Effects of oxcarbazepine on cognitive function in children and adolescents with partial seizures

Abstract—The authors investigated the effect of oxcarbazepine on cognitive function in children and adolescents (6 to younger than 17 years of age) with newly diagnosed partial seizures in an open-label comparison with standard antiepileptic drug therapy (carbamazepine and valproate). No differences in cognitive tests were observed between oxcarbazepine and carbamazepine/valproate over a 6-month treatment period.

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F. Donati, MD; G. Gobbi, MD; J. Campistol, MD; G. Rapatz, MSc; M. Daehler; Y. Sturm, PhD; and A. P. Aldenkamp, MD; on behalf of The Oxcarbazepine Cognitive Study Group

There is an increased risk of cognitive impairment in patients with epilepsy.¹ Antiepileptic drug (AED) therapy may have adverse cognitive effects.^{1,2} Cognitive function deficits can negatively affect school performance and psychosocial interactions.^{3,4} The differential effects of new vs standard AEDs on cognitive function in children with epilepsy merit investigation.

Carbamazepine and valproate, standard AEDs indicated for children and adolescents with newly diagnosed epilepsy, are considered to have similar, mild effects on cognitive functioning.⁵ Oxcarbazepine is a newer AED indicated for the treatment of partial seizures in adults and children (in the United States, monotherapy for patients 4 years old and older, adjunctive therapy for patients 2 years old and older; in most European countries, for patients 6 years old and older). Oxcarbazepine is well tolerated and effective^{6,7}; however, the effects of oxcarbazepine on cognitive functions have not been studied systematically in children. We therefore studied the effect of oxcarbazepine compared to that of standard AED therapy on selected cognitive functions in children and ado-

lescents (6 to younger than 17 years of age) with partial seizures.

Methods. We conducted a multicenter, open-label, randomized, active-control, three-arm, parallel-group study across Europe. Patients were randomized in a 2:1:1 ratio (oxcarbazepine: carbamazepine:valproate) and stratified into two age groups, 6 to younger than 12 years and 12 to younger than 17 years. The study consisted of a screening and a 6-month open-label treatment phase. AEDs were administered as monotherapy according to their respective prescribing information.

Eligible patients were previously untreated boys and girls, aged 6 to younger than 17 years, with a history of at least two unprovoked partial seizures (simple and complex partial seizure subtypes and partial seizures evolving to secondarily generalized seizures). Exclusion criteria included patients with more than two secondarily generalized tonic-clonic seizures within the 3 months prior to randomization, patients with generalized seizures (i.e., seizures without focal onset) in the previous 6 months, and patients with a history of clinically relevant psychiatric disorders (DSM-IV), attention deficit disorder, comorbid neurologic disease, or other diseases affecting cognitive abilities adversely.

Cognitive function testing. The “FePsy” computerized neuropsychological test battery (attentional tests, information processing), the Rey Auditory Verbal Learning Test (AVLT; memory and learning), and Raven’s Standard Progressive Matrices for children (intelligence) were used in this study. All tests were performed at untreated baseline (visit 1) and at study completion (6 months post-randomization; visit 3) or at the time of premature discontinuation. The primary cognitive variable was mental information processing speed, as assessed with the Computerized Visual Searching Task⁵ (CVST; part of the FePsy). Secondary cognitive variables assessed psychomotor speed and alertness, memory and learning, and attention. Nonverbal intelligence was assessed using the Raven Standard Progressive Matrices.⁸

Efficacy and safety assessments. Seizure occurrence was recorded at baseline, during treatment, and at study completion. Safety was assessed by the frequency of adverse events and the number of laboratory values outside of predetermined notable ranges.

Statistical analyses. All randomized patients who received at least one dose of study medication and who performed a CVST assessment at baseline and at 6 months (per-protocol population) were used for the primary analysis. Intent-to-treat patients included all randomized patients who received study medication and from whom a neuropsychological measurement was obtained pre- and post-randomization. All randomized patients who received study medication were used for the safety analysis. Primarily, oxcarbazepine was compared with the combined carbamazepine and valproate groups. Differences between treatment groups on the cognitive endpoints were tested using analysis of covariance (ANCOVA), with endpoint test score as the dependent variable, country and age group (6 to younger than 12 years; 12 to younger than 17 years) as factors, and baseline score as covariate. The intelligence test was analyzed using a Van Elteren test stratified by age group.

