Oxcarbazepine as Add-On Therapy in Thai Epileptic Patients with Refractory Partial Seizures

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Objectives: *To evaluate efficacy and safety of oxcarbazepine (OXC) as add-on therapy in Thai refractory epileptic patients.*
Material and Method*: A randomized, double-blind clinical trial was conducted in outpatients of the Epilepsy Clinic of Phramongkutklao Hospital. OXC in the doses of 600 or 1200 mg/d were added to 39 refractory epileptic patients with the median baseline seizure frequency of at least 2 per 28 days.*
Results*: Of 35 patients who completed the 98-day treatment period, 4 became seizure free. A reduction in median seizure frequency of 47% and 58% was observed in patients in the 600 and 1,200 mg OXC/d groups, respectively. Among them, 44% and 53% demonstrated ≥ 50% reduction in median seizure frequency. About 85% of patients in each group reported one or more mild to moderate adverse events.*
Conclusion*: OXC in the doses of 600 and 1200 mg/d appear to be safe and effective as adjunctive therapy in Thai refractory epileptic patients. Further studies are needed to confirm its long-term efficacy and tolerability.*

Keywords: *Partial seizure, Oxcarbazepine, Antiepileptic drug, Add-on therapy*

J Med Assoc Thai 2005; 88(Suppl 3): S193-201
Full text. e-Journal: *http://www.medassocthai.org/journal*

Oxcarbazepine (OXC) is an antiepileptic drug (AED) currently approved in most countries worldwide as monotherapy and adjunctive therapy for the treatment of partial seizures as well as generalized tonic-clonic seizures in adults and children. OXC is structurally related to carbamazepine (CBZ), with a similar spectrum of activity and anticonvulsant efficacy in animal models of seizure. However, unlike CBZ, which undergoes oxidative metabolism, OXC is extensively and rapidly metabolized by reduction to 10-monohydroxy derivative (MHD), which is likely to be the major active component responsible for the pharmacologic effect of OXC[1]. OXC has an extremely low potential for the induction or inhibition of hepatic cytochrome P450 (CYP450), the major human drug metabolizing enzymes, resulting in a low propensity for its drug-drug interactions.

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Previous clinical experience with OXC indicates that OXC has an efficacy spectrum similar to that of phenytoin (PHT)[2,3], valproic acid (VPA)[4] and CBZ[5] but may have advantages in tolerability and clinical usefulness. OXC has demonstrated efficacy as monotherapy in presurgical hospitalized patients with refractory partial seizures[6] and as adjunctive therapy in adults[7] and children[8]. Therapeutic effects in monotherpy and adjunctive therapy were seen at dosages between 600 and 2400 mg/d.

OXC was registered in Thailand as a new antiepileptic drug in 2001. Until now no appreciable clinical information has been reported. Therefore, the authors considered evaluating the efficacy and safety of OXC as adjunctive therapy in Thai patients whose partial seizures were not adequately controlled by currently used AEDs.

Material and Method

The present study was conducted in outpatients of the Epilepsy Clinic of Phramongkutklao

Hospital during April 2003-January 2004. Eligible patients were adults 18-65 years of age with a history of partial seizures classified as simple, complex, or partial seizures evolving to secondary generalized seizures, according to the International League Against Epilepsy 1981 and 1989 classifications.

Before randomization, each patient underwent a complete physical and neurological examination, a laboratory analysis for determination of concomitant AED plasma concentrations and a routine hematological screen.

