Multicentre observational study evaluating immediate and progressive switching from carbamazepine to oxcarbazepine in patients with epilepsy

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Summary

This observational study was performed to identify the clinical reasons leading physicians to opt for immediate or progressive procedures when switching patients from carbamazepine to oxcarbazepine, and to evaluate the clinical feasibility of the two procedures in a general unselected patient population.

Five hundred and twenty-seven patients (aged 14 years or older, treated with carbamazepine as monotherapy or in combination therapy) were recruited at 50 Italian centres and freely assigned to immediate (n=361) or progressive (n=166) switch procedures. Vital and clinical data (including seizure frequency) were comparable in the two groups at baseline. The proportion of patients with simple partial seizures only was significantly higher in the immediate group (immediate: 33.0% vs progressive: 23.5%, \(p=0.0275\)), whereas the proportion of patients on combination therapy was slightly higher in the progressive group (immediate: 47.1 vs progressive: 55.4%, \(p=0.0756\)). At the end of the switch period, overall treatment satisfaction was greater in the immediate switch group, both in patients (\(p<0.002\)) and physicians (\(p<0.0005\)). Physicians preferred the immediate over the progressive switch procedure. The only clinical features of patients found to relate to the physician’s choice of switch procedure were simple partial seizures only (favouring the immediate switch) and, possibly, combination therapy with other anti-epileptic drugs (favouring the progressive switch). “Overnight” switching from carbamazepine to oxcarbazepine also appears feasible in most patients on polytherapy.

KEY WORDS: carbamazepine, epilepsy, immediate, oxcarbazepine, progressive, switch.

Introduction

Oxcarbazepine is an antiepileptic drug (AED) indicated for use as monotherapy or combination therapy in adults and children with partial seizures (including the simple and complex subtypes, and secondarily generalised tonic-clonic seizures) and/or primary generalised tonic-clonic seizures (1). Clinical trials have shown that oxcarbazepine monotherapy is as effective as carbamazepine, valproic acid, and phenytoin in previously untreated patients with partial and/or generalised seizures and that it is more effective than placebo as an adjunctive therapy in patients with refractory seizures (1). Compared with carbamazepine, oxcarbazepine has a better tolerability profile, a reduced interaction with other drugs, and exerts no autoinduction effect on its own metabolism. Consequently, it is more manageable than carbamazepine, and has a higher therapeutic index (2).

Changing to oxcarbazepine monotherapy from carbamazepine and other AEDs has proved effective in improving seizure control and tolerability, both in controlled clinical trials and in extensive clinical experience (3-8).

Generally, physicians choose to switch patients progressively from one AED to another over several days or weeks. But the fact that oxcarbazepine and carbamazepine share a similar chemical structure and mode of action suggests that the two drugs may also be safely switched “overnight”, i.e. over one-two days (immediate switch).

This suggestion is supported by clinical experience (9-14) and was confirmed by a recent randomised Italian multicentre study (15). This study assessed the therapeutic equivalence and clinical feasibility of immediate and progressive switching from carbamazepine to oxcarbazepine in 286 patients presenting with partial seizures unsatisfactorily treated with carbamazepine monotherapy due to poor tolerability or scant clinical efficacy. The protocol design included an initial fixed dose ratio of 1:1.5 for the switch. The patients randomised to the immediate switch replaced the final carbamazepine dose with the corresponding oxcarbazepine dose over one to two days, whereas the patients allocated to the progressive switch replaced 200 mg of carbamazepine with 300 mg of oxcarbazepine every two to three days, until the switch was completed. The authors concluded that the two switch procedures are equally feasible and suggested further investigation in the general population of patients switching from carbamazepine to oxcarbazepine. Those conclusions prompted us to perform the present study.
Aim

The aim of this study was to identify the clinical variables leading physicians to choose the immediate or the progressive switch procedure and to evaluate the clinical feasibility of the two procedures in an unselected general population.

Materials and methods

Patients

Patients were eligible for inclusion if they met the following criteria: male or female inpatients or outpatients with epilepsy (presenting with partial seizures, simple, complex, or evolving into secondarily generalised seizures, and/or primary generalised tonic-clonic seizures) aged 14 years or older, treated with carbamazepine (Tegretol® or generic) in monotherapy or in combination with other medications and requiring, in the clinical opinion of their treating physician, a switch to oxcarbazepine (Tolep®) for any medical reason.

Patients were excluded if they met any of the following criteria:
- clinical conditions judged by the physician to compromise the patient’s participation in the study;
- known or suspected hypersensitivity to oxcarbazepine;
- contraindications to the use of oxcarbazepine as indicated in the prescribing information sheet.

