RESEARCH ARTICLE

THE EFFICACY AND SAFETY OF OXCARBAZEPINE AS ADD-ON THERAPY IN INTRACTABLE EPILEPSY IN CHILDREN

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Abstract

Objective

1-3% of the population suffer from epilepsy. Up to 30% of them develop refractory epilepsy and their seizures occur more than once per month despite receiving at least 2 first line antiepileptic drugs. In this group, more efficacious antiepileptics are needed. This study was undertaken to evaluate the efficacy and safety of Oxcarbazepine as an adjunction therapy in children with refractory epilepsy.

Materials & Methods

From Feb 2004 until Sep 2006, 30 patients with refractory epilepsy aged between 4 and 14 years were evaluated in a before and after type study. The patients had seizure ranging from once monthly to more than 10 times daily and none of them had used Oxcarbazepine previously. They received Oxcarbazepine 30 to 50 mg/kg/day orally in combination with their current antiepileptic drugs and were regularly assessed for seizure frequency and side effects for 10 months.

Results

With Oxcarbazepine adjunction therapy, 10% of the patients became seizure-free, 36.6% experienced more than 50% reduction in seizure frequency, and 13.3% had increasing seizures. The drug was especially effective in the patients with partial seizures (77.7%). Brief and transient adverse effects were seen in 36.6% of the patients which disappeared with treatment continuation. Wilcoxon signed ranks test showed that oxcarbazepine was effective in the treatment of refractory seizures (P=0.003) and as shown by Fisher's exact test, it was more effective in partial seizures (P=0.0043).

Conclusion

The results showed that Oxcarbazepine was a useful medication in the treatment of refractory epilepsy, especially the partial type, in children.

Keywords: Add-on therapy, children, intractable epilepsy, oxcarbazepine, side effect

Introduction

Epilepsy is one of the most common neurologic diseases(1). 1-3% of people in the world suffer from epilepsy. Mean incidence of epilepsy in childhood (from birth to 16 years of age) is approximately 40 in 100,000 children in each year (2).

Generally used Anti Epileptic Drugs (AED) are associated with side effects and drug interactions; however, in many epileptic patients, epilepsy is controlled after using one of these antiepileptic agents. On the other hand, up to 30% of the patients develop refractory epilepsy which is frequently common in patients with partial seizures (3).

Refractory epilepsy is defined as lack of seizure control although the patient has received at least 2 first-line AEDs, having more than 1 seizure per month in an 18-month period (2). When the patient is resistant to the medications or cannot tolerate the treatment due to the drug's adverse effects, more efficacious or better tolerable medications are needed (4). One of these newly introduced medications is Oxcarbazepine (OXCBZ) which was approved by Food and Drug Administration (FDA) in 2000 for adjunctive therapy of epilepsy in children aged over 4 years (5). Many studies have shown OXCBZ to be a valuable medication in the treatment of partial seizures in children and adults both in monotherapeutic or adjunctive settings (6-10). OXCBZ is chemically similar to carbamazepine (CBZ) but with a different metabolism (11). Its antiepileptic effect is due to blockade of voltage-dependant sodium channels and modulating calcium channels (7,10), it is safer, is tolerated much better, has less drug reactions and the risk of over dose is extremely low in comparison with CBZ. No significant side effects have been reported for OXCBZ (12).

This study was performed to evaluate the efficacy and safety of OXCBZ in an adjunctive therapeutic setting in pediatric patients with resistant epilepsy.