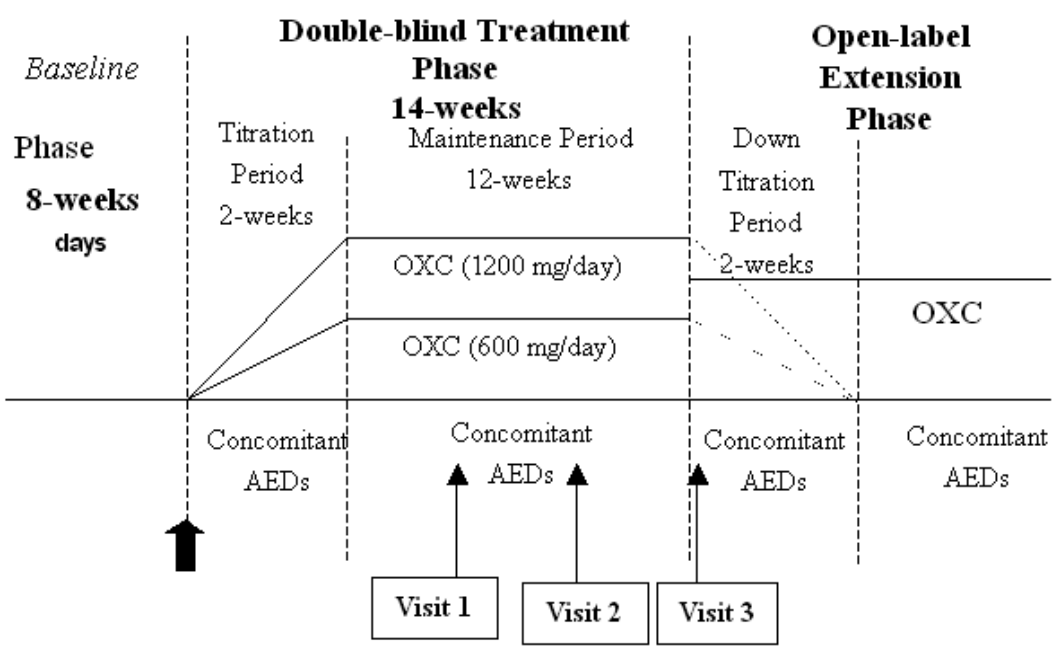
Patients had to experience at least four partial seizures during the 8-week baseline phase (at least one of which occurred during each of the first and second 4-week period of this). Patients were on a stable regimen of one or more concomitant AEDs. For those who were receiving only one concurrent AED, they must have previously failed in the treatment with any available AEDs, as monotherapy or in combination. The dosage regimen of primary concomitant AED, in patients receiving polytherapy, had to be above the average recommended effective dose or at its maximally tolerated dose, and the other concomitant AEDs had to be at least at their respective minimum effective doses.

The frequency and seizure patterns of each patient were recorded by the patients themselves or by caregivers in a diary issued by the investigators throughout the duration of the present study. The protocol excluded pregnant/nursing women or women trying to conceive, as well as patients with evidence or a history of generalized status epilepticus during the 3 months preceding the trial; seizure of metabolic or infectious origin; noncompliance; a hepatic, renal, or psychiatric disorder; a progressive structural lesion in the central nervous system or a progressive encephalopathy; hypersensitivity to CBZ; clinically significant laboratory abnormalities, serum sodium levels of less than 130 mmol/L; a history of OXC treatment and use of monoamine oxidase inhibitor or dihydropyridine calcium channel blockers.

The study protocol and consent forms were approved by the Ethical Committee of Phramongkutklao Hospital. Written informed consent was obtained from each patient before enrollment.

Design and procedure

A randomized, double-blind, parallel-group, adjunctive therapy trial was used to compare the efficacy and safety of two doses of OXC (600 mg/d



AEDs = antiepileptic drugs, OXC = oxcarbazepine

Fig. 1 Trial design

and 1200 mg/d). The study consisted of three phases: an 8-week baseline phase, a 14-week double-blind treatment phase, and an open-label extension phase (Fig. 1).

During the baseline phase, patients were maintained on a stable regimen of their current AEDs from the time of enrollment. In the double-blind treatment phase, those patients experiencing partial seizures at an average rate of at least two per month during the baseline phase and qualifying for the trial were randomized to adjunctive treatment with OXC at 600 or 1200 mg/d orally (in two divided doses). Both medications were dispensed as identical appearing capsules.

The 14-week double-blind treatment phase consisted of a 2-week titration period followed by a 12-week maintenance period. Titration schedule was 150 and 300 mg bid during day 1-12 and 13-14 respectively in the OXC 600 mg/d group, whereas it was 300, 450 and 600 mg bid during day 1-6, 7-12 and 13-14 respectively in the OXC 1200 mg/d group. The target doses (600 or 1200 mg/d) which were achieved within 2 weeks were then maintained throughout the 12-week maintenance period. Dosage of concomitant AEDs were maintained at their respective doses in the baseline period; however, the dosage could be decreased by the physician if needed e.g. if adverse effects occurred.

