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Oxicarbazepine potency add-on therapy on uncontrollable annexation in Children

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Abstract

Almost 50 million people in the world, a third of whom children, suffer from epilepsy. Up to 30% of them develop refractory epilepsy. In this group, there is a need for more efficacious antiepileptic drugs. This study was undertaken to evaluate the efficacy and safety of oxcarbazepine a new antiepileptic drug, as an adjunction therapy in children with refractory epilepsy. From February, 2004 until September 2006, 30 patients with refractory epilepsy aged between 4 and 14 years, were evaluated in a before and after type (pre-post) study in the department of neurology of Mofid children's hospital. Patients had at least one seizure per month to over 10 seizures daily and none of them had used oxcarbazepine previously. They received oxcarbazepine with a maximum dose 50 mg/kg/day orally in combination with their current antiepileptic drugs. The parents kept seizure diaries and the patients were regularly assessed for seizure frequency and side effects. The follow -up period was for 10 months. We compared the daily seizure frequency before and after starting the new medication. After 10 months of 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. Within the first days of treatment, brief and transient adverse effects including somnolence, dizziness and headache were seen in 36.6% of the patients which disappeared with continuation of treatment. In one patient with history of hypersensitivity to carbamazepine, skin rash occurred and resulted in withdrawal of the drug. Wilcoxon signed ranks test showed that oxcarbazepine was effective in the treatment of refractory seizures in children (P = 0.003) and as shown by Fisher's exact test, it is more effective in partial seizures. (P = 0.0043).The results showed that Oxcarbazepine is a useful medication in the treatment of refractory epilepsy especially partial type in children.

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

INTRODUCTION

Epilepsy is one of the most common neurologic diseases (Kalis, 2001). Mean incidence of epilepsy in childhood (from birth to 16 years of age) is approximately 40 in 100,000 children in each year (Peter et al., 2006).

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Antiepileptic drugs (AED) generally used 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 the patients with partial seizures (Castillo et al., 2000).

When the patient is resistant to the medication or cannot

tolerate the treatment due to the drug's adverse effects, more efficacious or better tolerable medications are needed (Connock et al., 2006).

One of these newly introduced medications is Oxcarbazepine (OXCBZ) which has been approved by Food and Drug Administration (FDA) (Malphrus and Wilfong, 2007).

Many studies have shown OXCBZ to be a valuable medication in treatment of partial seizures in children and adults both in monotherapeutic or adjunctive settings (Schimdt et al., 2001; Flesch, 2004; Bang, 2004; Arroyo, 2001; Schmidt and Elger, 2004). OXCBZ is chemically similar to carbamazepine (CBZ) but with a different metabolism (May et al., 2003). Its antiepileptic effect is due to blockade of voltage-dependant sodium channels and modulating calcium channels (Schmidt and Elger, 2004; Flesch, 2004), 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 has been reported for OXCBZ (Horga and Horga, 2006).

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

METHODS

In this before and after type study, 30 children between 4 and 14 years of age with refractory epilepsy including partial seizures with or without secondary generalization generalized tonic-colonic seizures and mixed type seizures, seeking treatment in department of pediatric neurology were recruited to be subjects of the study. None of these patients had ever used OXCBZ previously and the seizure frequency of them was from once a month to more than 10 times per day, before the commencement of the trial. We explained advantages and probable side effects of OXCBZ to the patient's parents and informed consent was obtained from them. 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 had 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" (Peter et al., 2006). 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 first week, 40 mg/kg/day for second week and 50 mg/kg/day for third week. This maintenance dose was then continued for 10 months. The 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 and we compared daily seizure frequency before and after starting the new medication. Clinical responses to OXCBZ treatment was defined as: seizure- free status or complete control the seizures, improvement or more than 50% decrease in seizures frequency, unchanged or less than 50% decrease and worsening or more than 50% 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 checked monthly. If any significant hematologic, renal, hepatic or systemic side effect was seen, the treatment with OXCBZ was stopped and the patient was excluded.

The 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.