Materials & Methods

This before and after type study was conducted on children with refractory epilepsy, seeking treatment in the department of pediatric neurology at Mofid children's hospital. We randomly studied 30 patients (based on the average number of patients in similar studies). Care was taken to include epileptic patients aged 4-14 yr (OXCBZ is approved in epileptic children older than 4 yr.) who had refractory epilepsy with seizure frequency from once a month to more than 10 times daily and were not on OXCBZ previously. We explained advantages and probable side effects of OXCBZ to the patient's parents and an informed consent was obtained from each one. The diagnosis of refractory epilepsy was made according to the definition of Berg and Shiner (2001) that defined intractability as "lack of seizure control while the patient has received at least 2 first-line antiepileptic medications, having more than 1 seizure per month in an 18- month period. Also, the patients should not be seizure free for more than 3 consecutive months" (2). We collected information such as sex and age of patients, seizure type and frequency and AEDs history at baseline. Then, we prescribed OXCBZ concomitantly with other AEDs that the patients were receiving. In the period of treatment with OXCBZ, other AEDs were not added but the dosage of current AEDs could be changed. The dosage of OXCBZ was 30 mg/kg/day for the first week and if the seizures were not controlled, it was increased to 40 mg/kg/day for the second week and finally 50 mg/kg/day for the third week if seizures were not controlled again. The maintenance dose was then continued for 10 months. Their parents kept seizure diaries (in view of frequency, duration and type of seizure) and the patients were regularly (every two weeks) assessed in the neurology clinic for seizure frequency and side effects of the new medication. The follow-up period was for 10 months (based on similar studies) and we compared daily seizure frequency before and after starting the new medication. Clinical response to OXCBZ treatment was defined as follows: seizure-free status means total cessation of seizures, improvement means more than 50% decrease in seizures frequency, unchanged means no notable change observed in seizure frequency and worsening means more than 25% increase in seizure frequency.

Laboratory investigations (CBC, BUN, Cr, Na, K, Ca, P, ALT, AST, U/A) were done in the beginning of the study and were re-checked monthly. If any significant hematologic, renal, hepatic or systemic side effects were seen, the treatment with OXCBZ was stopped and the patient was excluded.

Statistical analysis was performed using SPSS version 11.5 (SPSS; Chicago, IL, USA). Wilcoxon signed rank and Fisher's exact tests were used to evaluate the efficacy of OXCBZ in the treatment of refractory

epilepsy in children. Fisher's exact test was used for data analysis of qualitative variables.

Results

Thirty patients with intractable epilepsy were enrolled in this before and after type study. Mean age was 7.7±2.9 yr (range: 4-14 yr) and the group included 20 boys and 10 girls. The patients had received an average of nine AEDs before starting treatment with OXCBZ but their seizures were not controlled satisfactorily. During the period of treatment with OXCBZ, 18 patients (60%) were also receiving 1, 10 patient (33.3%) were receiving 2 and 2 patients (6.66%) were receiving 3 AEDs concomitantly. When seizures were controlled after OXCBZ therapy, 9 patients were receiving one and 6 were receiving two concomitant AEDs besides OXCBZ.

Nineteen patients (63.3%) had mixed type seizures, nine (30%) had partial seizures with or without secondary generalization and two (6.6%) had generalized tonic colonic seizures.

The effects of OXCBZ add-on therapy on intractable epilepsy are shown in table 1. OXCBZ was effective in controlling intractable seizure in children (P= 0.003). The best response was seen in patients with partial epilepsy (77.7%) (P=0.0043) and the patients with mixed-type seizures showed the least response to the drug. The average dose to control seizure was 45 mg/kg/day. No case of status epilepticus was reported during this period.

In one patient, the occurrence of an extensive skin rash led to discontinuation of the medication. Retrospectively, we found that history of skin reaction to CBZ was positive in this patient. In another patient, increasing dose of OXCBZ led to diplopia and dizziness that disappeared with reduction of the drug dose. Other side effects included asymptomatic transient hyponatremia (Na=130-132), drowsiness, headache, nausea and vomiting, ataxia and agitation (1 patient each). All these side effects were seen in the initiation of treatment and disappeared after a few days. Overall, transient side effects were seen in 11 patients (36.6%) but in 1 patient (3.3%), we had to discontinue the drug because of the adverse event (skin rash). Serious complications including bone marrow suppression and hepatic or renal involvement were not detected in any of our patients.