Throughout the maintenance period, patients returned to the clinic with their seizure diary at a 4-week interval for three times to evaluate efficacy and safety of OXC. During each study visit, patients were subjected to physical and neurological examinations as well as clinical laboratory testing (routine urine, blood chemistry and hematological analysis). Compliance was assessed by medication count. Type and frequency of seizure, adverse events (AEs) and concomitant medication use were documented. Plasma concentration of concomitant AEDs and MHD were determined.

After completing the double-blind treatment phase, double-blind code was disclosed. Patients were given the option of entering the open-label extension phase to continue treatment or to enter the optional 2-week tapering period. Only results from the double-blind treatment phase are reported here.

To determine therapeutic plasma MHD concentration, the average trough (Cmin) plasma concentrations (mg/ml) during the steady state were determined using blood samples collected before the morning dose of the second and the third visits of the double-blind treatment phase. MHD plasma concentrations were determined by high-performance liquid chromatography (HPLC).

Determination of plasma MHD concentration

Standard MHD, used as a reference for the determination of plasma concentration of MHD, was a generous gift from Novartis Pharma AG, Bangkok, Thailand. Analytical method was slightly modified from those previously described[9] and was validated for reliability and reproducibility[10]. Dichloromethan was used to extract MHD from plasma samples and then evaporated under nitrogen gas. The residue was dissolved in the mobile phase (water: acetonitrile = 80: 20) for chromatographic determination and injected into C_{18} column (4mm, 150mm·3.9mm I.D.) of HPLC. Detection was made by UV detector at the wavelength of 215 nm.

Efficacy endpoint

The primary efficacy endpoint was the percentage reduction in seizure frequency per 28 days during the double-blind treatment phase relative to the baseline phase. Secondary efficacy endpoint was response to treatment (defined as a 50% or more reduction in seizure frequency per 28 days during double-blind treatment phase relative to the baseline phase).

Safety endpoint

The safety of each OXC dose was evaluated by comparing baseline physical/neurological examinations, vital signs, and laboratory data with those collected during the treatment. In addition, AEs were monitored throughout the trial.

Data analysis and statistical method
Efficacy

a) The primary efficacy endpoint was analyzed by Wilcoxon Signed Rank Test comparing between before (baseline phase) and after (double-blind treatment phase) treatment. A regression analysis between dose, sex, age, weight, baseline seizure frequency and Cmin of MHD as contributable variable was performed. Wilcoxon Rank-Sum Test was used to compare efficacy between the 2 treatment groups.

b) The secondary efficacy end point (responder rate) was analyzed by Wilcoxon Rank-Sum Test comparing percentage of patients who experienced ≥50% reduction in seizure frequency between the 2 treatment groups.

c) Relationship between dosage regimen and plasma MHD concentration were assessed using Cmin as a contributable variable for the dosage.

Safety

AEs variables were summarized and reported as percentage of each treatment group.

Results

Patient characteristics

A total of 39 patients were randomized to the double-blind treatment with OXC at 600 mg/d (n=20; 51%) or 1200 mg/d (n=19; 49%). Demographic and baseline seizure characteristics are summarized in Table 1. There was no difference between the two dosage groups with regard to age, sex, and weight. The patient population included 20 men (51%) and 19 women (49%); mean age was 31.6±7.1 years and mean weight was 60±10.8 kg. The types and frequencies of partial seizures in both groups during the baseline phase were similar. The median partial seizure frequency per 28 days during the baseline phase was 4.5 in the 600 mg/d and 4 in the 1200 mg/d groups.

The majority of patients were receiving one concomitant AEDs (20/39; 51%), (Table 2). The most frequently prescribed concomitant AED was CBZ (22/39; 56%), followed by VPA (15/39; 39%), and PHT (14/39; 36%). On average, the patients were taking 1.83±0.79 concomitant AEDs in the 600 mg/d and 1.47±0.8 in the 1200 mg/d OXC groups. No statistical significant difference was observed on characteristics of concomitant AEDs between the two dosage groups (p=0.185).

Of the 39 patients randomized, one patient in the 1200 mg/d group was lost in the follow-up, and 3 patients discontinued because of AEs. Therefore, 35(90%) patients, who completed the double-blind treatment phase, were subjected to the evaluation of efficacy by per-protocol analysis whereas safety analysis including all patients was made by intention-to-treat (ITT) analysis.