To minimise the risk of bias, physicians were asked to propose participation in the study to all consecutive patients meeting the inclusion criteria.

Study design

This was an observational, multicentre, open-label study designed to reflect current daily clinical practice with regard to the use of immediate and progressive procedures for switching from carbamazepine to oxcarbazepine in patients with epilepsy. The recruitment period lasted 14 months, from September 2003 to November 2004. The decision to switch the patient from carbamazepine was taken by the physician on the basis of his/her clinical judgement alone. Assignment of the patient to one of the two switching procedures, the timing of the switch, and the doses were also decided by the treating physician.

The study consisted of two phases: screening and open-label treatment. Unless data on seizure type and frequency could be obtained retrospectively from a patient diary or other document considered reliable by the investigators, patients entered the screening phase, which lasted up to eight weeks, so that these data could be collected. Prior to their enrolment in the study, all the patients were asked to sign a written informed consent form. At the end of the screening phase, they were assigned to one of the two switching procedures. The 24-week treatment phase was divided into two periods: switch and maintenance. Patients were followed as outpatients and were advised to call their physician if any problems arose. There were four scheduled clinical visits: randomisation (visit 1), end of switch (visit 2, the second day after the end of the switch), after 12 weeks of treatment (visit 3), and at the end of the 24-week treatment phase (visit 4). Visits 2 and 3 could be substituted by a telephone interview. At visit 1, inclusion and exclusion criteria were checked and an investigation of vital parameters (blood pressure, heart rate and weight) was carried out. Epilepsy history and baseline seizure frequency were also ascertained at this first visit. Seizure frequency, adverse events, and treatment satisfaction were assessed at visits 2, 3 and 4. Any laboratory assessments were carried out during the study as deemed necessary by the physician.

Seizures were recorded throughout the study using patient diaries and were classified according to the 1981 International Classification of Epileptic Seizures (16) and the 1989 International Classification of Epilepsies and Epileptic Syndromes (17) proposed by the International League Against Epilepsy.

Treatment

Oxcarbazepine was prescribed by the physician in accordance with his/her normal clinical practice. Any concomitant treatment administered and daily dosages were noted in the clinical research form. Dose adjustments of oxcarbazepine and of any associated AED were allowed at any time (switch and maintenance) during the study, as clinically required.

Assessments

The primary aim of the present study was to identify the clinical variables underlying the choice of an immediate or progressive switch from carbamazepine to oxcarbazepine. Secondary aims were to evaluate satisfaction with the two switching methods, in both patients and physicians, and to disclose any differences between them in terms of clinical efficacy and tolerability.

Clinical variables. The following data were collected to identify the clinical reasons underlying the choice of switching procedure: age; sex; use of carbamazepine (as monotherapy or in combination therapy) and total dosage of carbamazepine; concomitant therapies; clinical indication for switching; type of seizures; seizure frequency; adverse events.

Overall treatment satisfaction. At the end of the switch period, at each subsequent scheduled visit and on completion of the study, the patients and physicians also gave a global assessment of treatment satisfaction, rating their level of satisfaction on a four-point scale as ‘poor’, ‘fair’, ‘good’, or ‘very good’.

Efficacy variables. The primary efficacy endpoint was the average number of seizures per month, from baseline until study end. Secondary efficacy endpoints were the ‘between-group’ and ‘within-group’ differences in the average monthly seizure frequency before and after the switch (mean for the screening phase vs mean for the treatment phase).
Safety variables. The primary tolerability endpoint was the proportion of patients who did not experience any clinically significant adverse events during the study. Clinically significant adverse events were defined as moderate or severe events that required specific medical intervention or led to modification or interruption of AED therapy. Safety was assessed on the basis of reported adverse events, physical and neurological examinations, vital signs, and laboratory tests.

**Statistical analysis**

Correlations between patients’ clinical variables (age, sex, frequency and type of seizures, use of carbamazepine as monotherapy or in combination therapy, reason for the switch) and the switching procedure (immediate or progressive) were assessed by means of the chi-square test and logistic regression. The patients’ and physicians’ treatment satisfaction ratings were compared between the two switching procedures by means of the Cochran-Mantel-Haenszel test, stratifying by centre.

The difference in the mean monthly number of seizures (calculated by dividing the number of observed seizures by the length of the treatment phase in days and multiplying by 30.5) before and after the switch in the whole group and in the two subgroups of patients who underwent the switch due to unsatisfactory seizure control or poor tolerability, was summarized together with the within-group comparison of monthly number of seizures before and after the switch using the Wilcoxon signed rank test, and the between-group comparison of differences was performed using the Wilcoxon-Mann-Whitney test. The number of seizures before and after the switch was also analysed in relation to the type of switch and overall. Analyses were carried out in all patients who switched to oxcarbazepine, including those who did not complete the maintenance phase (the assessable patient population).

