Efficacy and safety of oral suspension of oxcarbazepine in children with epilepsy

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Epilepsy is a frequent child pathology, 40% of all epileptic people are younger than 15 years of age. Specific problems such as selecting the appropriate antiepileptic drug can be faced in the treatment of epilepsy as epileptic syndromes occur in a broad spectrum in children, and various drugs have different pharmacokinetic profiles. Treatment must avoid frequent and long-lasting seizures, however, at the same time must spare cognitive development. New antiepileptic drugs seem to have more specialized indications, less side effects, and thus, represent a very interesting tool for the neuropediatrician.[1] Oxcarbazepine (OXC) is similar to carbamazepine (CBZ) in its mechanisms of action and antiepileptic efficacy, yet has better tolerability, and fewer interactions with other drugs. Although side effects of OXC such as gait instability, dizziness, drowsiness, nausea, vomiting, fatigue, headache, ataxia, sedation, hyponatremia, skin rash, hypersensitivity reaction, and diplopia are similar to those of CBZ, they are less severe and rare. Oxcarbazepine has been reported to be beneficial in children in terms of seizure control and tolerability both as a monotherapy, and an add-on drug.[2,3] In this study, we aimed to determine the efficacy and safety of oral suspension of OXC, in a group of pediatric patients who received this drug as mono/polytherapy.

This study was conducted as an open-label, single-center, retrospective, chart review study on children with epilepsy. Thirty-four patients who were referred to the Pediatric Neurology Department, Izmir Dr. Behcet Uz Children's Hospital, Izmir, Turkey between June 2004 and January 2007 were investigated following Institutional Ethical Committee approval. Inclusion criteria were age ≥1 year, diagnosis of generalized and partial epilepsy according to the International League Against Epilepsy (ILAE) 1998 classification, and ≥2 seizures in the previous month. A limitation of the study is that children who had myoclonic epilepsy and absence epilepsies, any of the contraindications for OXC administration. Age, gender, type of epilepsy, dose of OXC, other drugs used, side effects, number of seizures, follow-up period and response to treatment were recorded. Side effects were recorded on the standard checklist for side effects of antiepileptic drugs, while frequency and duration of seizures were recorded in an epilepsy diary. Records were controlled during each physical exam as a standard application, and these data were evaluated for assessing efficacy of therapy. To minimize its side effects, OXC treatment was initiated in a 10 mg/kg dose, which was increased by 10 mg/kg once a week. In very young patients, however, OXC dose was increased once every 2-3 days. Responses to therapy were classified as 100%, 50-98% and <50%. Hemogram, liver function tests, and serum sodium concentrations were examined before the treatment, and once every 3-6 months during the treatment in all patients. Statistical analyses were made by Chi-square, Student's t-test, and logistic regression tests using SPSS Version 12.0 for Windows software. $P<0.05$ was considered statistically significant.

Of the 34 children with epilepsy, 16 (47%) had partial and 18 had generalized epilepsy. Males comprised 19 (55.9%), and females 15 (44.1%). The mean age of patients was 6.2±2.7 (range 1-15) years. Twenty-four patients (70.5%) had symptomatic epilepsy, while 6 (17.6%) had cryptogenic, and 4 (11.7%) had idiopathic epilepsy. Nineteen (55.9%) patients received OXC as monotherapy. Fifteen (44.1%) patients had been on polytherapy, 1/15 (6.7%) patient used a combination of 3 drugs, while 14/15 (93.3%) of them used a combination of 2 drugs (**Table 1**). Concomitant antiepileptic drugs included valproate, phenobarbital, topiramate and carbamazepine.

Of the 34 patients with mental retardation, 11 (32.3%) had an accompanied epilepsy, 4 had generalized epilepsy, and 7 (63.6%) had partial epilepsy. Seven (64%) showed 50-98% and 4 (36%) showed <50% recovery. Mean OXC dose was 28.9±9 (range 10-50 mg/kg/day). Mean daily OXC dose in patients younger than 4 years of age was 32.8±6.7 (range 20-40 mg/kg), and in those older than 4 years of age was 26.4±9.3 (range 10-50

Table 1 - Between group comparison of the effectiveness and age, gender, epilepsy etiology, seizure type, mental retardation, mono- and polytherapy.