Efficacy

Percentage change in seizure frequency (PCH)

Thirty-five patients were included in the ef-

Table 2. Number of patients using concomitant AEDs by treatment group; n (%)

Number of AEDs	Treatment group OXC (mg/d)		Total (n=39)
	600 (n=20)	1,200 (n=19)	
1	7 (35%)	13 (68%)	20 (51%)
2	8 (40%)	2 (11%)	10 (26%)
3	5 (25%)	4 (21%)	9 (23%)

Table1. Baseline demographic and clinical characteristics of all randomized patients

Characteristic	OXC (mg/d)		
	600 n=20	1200 n=19	total n=39
Sex [no. (%)]			
Males	12 (60)	8 (42)	20 (51)
Females	8 (40)	11 (58)	19 (49)
Age [y]			
Mean–SD	30.4±7.3	31.7±6.9	31.6±7.1
Range	18-44	18-44	18-44
Weight [kg]			
Mean±SD	58.4±10.5	61.7±11.1	60.0±10.8
Range	42-78	46-80	42-80
28-day baseline seizure frequency [Median (mean)]			
- All partial	4.5 (7.6)	4.0 (7.7)	4 (7.7)
- Complex partial	3.0 (6.0) [n=16]	3.0 (5.7) [n=17]	3 (5.8) [n=33]
- Simple partial	4.5 (10.5) [n=4]	7.0 (7.3) [n=6]	5 (8.6) [n=10]
- Secondarily generalized tonic-clonic	1.5 (2.9) [n=5]	3.0 (3.0) [n=2]	1.5 (2.9) [n=7]

ficacy analysis. Basal median seizure frequency of 4.5 and 4 in the 600 and 1200 mg/d groups were statistically decreased to 2.5 (p=0.003) and 1.8 (p=0.017) respectively in the treatment period. A 47% median percentage reduction from baseline was observed in patients treated with 600 mg OXC/d compared with 58% in those treated with 1200 mg OXC/d.

A regression analysis of the percentage change from baseline in seizure frequency (PCH) with dose, sex, age, weight, baseline seizure frequency, and Cmin as explanatory variables demonstrated that only weight was statistical significant correlated with reduction in seizure frequency (p = 0.010).

The benefit of OXC was apparent when OXC was added to refractory patients using CBZ (18/35; 51.4%) either in a monotherapy or polytherapy at baseline. The median reduction in seizure frequency was 47% and 58% in 600 and 1200 mg/d groups, respectively. No statistical significant difference between the two treatment groups was noted (p = 0.587) (Table 3).

Responder rate

Response to treatment was defined as having at least a 50% reduction in 28-day seizure frequency during double-blind treatment compared with baseline. In the protocol analysis for responder rate, it was found that 44% of patients in the 600 mg/d group had at least 50% reduction in seizure frequency compared to 53% in the 1200 mg/d group, whereas 11% (2/18) in the 600 mg/d group and 12% (2/17) in the 1200 mg/d group were seizure free.

Table 3. Analysis of the percentage change from baseline in 28 days seizure rate (primary efficacy variable) for the completers and for the patients who received CBZ

Population	Treatment group	
	OXC 600 mg/d	OXC 1200 mg/d
Completers		
N	18	17
Median change in seizure Frequency (%)	- 47%	- 58%
p-value	-	0.729
Patients who took CBZ		
N	11	7
Median change in seizure Frequency (%)	- 47%	- 58%
p-value	-	0.587

Table 4. Incidence of AEs reported during double-blind treatment in each treatment group (all patients)

AEs	OXC (mg/d)		
	600 (n=20) n (%)	1200 (n=19) n (%)	total n (%)
Number reporting an AE	17 (85%)	16 (84.2%)	33 (84.6%)
Nervous system			
Somnolenc	10 (50%)	8 (42.1%)	18 (46%)
Ataxia	7 (35%)	5 (26.3%)	12 (30.8%)
Dizziness	3 (15%)	8 (42.1%)	11 (28.2%)
Headache	3 (15%)	3 (15.8%)	6 (15.4%)
Special senses			
Abnormal vision	4 (20%)	3 (15.8%)	7 (18%)
Diplopia	1 (5%)	1 (5.3%)	2 (5.1%)
Digestive system			
Vomiting	0 (0%)	2 (10.5%)	2 (5.1%)
Nausea	1 (5%)	1 (5.3%)	2 (5.1%)
Body as a whole			
Fatigue	2 (10%)	1 (5.3%)	3 (7.7%)
Skin			
Rash	0 (0%)	1 (5.3%)	1 (2.5%)

The proportion of patients who responded to OXC seem to be increased with increasing dose; however, the 1200 mg/d group did not exert statistical significant higher percentage of responders than those receiving 600 mg OXC/d (p=0.615).

