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Efficacy of low to moderate doses of oxcarbazepine in adult patients with newly diagnosed partial epilepsy

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ABSTRACT

Purpose: The objective of this study was to explore the efficacy of low dose of oxcarbazepine (OXC) in adult patients with newly diagnosed partial epilepsy in an actual clinical setting. The associated factors influencing the poor control of seizures were also evaluated.
Methods: The epilepsy database (2010–2014) from the Epilepsy Clinic of West China Hospital was retrospectively reviewed.
Results: A total of 102 adult patients with newly diagnosed, previously untreated partial epilepsy initially treated with OXC were included, and divided into good response group (64) and poor response group (38) according to whether they were seizure-free for at least 12 months. There were 27 (26.5%) patients becoming seizure-free with OXC 600 mg/day monotherapy. The remaining 75 patients had doses of either increasing OXC to 900 mg/day ($n = 59$) or the addition of another antiepileptic drug (AED) ($n = 16$), with another 20 (19.6%) and six (5.9%) patients becoming seizure-free, respectively ($P = 0.788$). In addition, two (2.0%) and nine (8.8%) patients became seizure-free with OXC $>$ 900 mg/day monotherapy and OXC $\geq$ 900 mg/day combination therapy, respectively. Multivariate binary logistic regression analysis revealed that the time from onset of epilepsy to treatment initiation is significantly associated with seizure control ($P = 0.02$).
Conclusion: Our results indicated that OXC at low to moderate doses is effective for the treatment of Chinese adult patients with newly diagnosed, previously untreated partial epilepsy, and a longer time interval from the onset of epilepsy to the start of treatment significantly predicts poor seizure control.

1. Introduction

Oxcarbazepine (OXC) is a second generation AED as a first-line treatment for adults and children with simple partial seizures, complex partial seizures, and partial seizures evolving to secondarily generalized seizures [1–3]. OXC is chemically related to carbamazepine (CBZ), but with a more favourable pharmacokinetic profile and improved tolerability profile [4,5]. To better manage and improve the prognosis of epilepsy, it is important to assess the treatment effects of AED accurately and formulate rational treatment plans, ideally by following outcomes from the point of treatment initiation. The efficacy and tolerability of OXC as monotherapy or adjunctive therapy, has been previously evaluated in a number of clinical trials [4,6–10]. For adults, this drug has been shown to be efficacious at a usual maintenance dose of 900–1200 mg/day and a maximum dose of 2400 mg/day as monotherapy or adjunctive therapy [4,7,9–11], but limited data are available for Chinese patients [12], and since there exists difference in race between Chinese and Occidentals, a different dose of OXC treatment in Chinese adult patients may be required. On the other hand, with strict entry and dosing criteria, regular clinical trials may fail to include practical, real world information [13,14]. Moreover, the duration of follow-up in trials is usually short, and may not be long enough to assess drug side effects [15]. Therefore, rational studies in clinical practice are increasingly recognized to provide data that further confirm and complement information derived from regulatory trials [13]. To our knowledge, for patients who are failure with the initial OXC treatment, whether increasing

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the dose of OXC is better than a second AED added is controversial and no data are available.

Therefore, we designed this retrospective study to explore the efficacy of OXC treatment in adult patients with newly diagnosed, previously untreated partial epilepsy in west China in an actual clinical setting. And the associated factors influencing the poor seizure outcome were also evaluated.

2. Methods

2.1. Patients

This was a retrospective, uncontrolled study conducted at the Epilepsy Clinic of West China Hospital, a tertiary referral centre in Chengdu, China. The epilepsy database (2010–2014) from this Epilepsy Clinic was retrospectively reviewed. The Ethics Committee of the West China Hospital, Sichuan University approved the study, and informed consent was obtained from each patient.

Patients who fulfilled the inclusion and had no exclusion criteria were consecutively included in this study. The inclusion criteria were as follows: (1) at least 16 years old and weight more than 40 kg; (2) at least two well documented, unprovoked, clinically evaluated and classified partial seizures (with or without secondary generalization) within 12 months; (3) the first AED was OXC prescribed at the epilepsy clinic at the West China Hospital, which was continued for at least 3 months; (4) no previous use of AEDs before attending our clinic; and (5) follow up by at least for 12 months. Patients were excluded from the study if they had less than one seizure per year prior to treatment. Patients with suspected partial seizures who have a clear IGE EEG were also excluded. Compliance with the treatment regimen was monitored at the clinic, and patients with persistent poor adherence to treatment, unrelated to efficacy or tolerability, seizures secondary to drug or alcohol abuse, or documented psychogenic nonepileptic seizures were also excluded.

