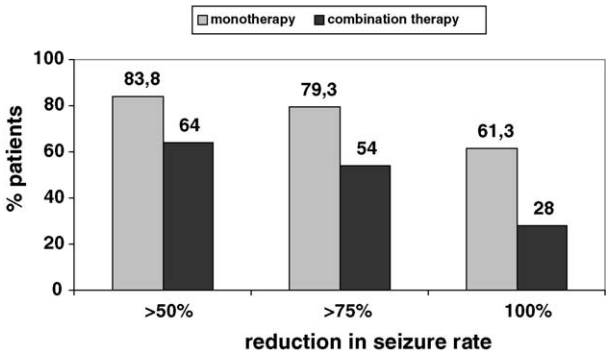

Figure 4 Reduction in seizure rate achieved by OXC monotherapy and OXC combination therapy after 1 year of observation.

sleepiness (n = 7—3.5%), dizziness (n = 5—2.5%) and ataxia (n = 4—2%). Other infrequent undesirable effects were: hyponatremia (n = 3—1.5%); asthenia, headache and nausea, skin rash (all n = 2—1%); vomiting, constipation, increase in transaminases (all n = 1—0.5%).

During follow-up mild or moderate undesirable effects were reported in 9% of patients. They were similar to those reported in the first phase.

Discussion

This study shows that OXC is effective and well tolerated in the treatment of partial seizures in clinical practice, independently of the type of seizure and the mode of use, i.e. as monotherapy or adjunctive therapy. In particular, it shows that OXC monotherapy is able to improve seizure control in patients who do not respond adequately or do not tolerate other AEDs and that OXC adjunctive therapy improves seizure control in combination with other AEDs. It also shows that therapeutic benefits are not only maintained in the long-term, but actually increase with time, especially after the first 6 months of treatment.

The benefits were achieved with a medium to low mean dosage (about 1200 mg daily).

The results of this study are better than those observed in retrospective studies: Friis et al.[17] reported a 32—48% improvement in seizure control with OXC in a large multicenter trial in 947 patients with various types of seizures, covering 9 years of experience. Van Parys and Meinardi[18] assessed the outcome of 260 epileptic patients who replaced CBZ with OXC and followed them up for 43 months: only 8% were seizure free and 32% experienced at least a 50% reduction in seizure frequency. Seizure control was adequate in 41.7% of children with refractory epilepsy treated with OXC for 5 years.[19]

On the other hand, the results of this study are consistent with those of other recent, prospective open-label studies. Sturm et al.[20] reported a seizure free rate of 70% in 362 newly diagnosed patients on monotherapy for 1 year versus 72.2% in this study. Walker et al.[21] reported a similar success rate in refractory patients with OXC combination therapy in terms of seizure frequency reduction (50% versus 57%), whereas the proportion of seizure free patients was slightly lower (4.8% versus 10.3%). Zeising et al.[22] reported an overall seizure free rate of 58.8%, results being better in subjects on OXC monotherapy as was the case in this study (66.8% versus 61% with monotherapy and 39.8% versus 28% with adjunctive therapy). Also in this study the maintenance dose was about 1000 mg daily.

Long-term open-label extensions of controlled trials show that therapeutic benefits are maintained in the long-term, as in this study: 48.2% of patients improved significantly and 7% became seizure free in a population of patients with refractory epilepsy in a study by Minecan et al.[23]. Long-term efficacy is supported also by the studies by Beydoun et al.[24] and Gilliam et al.[25], who documented continuation of OXC therapy for 4 years in 75—90% of patients with refractory epilepsy, indicating that the drug was well tolerated and provided adequate seizure control.

Undesirable effects were few and well known adverse reactions to the drug.[26]

In conclusion, this observational trial has shown that OXC is an effective and well-tolerated antiepileptic agent when it is used in clinical practice for the long-term treatment of partial epilepsy in adults both as monotherapy and adjunctive therapy.

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