Paradoxically, seizure frequency was found to be increased (>25% as compared with baseline) in 5 patients; however, the severity of seizure was decreased in three of them. One patient receiving OXC at 1200 mg/d changed the seizure type from complex partial seizures (3 times per 28 day) to simple partial seizures (8 times per 28 days), and a decrease in duration of seizure was found in two patients (one in each treatment group).

Among all combinations, the most effective combination was seen in patients receiving OXC and topiramate (TPM) in which 3 out of 4 patients demonstrated >50% reduction in seizure frequency. Other effective combinations included OXC and PHT (6/14), OXC and CBZ (9/22), OXC and VPA (6/15), and OXC and phenobarbital (PB) (2/10), whereas no responder was found in patients receiving OXC and lamotrigine (LTG) (0/2).

Safety

Report of AEs

AEs, defined as any adverse experienced regardless of its relationship to OXC, that developed during double-blind treatment phase of 39 patients, was assessed by interviewing. They were summarized and being analyzed by intention-to-treat basis (Table 4). The overall incidences of AEs (patients reporting at least one AE) were 85% in the 600 mg/d group, and 84% in 1200 mg/d group. These AEs mostly occurred in the first 3 weeks of initial treatment especially in the titration period with mild to moderate in severity and were transient in nature, with tolerance developing in the majority of patients.

The most common AEs in both OXC treatment groups involved the central nervous system (CNS) e.g. somnolence, dizziness, ataxia, headache and the special senses (abnormal vision, diplopia). Dizziness and vomiting are AEs that appeared to increase with increasing dose while the rest are rather comparable.

Three patients (2 in the 600 mg/d and 1 in the 1,200 mg/d groups) discontinued prematurely due to CNS-related AEs. Among them, one patient receiving OXC at 600 mg/d exhibited an increase in seizure frequency (30 seizures in a day despite baseline seizure frequency of 5 seizures/28 days).

It is noteworthy that all of premature discontinuation patients were taking OXC with more than one concomitant AEDs while all patients who did not experience AEs were those receiving OXC with only one concomitant AED. Discontinuation occurred within 3 weeks of initiation trial treatment. No patients discontinued prematurely because of abnormal laboratory values.

Laboratory evaluations

Routine clinical laboratory evaluations were performed at baseline and at designated visits during the double-blind treatment phase. Differences between baseline and post-randomized values were not found to be of any clinical significance in both dosage groups. The mean serum sodium levels remained unchanged following treatment with OXC in both groups, albeit, a decrease from baseline but still within a normal range of serum sodium levels was observed in 3 patients. Furthermore, no significant change was noted on any other parameters of clinical blood chemistry, hematology and urinalysis.

Plasma MHD concentrations

Cmin of MHD at steady state were proportionally correlated with the OXC dose (p=0.000); 6.77±2.52 mg/ml and 12.46±4.99 mg/ml in the 600 mg/d and the 1200 mg/d groups, respectively. No correlation was observed between trough MHD concentrations and primary efficacy parameter (PCH). Of patients who had ≥ 50% reduction in partial seizure frequency per 28 days (responder), mean trough plasma were 7.26±3.22 and 13.97±5.86 mg/ml in the 600 and 1200 mg/d groups, respectively, whereas they were 6.39±1.93 and 10.75±3.39 mg/ml in non-responders of each group.

Interactions with concomitant AEDs

Plasma concentrations of concomitant AEDs in both treatment groups were unaffected by co-administration of OXC.