Follow-up was started at the introduction of OXC and was ended at the discontinuation of treatment or closing date (July 2014), or death.

2.2. Treatment

For the majority of adult patients, OXC was prescribed initially as 300 mg/day for two weeks, increasing to 600 mg/day in one month. The OXC doses were adjusted as clinical circumstances dictated, with particular attention paid to efficacy and tolerability. If the patient reported intolerable adverse effects with treatment, an alternative was substituted. If the AED was well tolerated but did not completely abolish the seizures, it was continually increased to the doses or combination therapy was used, which to a large degree was consistent with previous studies [16]. However, because of the pragmatic nature of this study, there were no rigid rules concerning dose adjustments, and doses of OXC were individualized. And moreover, based on the experience of clinic practice and previous finding that Chinese patients receiving a dose of more than 900 mg/day could be more likely to develop side effects [17], and a higher risk of OXC-induced cutaneous adverse reactions [18,19], the usual maintenance dose of OXC in our patients was 600–900 mg/day and rarely more than 900 mg/day. When possible, the patients were reviewed by the same clinician every 8–12 weeks, or sooner if required. The follow-up clinical data were collected in a structured record sheet and entered into a computerized database.

2.3. Clinical information and demographic status

The following data regarding the clinical information and demographic status were obtained from the medical records and interview: age, gender, body weight, age at seizure onset, epilepsy duration, seizure type, imaging (MRI/CT) findings, previous and current AED use, time from onset of epilepsy to initiation of AED treatment, OXC treatment (initiation date, daily dose, titration regimen, date of discontinuation and reasons for discontinuation) and the occurrence of any adverse events. Previous medical history, including history of febrile seizures, cerebral infection and brain injury, and family history of epilepsy were also obtained. Duration of epilepsy was defined as the period from the seizure onset to the end of follow-up.

2.4. Statistical analysis

Data processing and analysis were performed with SPSS version 17.0 (SPSS Inc., Chicago, Illinois) for Windows. All outcome variables were summarized using descriptive statistics. Continuous variables were summarized as the mean ± SD, and categorical variables were summarized using counts and percentages. The patients were divided into two groups: those who had been seizure-free for at least 12 months were considered to have a good response (good response group) and the remaining patients (were never seizure-free for a complete year) were classified as having a poor response (poor response group). Several continuous variables were categorized. The current age was divided into 10-year groups. The median age of epilepsy onset 21 years old was selected as the cut-off point for onset age. The time from onset of epilepsy to the start of treatment was divided into 1-year groups. The two-tailed chi-square or Fisher's exact tests were used for the comparison of categorical data, whereas Student's t test or the Mann–Whitney test were used for the comparison of continuous data. Univariate binary logistic regression was performed to determine the association between the clinical and demographic variables and poor seizure outcome. A model of multivariate logistic regression analysis was constructed to determine the independent association with seizure outcome using a backwards selection of covariates, and all results were expressed as the odds ratios (ORs) and 95% confidence intervals (CIs). All P-values were two-sided, with $P < 0.05$ considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics of the included patients

A total of 102 eligible patients were included. The demographic and clinical characteristics of the included patients are summarized in Table 1. The mean age of all of the patients was 30.1 ± 12.1 years. The mean age at seizure onset was 25.6 ± 12.7 years. For the brain MRI/CT results, 82 (80.4%) were normal and the other 20 (19.6%) were abnormal. For seizure types, 28 (27.5%) patients had simple partial seizures, 22 (21.6%) had complex partial seizures and the remaining 52 (51.0%) showed partial seizures with secondary generalization. The mean age at the initiation of OXC therapy was 27.9 ± 12.0 years. The mean daily dose of OXC was 796.0 ± 185.8 mg, ranging from 600 to 1200 mg, and the time interval from onset of epilepsy to the start of treatment averaged 2.3 ± 3.3 years.

The seizure-free rates with successive regimens were shown in Fig. 1 and Table S1. Twenty-seven (26.5%) of the 102 patients achieved seizure-free with OXC 600 mg/day monotherapy. The remaining 75 patients either had daily doses of OXC increasing to 900 mg ($n = 59$) or the addition of another AED ($n = 16$), with a seizure-free rate of 33.9% (20) and 37.5% (6), respectively ($P = 0.788$) (Table S2). For the 39 patients who did not become seizure-free with OXC 900 mg/day, three were maintained on the 900 mg/day, and the remaining 36 patients either had daily doses of OXC increasing to more than 900 mg ($n = 10$) or the addition of another AED ($n = 26$), with two (20.0%) and eight (30.8%) patients becoming seizure-free, respectively. Furthermore, one of four