**Results**

A total of 527 patients switching from carbamazepine to oxcarbazepine were recruited at 50 centres in Italy. Of these, 361 patients followed the immediate and 166 patients the progressive switch procedure. Table I shows the baseline characteristics of all the patients, the type of carbamazepine medication used, the proportion of patients receiving other AEDs, the proportion of patients with other reported concomitant medical conditions, and the proportion of patients receiving other (non-AED) concomitant medications. The majority of patients in both groups underwent the switch due to unsatisfactory seizure control (Table I).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Immediate switch (n=361)</th>
<th>Progressive switch (n=166)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (range)</td>
<td>44.3 (13-84)</td>
<td>43.5 (17-79)</td>
</tr>
<tr>
<td>Males:females, %</td>
<td>49.3:50.7</td>
<td>56.6:43.4</td>
</tr>
<tr>
<td>Reason for undergoing switch, n (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unsatisfactory control</td>
<td>224 (62.1)</td>
<td>107 (64.5)</td>
</tr>
<tr>
<td>Poor tolerability</td>
<td>128 (35.5)</td>
<td>54 (32.5)</td>
</tr>
<tr>
<td>Need of treatment with interacting drugs</td>
<td>12 (3.3)</td>
<td>8 (4.8)</td>
</tr>
<tr>
<td>Mean number of seizures per month</td>
<td>5.6</td>
<td>5</td>
</tr>
<tr>
<td>Mean final dosage of carbamazepine before starting switch, mg/day</td>
<td>829.9</td>
<td>900</td>
</tr>
<tr>
<td>Type of carbamazepine received, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tegretol®</td>
<td>155 (43.4)</td>
<td>61 (36.7)</td>
</tr>
<tr>
<td>Tegretol CR®</td>
<td>202 (56.6)</td>
<td>105 (63.3)</td>
</tr>
<tr>
<td>Patients receiving other AEDs</td>
<td>47.1%</td>
<td>55.4%</td>
</tr>
<tr>
<td>Patients with other concomitant medical conditions</td>
<td>41.3%</td>
<td>44.0%</td>
</tr>
<tr>
<td>Patients receiving concomitant, non-AED treatments, n (%)</td>
<td>101 (28.0)</td>
<td>49 (29.5)</td>
</tr>
</tbody>
</table>

**Abbreviations:** n=number of patients; AED=antiepileptic drug. *Patients may be included in more than one of the reasons for switching; **includes medications that can potentially interact with oxcarbazepine.
In the same way, at the end of the 24-week study the 'good' or 'very good', (p=0.0005). Similarly, 86.4% of the patients in the immediate group rated the treatment as 'good' or 'very good' (p=0.0017). Similarly, 86.4% of the patients in the immediate group had simple partial seizures (33.0% vs 23.5% in the progressive group, p=0.0275). Inversely, a higher proportion of patients in the progressive group were on AED polytherapy (55.4% vs 47.1% in the immediate group), but this difference did not reach statistical significance (p=0.0756).

Switch feasibility

Overall, 98.4% (519/527) of the patients completed the switch: 99.4% (359/361) in the immediate group and 96.3% (160/166) in the progressive group. Similarly, 89.2% of the patients completed the 24-week study: 91.1% (329/361) in the immediate switch group and 84.9% (141/166) in the progressive switch group (n.s.). Of the 57 patients who discontinued oxcarbazepine prematurely, eight discontinued during the switch period: two in the immediate group, due to adverse events (n=1) and withdrawal of consent (n=1), and six in the progressive group, due to adverse events (n=3), withdrawal of consent (n=1), or death (n=1), while one patient was lost to follow up. The other 49 patients discontinued oxcarbazepine during the maintenance period, due to adverse events (n=22), unsatisfactory therapeutic effect (n=11), abnormal laboratory values (n=4), withdrawal of consent (n=2), withdrawal on account of administrative problems (n=1), the decision to start pre-surgery evaluation (n=1), and death (n=1), while seven patients were lost to follow up. In the 49 patients who discontinued oxcarbazepine while on maintenance therapy, irrespective of their switch group, the mean duration of maintenance therapy was 59.4 (range 0-223) days. Proportionally more patients in the progressive switch group discontinued the treatment (8.9% immediate vs 15.1% progressive).