Discussion

The results of the present trial clearly demonstrated that adjunctive therapy with OXC at dosages of 600 and 1200 mg/d were effective in Thai patients with uncontrolled partial seizures with or without secondarily generalized seizures. There was a statistical significant decrease in seizure frequency per 28 days (47% in the 600 mg/d group (p=0.003) and 58% (p=0.017) in the 1200 mg/d group) in double-blind treatment phase relative to the baseline phase. Accordingly, the

responder rate was found to be 44% in the 600 mg/d group and 53% in the 1200 mg/d group. Both efficacy variables (PCH and responder rate) seemed to increase with increasing dose; however, no statistical significance was found.

Comparatively, OXC in both doses appeared to exhibit higher efficacy than those previously reported in non-Asian patients[7]. This may be accounted by 2 reasons. Firstly, the patients of the present study had a lower median baseline seizure frequency (4-4.5 VS. 9-10 seizures/28 days in a previous study). This assumption was supported by the study of Brodie and Kwan[11], which reported that patients with a high number of seizures were less likely to be controlled. Secondly, the patients had a lower mean body weight (60 kg VS. 71 kg in the previous trial). Similar to the finding that smaller body weight seemed to account for a lower minimum effective dose of TPM required by Chinese patients compared to that required by non-Asian patients[12,13], a regression analysis of the present study demonstrated a correlation between reduction in seizure frequency and weight. Patients with smaller body weight tended to respond better. As clearance and volume of distribution were significantly related to body weight, lower clearance and volume of distribution are expected in the studied population. This may also explain the rather high trough plasma concentration of MHD in the present study (6.77 mg/mL) compared to 4.7 mg/mL from the previous study[7].

Generally, combinations of AEDs with different and multiple mechanisms of action are more likely to result in synergy than combination of drugs sharing a similar mechanism[14]. More patients become seizure free with the add-on combination of a sodium channel blocker and a drug with multiple mode of action than with other combinations[15]. Synergy between TPM and CBZ has been shown by isobolographic analysis[14]. In line with these, it was found that an addition of OXC, a sodium channel blocker[11], to patients currently using TPM, an AED with multiple mechanisms of action[11], was the most effective combination with 75% responders. Additionally, based on the result that improving efficacy was exhibited by a combination of OXC and CBZ (Table 3), it is suggested that OXC may have some other mechanisms than blocking of sodium channels.

In line with a previous study, the AEs that were most frequently reported hereby were CNS-related. Most of them were rated as mild to moderate in severity and were transient in nature. The incidence of AEs in the two treatment groups are rather similar (85% for the 600 mg/d and 84% for the 1200 mg/d groups). The incidences of AEs as well as premature discontinuations due to AEs were apparent during the first 3 weeks of double-blind treatment phase. In addition, OXC therapy in the present trial did not adversely affect hematologic, renal and hepatic functions or cause hypersensitivity reactions like those previously reported in OXC-controlled clinical trials[7, 8].

The observation that all of the patients who prematurely discontinued were taking OXC with more than one concomitant AEDs while all the patients who did not experience AEs were the patients receiving OXC with only one concomitant AED, implies that the preexisting AED drug load, rather than any specific background AEDs or interactions with any one specific AEDs, accounted for most AEs and premature discontinuation incidences.

Although the incidence of hyponatremia has been reported with OXC[16], no patient demonstrated a clinically significant low plasma sodium levels (plasma sodium < 125 mEq/L) on consecutive visits during the double-blind treatment phase.

Cmin of MHD at a steady state were proportionally correlated with the OXC dose (6.77 mg/mL for the 600 mg/d group and 12.46 mg/mL for the 1200 mg/d group, p=0.000). These results are in line with other pharmacokinetic studies[17,18], which provided evidence that there was a linear relationship between oral OXC dosages and plasma MHD concentrations in healthy volunteers and patients with epilepsy who were receiving OXC monotherapy or polytherapy[19]. Thus, routine monitoring serum concentration of OXC or its active metabolite (MHD) is not necessary except in the case of checking for compliance or toxicity[20]. Interestingly, it was found that Cmin in responders was higher than that in non-responders (7.26 and 13.97 mg/mL in the 600 and 1200 mg/d groups, respectively, VS. 6.39 and 10.75 mg/mL in non-responders). Taken into consideration that therapeutic range of MHD was about 12-35 mg/mL[2], it can be anticipated that a higher dose than 1200 mg/d of OXC could be applied to achieve better control if the patients can tolerate AEs.

