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Oxcarbazepine long-term treatment retention in patients switched over from carbamazepine

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Abstract We evaluated the long-term outcome of oxcarbazepine (OXC) monotherapy in a population of patients switched over from carbamazepine (CBZ) monotherapy. Subjects of the study were recruited among patients who had successfully completed the PRIMO study, a recent multicentre Italian study that assessed the therapeutic equivalence of immediate (overnight) and more progressive switching from CBZ to OXC monotherapy in patients with partial seizures unsatisfactorily maintained on CBZ monotherapy due to poor tolerability or scant clinical efficacy. Treatment retention rate was chosen as a composite parameter for both efficacy and tolerance of OXC. Twelve months after having completed the PRIMO study, 91 of 105 patients (87%) were still taking OXC, 80 of them (76%) as monotherapy. Mean OXC dose was 1250±459 mg/day. Eighty-four out of 105 patients (80%) rated OXC tolerability as "good" or "very good". The mean ratio of the last dose of OXC to the last dose of CBZ increased from 1.54 (end of PRIMO study) to 1.69 (end of follow-up). The large majority of a population of patients who were successfully switched from CBZ monotherapy to OXC monotherapy maintained OXC treatment for at least a further 12 months. The 1.5 OXC/CBZ ratio appears to be close to the optimal for the switch from CBZ to OXC, at least in patients treated with CBZ monotherapy.

Key words Epilepsy • Switch • Oxcarbazepine • Carbamazepine • Long-term efficacy

Introduction

The clinical efficacy of oxcarbazepine (OXC) monotherapy in partial seizures with or without secondary generalisation, and in generalised tonic-clonic seizures has been confirmed in various clinical trials [1]. To date, however, few papers have reported long-term experience with OXC in prospective [2, 3] or retrospective studies [4, 5].

In this prospective observational study we assessed the long-term outcome of OXC monotherapy in a population of patients switched over from carbamazepine (CBZ) monotherapy. Treatment retention rate was chosen as a composite parameter for both efficacy and tolerance of OXC.

Subjects of the study were recruited among patients who had successfully completed the PRIMO study, a recent multicentre Italian study [6] that assessed the therapeutic equivalence of immediate (overnight) and more progressive switching from CBZ to OXC monotherapy in patients with partial seizures unsatisfactorily maintained on CBZ monotherapy due to poor tolerability or scant clinical efficacy.

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Methods

All the centres involved in the PRIMO study [6] were invited to take part in this long-term study, and 15 of them agreed to participate. One year after completing the PRIMO study, all patients at the participating centres were reassessed for the following parameters: vital data; treatment retention; seizure frequency; patient assessment of OXC tolerability; daily dose of OXC (or possible OXC withdrawal); antiepileptic drugs (AEDs) associated with OXC.

Data were collected on a specifically designed clinical research form (CRF).

Results

Patients

A total of 111 patients completed the PRIMO study in the 15 centres participating in this long-term study. Patients were aged over 16 years and had a diagnosis of partial seizures (including the subtypes of simple, complex and partial seizures evolving to secondarily generalised seizures). After CRF screening and database creation, 105 patients were available for retention rate analysis (61 males, 44 females; mean age±SD, 43±15 years). Three patients were lost to follow-up and three were excluded from retention rate analysis for incomplete CRFs. Seizure frequency could be determined in 98 patients. Patients' data were analysed for the whole population or dividing the patients into groups based on previous treatments (patients who had received OXC as the second AED treatment after CBZ *vs*. patients who had previously tried two or more AEDs) or the reason for switch (patients switched over due to poor tolerability *vs*. patients switched over due to insufficient clinical efficacy).

Oxcarbazepine treatment retention, clinical efficacy and tolerability

At the end of follow-up (12 months after the end of the PRIMO study), 91 of the 105 patients (87%) were still taking OXC, 80 of them (76%) as monotherapy. Of the 14 patients withdrawing from OXC, 5 went back to CBZ, 5 used levetiracetam, 3 lamotrigine and 1 topiramate. No differences were observed between patients who had received OXC as the second AED treatment and patients who had previously tried two or more AEDs in terms of patients discontinuing OXC (6/56 and 8/49, respectively) or number of patients who received OXC as polytherapy at the end of follow-up (5/56 and 6/49, respectively) (both NS, Chi square test).

Retention rate was also similar in patients originally switched over due to insufficient clinical efficacy and patients switched over due to poor tolerability: 46/53 and 60/69, respectively (some patients were included in both groups). However, patients switched over due to insufficient clinical efficacy had a greater probability of being treated with two drugs at the end of follow-up: 9/53 *vs*. 4/69 ($p<0.05$, Chi square test).

In the 98 evaluable patients, the median frequency of monthly seizures was 0.45 (median frequency of monthly seizures during PRIMO study baseline in the same patients was 1.05). OXC tolerability was rated as "good" or "very good" by 84 out of 105 patients (80%). Among the 14 patients who withdrew from OXC treatment, 9 rated OXC tolerability as "poor" or "fair". In five cases OXC withdrawal was only due to unsatisfactory seizure control.

Oxcarbazepine dose

The mean daily dose of OXC at the end of follow-up was 1250±495 mg/day in the whole population, and it was higher in patients switched over due to insufficient clinical efficacy with respect to patients switched over due to poor tolerability: 1475±465 *vs*. 1105±444 mg/day, mean±SD.

The mean ratio of the last dose of OXC/last dose of CBZ increased from 1.54 (end of PRIMO study) to 1.69 (end of follow-up).

OXC daily dose had not been adjusted in 67 patients (64%), while it had increased up to 2400 mg/day in 27 (26%) (all but one in monotherapy) and reduced in 11 (10%).

Discussion

This observational long-term study, conducted in patients with partial seizures switched over from CBZ monotherapy, showed that the large majority of patients who successfully completed the switch to OXC monotherapy maintained OXC treatment for at least a further 12 months.

About one third of our patients received an OXC dose greater than 1500 mg/day. A recent paper [7] suggested that therapeutic monitoring of plasma concentration of the OXC mono-hydroxy derivative, the active moiety during OXC therapy, could be helpful in optimising the clinical management of patients treated with OXC at high doses. In our study, however, OXC therapeutic monitoring was not mandatory, and was performed in a few patients only.

A debate exists in the literature about the optimal switching ratio between CBZ and OXC [8], with suggested values ranging from 1.2 to 1.5. In our population, at the end of the follow-up period, the ratio last OXC dose/last CBZ dose was about 1.7. As in the PRIMO study CBZ

therapy was switched to OXC at the fixed dose ratio of 1:1.5 (200 mg of CBZ were substituted with 300 mg of OXC), and an increase in daily dose for patients with unsatisfactory seizure control is common in clinical practice, whereas physicians more rarely search for the minimal effective dose in patients with good seizure control; the increase in mean last OXC dose/last CBZ ratio at the end of follow-up might be due to study design.

Overall, however, these findings suggest that the 1:1.5 CBZ/OXC ratio is close to the optimal for the switch, at least in patients treated with CBZ in monotherapy.

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