RESULTS

Thirty patients with intractable epilepsy were enrolled in this before and after type study. Mean age was 7.7 ± 2.9 years range 4 - 14 years 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%) received 1, 10 patient (33.3%) received 2 and 2 patients (6.66%) received 3 AEDs concomitantly. In patients with control of seizures after OXCBZ therapy, 9 patients had received one and 6 had received two concomitant AEDs.

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. Table 1 shows patient information.

The effects of OXCBZ add- on therapy on intractable epilepsy is shown in Table 2. 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 extensive skin rash led to discontinuation of the medication. Retrospectively, we found that a history of skin reaction to CBZ was present in this patient. In another patient, increasing dose of OXCBZ led to diplopia and dizziness that disappeared with reduction of the drug dose. The other side effects include asymptomatic transient hyponatremia (Na = 130 - 132), drowsiness, headache, nausea and vomiting, ataxia and agitation (each in 1 patient). All of 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%) and in 1 patient (3.3%) we had to discontinue the drug because of adverse event (skin rash). Serious complications including bone marrow depression 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-

Table 1. Comparison between efficacies of OXCBZ in different types of refractory epilepsy.

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

Table 2. Total evaluation of 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

monohydroxy derivative (MHD) which is glucorunidated and excreted in the urine, with minimal involvement of the hepatic cytochrome P450- dependent enzymes. Oxcarbazepine has no auto induction and has minimal interaction with other antiepileptic medications (Glasuer, 2001). It is quite efficient in the treatment of partial seizures in children when administered both alone and in combination with other antiepileptic medications (Bang and Goa, 2003).

According to our results, in 46.6% of the patients, the seizures were completely controlled or a minimum of 50% reduction in seizure frequency was obtained. In the study of Gaily and coworkers, 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 (Gaily et al., 1998). In the studies by Rufo-Campas et al and Freidel and colleagues, similar results were obtained (Rupo-Campos et al., 2006; Freidel et al., 2007). 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. A 35% reduction in the frequency of seizures was detected, whereas, this rate was 9% in the placebo group (Bang and Goa, 2003).

In our study, the best result was seen among the patients with partial seizures (22.2% seizure-free rate and 55% reduction in the frequency of seizure), which is in accordance with other studies (Kalis, 2001; Gaily et al., 1998; Glauser et al., 2000; Wellington and Goa 2001)

Adverse effects of drug appeared in 40% of our patients. Most common side effects of OXCBZ are nausea, vomiting, dizziness, fatigue, diplopia and somnolence (Kalis, 2001; Arroyo, 2001; Horga and Horga, 2006; Wellington and Goa 2001).

Usually these side effects are transient and disappear with dose decrease (Arroyo, 2001). OXCBZ shows better tolerability and safety than CBZ which is due to absence of 10 - 11 epoximetabolites of CBZ, less drug interaction with other antiepileptic, less risk of overdose for the patient and no severe hematologic, renal, hepatic or nervous system side effects (Peter et al., 2006; Horga and Horga, 2006). In 3% of the patients (regardless of child or adult), 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) (Schmidt et al., 2001; Arroyo, 2001).

Hyponatremia generally improves a few days after discontinuation of the medication (Rene and Richard, 2002). Therefore measurement of the baseline serum sodium level is not necessary except for the conditions previously mentioned. When the patient is on the maintenance therapy with OXCBZ, serum level of sodium

should also be measured when the symptoms of hyponatremia develop (Schmidt et al., 2001). The risk of symptomatic hyponatremia is greater when the child has an infection or the seizure is prolonged (Rene and Richard, 2002). 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 (Rene and Richard, 2002). Cross reactivity is also detected in 25% of the patients who are hypersensitive to CBZ (Dam, 1994). In our study one patient (3.33%) developed skin rash in the first week of treatment. She has the history of skin rash to CBZ previously. The uncommon side effects of OXCBZ include abdominal pain, acne, alopecia, apathy, diarrhea, gum hyperplasia, tremor and weight gain (Rene and Richard, 2002). 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 (Flesch, 2004; Schmidt and Sachdeo 2000).

CONCLUSION

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

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