In conclusion, the present study demonstrated the efficacy of OXC at 600 and 1200 mg/d as add-on therapy in Thai adult epileptic patients with uncontrolled partial seizures including the seizure subtypes of simple, complex, and partial seizures evolving to secondarily generalized seizures. Comparatively, a higher percentage of reduction in seizure frequency as well as a higher rate of responders was exhibited by OXC at 1200 mg/d with no statistically significant dif-

ference from those of 600 mg/d group. While exhibiting mild to moderate degree, transient in nature and comparable adverse effect profile with those previously reported in non-Asian patients, OXC was found to be more effective in controlling seizures.

Bases on the authors finding, it is suggested that a study on efficacy and safety of different doses of OXC especially those lower than 600 mg/d or higher than 1200 mg/d as add-on therapy or monotherapy in Thai epileptic patients should be further conducted. Furthermore, wider and longer clinical experiences in these groups of patients are also needed to confirm long-term efficacy as well as tolerability of OXC since treatment of epilepsy by AEDs could be life-long in many patients.

Acknowledgment

This study was supported by the Graduate School, Chulalongkorn University and Novartis Pharma AG, Bangkok, Thailand Limited.

References

1. Grant SM, Faulds D. Oxcarbazepine: a review of its phamacology and therapeutic potential in epilepsy, trigerminal neuralgia, and affective disorders. Drugs 1992; 43: 873-88.
2. Bill AP, Vigonius U, Pohlmann H, Guerreior C, Kochen S, Saffer D, et al. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in adults with previously untreated epilepsy. Epilepsy Res 1997; 27: 195-204.
3. Guerreiro MM, Vigonius U, Pohlmann H, Manreza M, Fejerman N, Antoniuk S, et al. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy. Epilepsy Res 1997; 27: 205-13.
4. Christe W, Kramer G, Vigonius U, Pohlmann H, Steinhoff B, Brodie M, et al. A double-blind controlled clinical trial: oxcarbazepine versus sodium valproate in adults with newly diagnosed epilepsy. Epilepsy Res 1997; 26: 451-60.
5. Dam M, Ekberg R, Loyning Y, Waltimo O, Jakobsen K. A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy. Epilepsy Res 1989; 3: 70-6.
6. Schachter SC, Vazques B, Fisher RS, Laxer KD, Montouris GD, Faught E, et al. Oxcarbazepine: double-blind, randomized, placebo-control, monotherapy trial for partial seizures. Neurology 1999; 52: 732-7.
7. Barcs G, Walker EB, Elger CE, Scaramelli A, Stefan H, Sturm Y, et al. Oxcarbazepine placebo-control, dose-ranging trial in refractory partial epilepsy. Epilepsia 2000; 41: 1597-607.
8. Glauser TA, Nigro M, Sachdeo R, Pasteris LA, Weinstein S, Abou-Khalil B, et al. Adjunctive therapy with oxcarbazepine in children with partial seizures. Neurology 2000; 54: 2237-44.
9. Matar KM, Nicholls PJ, Al-Hassan MI, Tekle A. Rapid micromethod for simultaneous measurment of oxcarbazepine and its active metabolite in plasma by high-performance liquid chromatography. Clin Pharmacy Therapeutics 1995; 20: 229-34.
10. Causon R. Validation of chromatographic methods in biomedical analysis viewpoint and discussion. Chromatography B 1997; 689: 175-80.
11. Brodie MJ, Kwan P. Stage approach to epilepsy management. Neurology 2002; 58(Suppl 5): S2-8.
12. Sharief M, Viteri C, Ben-Menachem E, Weber M, Reife R, Pledger G, et al. Double-blind, placebo-controlled study of topiramate in patients with refractory partial epilepsy. Epilepsy Res 1996; 25: 217-24.
13. Yen JD, Yu YH, Guo CY, Chen C, Yiu HC, Su SM. A double-blind, placebo-controlled study of topiramate in adult patients with refractory partial epilepsy. Epilepsia 2000; 41: 1162-6.
14. Czuczwar SJ. Drug resistant epilepsy: what can we learn from experimental studies? Pol J Pharmacol 2003; 55: 115-21.
15. Kwan P, Brodie MJ. Epilepsy after the first drug fails: substitution or add-on?. Seizure 2000; 9: 464-8.
16. Nielsen OA, Johannessen AC, Bardrum B. Oxcarbazepine-induced hyponatremia, a cross-sectional study. Epilepsy Res 1988; 2: 269-71.
17. Dickinson RG, Hooper WD, Dunstan PR, Eadie MJ. First dose and steady-state pharmacokinetics of oxcarbazepine and its 10-hydroxy metabolite. Eur J Clin Pharmacol 1989; 37: 69-74.
18. Lloyd P, Flesch G, Dieterle W. Clinical pharmacology and pharmacokinetics of oxcarbazepine. Epilepsia 1994; 35(Suppl 3): S10-3.
19. Cloyd JC, Remmel RP. Antiepileptic drug pharmacokinetics and interactions: impact on treatment of epilepsy. Pharmacotherapy 2000; 20(8Pt2): S139-51.
20. Schmidt D, Sachdeo R. Oxcarbazepine for treatment of partial epilepsy: a review and recommendations for clinical use. Epilepsy Behavior 2000; 1: 396-405.