The mean switch duration was 1.77 (range 1-9) days in the immediate group, and 9.92 (range 2-38) days in the progressive group. Following the switch to oxcarbazepine, the mean duration of maintenance treatment (from the day after the last carbamazepine dose until the day of the last oxcarbazepine dose) was 169.33 days in the immediate group and 165.35 days in the progressive group. The last mean daily dose of carbamazepine before the switch was 829.9 mg (range 200-2000 mg) in the immediate group and 900 mg (range 100-2400 mg) in the progressive group. At study end, both groups of patients were receiving similar mean doses of oxcarbazepine (immediate group 1295.8 mg/day and progressive group 1393.5 mg/day) and the dose ratios of carbamazepine: oxcarbazepine were 1:1.61 in both groups.

Overall treatment satisfaction. At the end of the switch period, 87.3% of the physicians in the immediate switch group versus 71.2% of the physicians in the progressive group rated the treatment as ‘good’ or ‘very good’ (p=0.0017). Similarly, 86.4% of the patients in the immediate switch group versus 67.9% of the patients in the progressive group rated their level of satisfaction as ‘good’ or ‘very good’, (p=0.0005). In the same way, at the end of the 24-week study the physicians’ satisfaction rating was consistent with that of the patients: 79.9% (immediate) and 74.8% (progressive) of physicians, and 81.1% (immediate) and 75.7% (progressive) of patients rated their level of satisfaction with the oxcarbazepine treatment as ‘good’ or ‘very good’ (n.s.).

Efficacy. The switch from carbamazepine to oxcarbazepine was associated with a decrease in average monthly seizure frequency: from 5.6 ± 20.6 (mean ±SD) to 2.3±6.0 in the immediate switch group, and from 5.0±12.3 to 4.0±13.7 in the progressive switch group, both p<0.0001. The difference between the groups was significant in favour of the immediate switch (p=0.0173). Of the 331 patients switching treatments due to unsatisfactory seizure control, 67.4% (223/331) showed a decrease in monthly seizure frequency.

There was a significant trend in favour of immediate switching in these patients (p=0.0267), with a median monthly seizure reduction of 0.96 in the immediate group vs 0.33 in the progressive group.

Safety and tolerability. Overall, 38 patients (10.5%) in the immediate switch group and 33 patients (19.9%) in the progressive switch group experienced clinically significant adverse events (p=0.0035). Of these patients, 17/38 and 12/33 had experienced poor tolerability with carbamazepine. Considering the study as a whole, no unexpected adverse events were observed. Overall, 13 patients (3.6%) in the immediate switch group and 13 (7.8%) in the progressive switch group discontinued the study due to an adverse event.

Hyponatraemia was seldom reported in either group: three patients in the immediate (0.8%) and one in the progressive group (0.6%). Six immediate switch patients and three progressive switch patients reported serious adverse events including death (two cases: one in the immediate and one in the progressive group). In the immediate switch group, these serious events were intestinal infarction causing death of a 61-year-old female (n=1), a fall causing spinal fracture and meningoima (n=1), cerebral haemorrhage (n=1), haemorrhagic stroke (n=1), and seizure exacerbation (n=2). In the progressive switch group, the serious adverse events were cardiorespiratory arrest (the only serious adverse event occurring during the switch period) causing the death of a 68-year-old man (n=1), bronchopneumonia (n=1) and colon cancer (1). The investigators considered all the serious adverse events but one (fall and spinal fracture) to be unrelated to the oxcarbazepine treatment.

Discussion

This observational study revealed that more clinicians preferred to switch their patients from carbamazepine to oxcarbazepine in an immediate rather than progressive fashion. The one clinical variable found to be related to this choice was the presence of simple partial seizures only (favouring the immediate switch, with a statistically significant difference), while AED polytherapy showed a trend in favour of the progressive switch procedure. Oxcarbazepine efficacy and safety data after switching support the conclusion that both procedures are feasible, showing similar efficacy and tolerability: 99.4% of
Immediate and progressive switching from carbamazepine to oxcarbazepine

patients completed the switch using the immediate procedure vs 96.3% using the progressive procedure. Compared to the progressive approach, the immediate procedure was associated with higher levels of treatment satisfaction, both in patients and clinicians. Our observations also included some data supporting the good efficacy and safety of oxcarbazepine after the switch, with 67.4% of the 331 patients who switched due to unsatisfactory seizure control showing a decrease in monthly seizure frequency, and only 13.5% (71/527) of patients reporting clinically significant adverse events at any time after the switch. However, the methodological limitations of the observational protocol should be borne in mind when evaluating these data.

In conclusion, the results of this observational trial suggest that the "overnight" switch from carbamazepine to oxcarbazepine is also feasible in most patients on combination therapy, and indicates the presence of simple partial seizures only as the only factor inducing physicians to prefer an immediate rather than a progressive switch.

References