Characteristics		Effectiveness		Chi-square	Logistic regression	
	n	Present	Absent	*P*-value	95% CI	*P*-value
Age						
≤4 years	9	7	2	0.590	0.25 - 0.37	0.685
>4 years	25	22	3			
Gender						
Male	19	17	2	0.634	0.17 - 0.33	0.546
Female	15	12	3			
Epilepsy type						
Partial	16	12	4	0.164	0.20 - 0.37	0.549
Generalized	18	17	1			
Etiology						
Idiopathic	10	8	2	0.618	0.18 - 0.42	0.426
Symptomatic	24	21	3			
Mental retardation						
Positive	11	7	4	0.028	0.03 - 0.61	0.028
Negative	23	22	1			
Treatment						
Monotherapy	19	17	2	0.634	0.26 - 0.32	0.822
Polytherapy	15	12	3			

CI - confidence interval

mg/kg) (p=0.063). Nine (26.4%) out of 34 patients who received OXC treatment recovered completely (100%), while seizure frequency decreased by 50-98% in 20 (58.8%) patients. Children with partial epilepsy showed complete recovery in 3 (19%), 50-98% decline in seizure frequency in 9 (56%) and <50% decline in seizure frequency in 4 (25%) patients. Children with generalized epilepsy showed complete recovery in 6 (34%), 50-98% decline in seizure frequency in 11 (61%) and <50% decline in seizure frequency in 1 (5%) patient. Mean OXC doses in patients with greater than 50% response (n=29) was 26±8.1 (range 10-40 mg/kg), and in those with less than 50% response (n=5) was 38±8.4 (range 30-50 mg/kg) (p=0.006). Mean duration of treatment was 20.5±10.6 (range 6-36 months). The OXC was not stopped in any of the cases including 3 (8.9%) patients who felt drowsiness, nevertheless, recovered spontaneously. Multivariate analyses revealed that mental retardation significantly affected drug efficiency (p=0.028).

Selection of the antiepileptic drug in young children is of particular importance as most of these drugs exhibit cognitive and behavioral side effects. We show in our study that oral suspension of OXC is efficient and safe, both as monotherapy or polytherapy in children with epilepsy. Oral suspension of OXC was generally well-tolerated and did not exhibit such side effects as rash and hyponatremia even during long-term use. The OXC treatment caused greater than 50% decline in seizure frequency in 85.3% of the patients. It was notable that OXC caused greater than 50% decline in seizure frequency in 75% of patients with partial epilepsy and in 95% of those with generalized epilepsy. Epilepsy was symptomatic in most generalized epilepsy patients and OXC had been added on polytherapy. Hence, OXC also is efficient in adjuvant therapy of symptomatic generalized epilepsy.

We preferred prescribing OXC as the first-line treatment in 55.8% of all patients since metabolic diseases could not be excluded and OXC is known not to affect cognitive functions severely. Different results have been obtained with different methods in the literature in terms of OXC usage in children. Kothare et al[2] reported complete recovery in 42%, and partial recovery in 85% of partial epilepsy patients who received OXC as monotherapy. Martinez et al[3] reported complete and partial response in 18% and 50% of patients older than 12 years of age, with OXC as add-on treatment. In another study,[4] complete seizure control was achieved in 46.8% of 62 children between 2 months and 14 years of age with OXC as mono- and polytherapy. Greater than 50% decline in seizure frequency was observed in 80.6%. However, side effects were observed in 32% of patients, and the drug dose was reduced, or the drug was stopped in 17% of the patients. Skin rash was observed with a rate of 3.2%. Drowsiness and anger are the most common neurobehavioral side effects caused by OXC treatment. Another side effect is hyponatremia. We have not observed hyponatremia in any of our patients. The only side effect that we observed was drowsiness in 3 (8.8%) patients, which did not require stoppage of OXC. The same study reported that, compared with adults, young children required higher doses of OXC.[4] We have not found a significant difference in drug doses between children under and over 4 years of age.

In a study,[5] OXC was used both as mono- and polytherapy in children younger than 4 years of age, and total (50%) and partial (70%) recovery were observed all children. The drug was prescribed as monotherapy in 75% of children, and first-line drug in 73%. Partial epilepsy was rate 75% and generalized epilepsy rate was 25%. Drug efficiency in this study was higher than our study (26.4% and 58.8%). No side effects have been reported in patients younger than 2 years of age, however, temporary drowsiness was reported in 20% of the cases.[5] We have found a lower rate (8.9%) of temporary drowsiness in our study. Selection of antiepileptic drugs in children must rely not only the drug's efficacy, likewise on its side effects and tolerability.

We conclude that oral suspension of OXC is convenient, efficient, and safe, and can be an alternative to conventional antiepileptic drugs in young children with partial as well as generalized epilepsy (excluding absence and myoclonic seizures) and in particular in add-on treatment of symptomatic generalized epilepsies.

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