การใช้ยาออกซ์คาร์บาซีปีนเป็นยาเสริมในผู้ป่วยลมชักชาวไทยที่มีอาการชักชนิดบางส่วนซึ่งไม่สามารถควบคุมได้ด้วยยากันชักที่ใช้อยู่

เพทิสรา ไกรปราบ, โยธิน ชินวลัญช์, มยุรี ตันติสิระ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพและความปลอดภัยของยาออกซ์คาร์บาซีปีนเมื่อใช้ในรูปแบบเป็นยาเสริมในผู้ป่วยลมชักชาวไทยที่มีอาการชักชนิดบางส่วนซึ่งไม่สามารถควบคุมอาการชักได้ด้วยยากันชักที่ใช้อยู่*

วัสดุและวิธีการ: *ผู้ป่วยซึ่งไม่สามารถควบคุมอาการชักชนิดบางส่วน (มีอาการชักเฉลี่ยอย่างน้อย 2 ครั้งในเวลา 28 วัน) จำนวน 39 คนถูกประเมินโดยการศึกษาแบบสุ่ม, ปิดบังทั้ง 2 ด้าน โดยแบ่งผู้ป่วยออกเป็น 2 กลุ่มให้รับประทานยาออกซคาร์บาซีปีนในขนาด 600 และ 1200 มิลลิกรัม/วัน ร่วมกับยากันชักที่ผู้ป่วยได้รับอยู่เดิม*

ผลการศึกษา: *มีผู้ป่วยจำนวน 35 คนที่อยู่จนเสร็จสิ้นการศึกษาเป็นเวลา 98 วัน ในจำนวนนั้นมีผู้ป่วยที่ไม่มีอาการชักเลยจำนวน 4 คน ค่ามัธยฐานเปอร์เซ็นต์ความถี่ของการชักที่ลดลงในผู้ป่วยที่ได้รับยาออกซ์คาร์บาซีปีนในขนาด 600 และ 1200 มิลลิกรัม/วัน เท่ากับ 47% และ 58% ตามลำดับ และพบว่าผู้ป่วยที่มีความถี่ของการชักลดลงอย่างน้อย 50% มีค่าเท่ากับ 44% และ 53% ในกลุ่มที่ได้รับยาขนาด600 และ 1200 มิลลิกรัม/วัน ตามลำดับ ระหว่างการศึกษามีผู้ป่วยประมาณ 85% จากทั้ง 2 กลุ่มที่รายงานอาการไม่พึงประสงค์อย่างน้อย 1 ชนิดจากการ ใช้ยาซึ่งอาการดังกล่าวอยู่ในระดับรุนแรงเล็กน้อยถึงปานกลาง*

สรุป: *ยาออกซ์คาร์บาซีปีนทั้งขนาด 600 และ 1200 มิลลิกรัม/วัน มีประสิทธิภาพและความปลอดภัยในผู้ป่วยลมชักชาวไทยซึ่งไม่สามารถควบคุมอาการชักได้เมื่อใช้ในรูปแบบเป็นยาเสริมร่วมกับยากันชักตัวอื่น ควรมีการศึกษาต่อไปถึงประสิทธิผล และความทนต่อยาออกซ์คาร์บาซีปีนในระยะยาว*