Discussion

OXCBZ is a new medication similar to CBZ which has a favorable profile. It is rapidly absorbed and has a rapid and complete reductive metabolism to form active 10-monohydroxy derivative (MHD) which is glucorunidated and excreted in the urine, with minimal involvement of the hepatic cytochrome P450 - dependent enzymes. Oxcarbazepine has no autoinduction and has minimal interaction with other antiepileptic medications (13). It is quite efficient in the treatment of partial seizures in children when is administered either alone or in combination with other antiepileptic medications (14).

According to our results, in 46.6% of the patients, seizures were completely controlled or a minimum of 50% reduction in seizure frequency was obtained. In a study by Gaily et al., a minimal 50% reduction in the frequency of seizures was detected during the treatment with OXCBZ in 50% of the patients with localization related epilepsy and in 40% of patients with generalized epilepsy (15). In the studies by Rufo-Campas et al and Freidel and colleagues, similar results were obtained (16, 17). In a study assessing the efficacy of OXCBZ in an adjunctive setting (with median dose of 31.4 mg/kg/day), patients with partial seizures were evaluated and a 35% reduction in the frequency of seizures was detected, whereas this rate was 9% in the placebo group (14).

In our study, the best result was seen in patients with partial seizures which is in accordance with other studies (1, 15, 18, 19). Adverse effects of the drug appeared in 40% of our patients. Most common side effects of OXCBZ are nausea, vomiting, dizziness, fatigue, diplopia, and somnolence (1, 9, 12, 20). These side effects are usually transient and disappear with dose decrease (9). OXCBZ shows better tolerability and safety than CBZ which is due to absence of 10-11 epoximetabolites of CBZ, less drug interaction with other antiepileptics, less risk of overdose for the patient, and no severe hematologic, renal, hepatic or nervous system side effects (2,12) . In 3% of the patients (regardless of age), asymptomatic hyponatremia is

detected, most frequently in the patients predisposed to hyponatremia (because of diseases or medications such as diuretics or non steroidal anti inflammatory drugs) (6, 9). Hyponatremia generally improves a few days after discontinuation of the medication (21). Therefore, measurement of the baseline serum sodium level is not necessary except for the conditions mentioned above. When the patient is on the maintenance therapy with OXCBZ, the serum level of sodium should also be measured when the symptoms of hyponatremia develop (6). The risk of symptomatic hyponatremia is greater when the child has an infection or the seizure is prolonged (21). In our study, one patient (3.33%) developed asymptomatic hyponatremia in the first week of treatment.

Allergic skin reactions are rare and develop mostly within the 3 first months of the treatment (21). Cross reactivity is also detected in 25% of the patients who are hypersensitive to CBZ (22). In our study, one patient (3.33%) developed a skin rash in the first week of treatment. She had the history of developing a skin rash to CBZ previously. The uncommon side effects of OXCBZ include abdominal pain, acne, alopecia, apathy, diarrhea, gum hyperplasia, tremor, and weight gain (21). None of these side effects were seen in our patients. Based on other researches done so far, in patients with mild to moderate hepatic dysfunction, no adjustment in the dose of OXCBZ is needed (7, 23).

In conclusion, OXCBZ is a favorable medication in the treatment of epilepsy, especially partial seizures, in children. We observed some advantages of the drug including rapid titration, low rate of drug-drug interaction, low rate of serious side effects and good tolerability and safety. Also, based on other research done so far, there is no need for monitoring laboratory findings of the patients.

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Table 1. Comparison of OXCBZ efficacy in different types of refractory epilepsy

Seizure type \ Response		Complete control	Improvement	Unchanged	Worsening	Total
Partial onset	Number percent	3 33.3	5 55.5	1 11.1	0 0	9 100
Generalized tonic clonic	Number percent	0 0	1 50	1 50	0 0	2 100
Mixed type	Number percent	0 0	6 31.5	9 47.3	4 21.05	19 100

Table 2. Results of the treatment response to OXCBZ

Response	Number	Percent
Seizure-Free	3	10
Improvement	12	36.6
Unchanged	11	40
Worsening	4	13.3
Total	30	100

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