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From Neurologie (F.D.), Spitalzentrum Biel, University Hospital, Bern, Switzerland; Neuropsychiatria Infantile (G.G.), Ospedale Maggiore, Bologna, Italy; Servicio de Neuropediatría (J.C.), Hospital Sant Joan de Deu, Esplugues, Barcelona, Spain; Novartis Pharma AG (G.R., M.D., Y.S.), Basel, Switzerland; Epilepsie-centrum Kempenhaeghe (A.P.A.), Heeze and Department of Neurology, University of Maastricht, The Netherlands

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Address correspondence and reprint requests to: Dr. Albert P. Aldenkamp, Department of Behavioural Sciences, Epilepsy Centre Kempenhaeghe, P.O. Box 61, NL-5590 AB Heeze, The Netherlands; e-mail: aldenkampB@kempenhaeghe.nl

Table 1 Patient demographics and disposition including baseline seizure and epilepsy classification (safety population)

Characteristic	OXC (n = 55)	CBZ (n = 28)	VPA (n = 29)	CBZ/VPA (n = 57)
Male, no. (%)	21 (38.2)	16 (57.1)	14 (48.3)	30 (52.6)
Age, y				
Median (range)	10 (6–16)	10 (6–16)	9 (6–15)	9 (6–16)
Age group, no. (%)				
6 to <12 y	40 (72.7)	17 (60.7)	23 (79.3)	40 (70.2)
12 to <17 y	15 (27.3)	11 (39.3)	6 (20.7)	17 (29.8)
Weight, kg*				
Median	37.3	40.2	33.3	35.5
Range	18.5–82.0	20.9–65.5	22.0–61.0	20.9–65.5
Disposition, no. (%)				
Randomized	55 (100.0)	28 (100.0)	29 (100.0)	57 (100.0)
Completed	49 (89.1)	26 (92.9)	24 (82.8)	50 (87.7)
Evaluable	47 (85.5)	26 (92.9)	24 (82.8)	50 (87.7)
Discontinuations	6 (10.9)	2 (7.1)	5 (17.2)	7 (12.3)
Reason				
Adverse event(s)	1 (1.8)	1 (3.6)	0 (0.0)	1 (1.8)
Unsatisfactory therapeutic effect	3 (5.5)	1 (3.6)	4 (13.8)	5 (8.8)
Other	2 (3.6)	0 (0.0)	1 (3.4)	1 (1.8)
ILAE seizure classification, no. (%)				
Simple partial	23 (41.8)	9 (32.1)	12 (41.4)	21 (36.8)
Complex partial	23 (41.8)	17 (60.7)	15 (51.7)	32 (56.1)
Partial evolving into secondarily GTC	31 (56.4)	16 (57.1)	11 (37.9)	27 (47.4)
ILAE epilepsy classification, no. (%)†				
Idiopathic	31 (56.4)	16 (57.1)	17 (58.6)	33 (57.9)
Symptomatic	9 (16.4)	2 (7.1)	4 (13.8)	6 (10.5)
Cryptogenic	14 (25.5)	10 (35.7)	8 (27.6)	18 (31.6)

* OXC, n = 54; VPA, n = 28; CBZ/VPA, n = 56.

† Information on one patient in the oxcarbazepine group relating to epilepsy classification was not provided by the investigator.

OXC = oxcarbazepine; CBZ = carbamazepine; VPA = valproate; ILAE = International League Against Epilepsy; GTC = generalized tonic-clonic.

In total, ≥ 78 evaluable patients were required to detect a clinically meaningful difference of 4.5 seconds^a (if present) between treatment groups on the CVST (assuming a SD of 6 seconds) with at least 90% power, at the two-sided 0.05 significance level.

Results. Table 1 presents patient demographics and disposition. Of 112 patients randomized, 99 completed the study (per-protocol population, n = 97). Treatment groups were well balanced with respect to their baseline demographic characteristics. Distribution of seizure types was similar between the oxcarbazepine and combined carbamazepine/valproate treatment groups (table 1), indicating a homogeneous patient population. Mean daily doses (SD) during the 4 weeks prior to assessments at 6 months were 19.6 mg/kg (6.4) for oxcarbazepine, 14.4 mg/kg (3.6) for carbamazepine, and 20.7 mg/kg (7.5) for valproate.

Primary and secondary cognitive endpoint (per-protocol population). The primary endpoint comparison of information processing speed (CVST) did not show a differ-

ence between oxcarbazepine and combined carbamazepine/valproate (figure; $p = 0.195$). Mean CVST time decreased in all three treatment groups (indicating improvement) and similar CVST outcomes were found in the two age groups. A slight imbalance between treatment groups at baseline was accounted for by the ANCOVA model. There was no significant difference or worsening over the 6-month treatment period in the secondary neuropsychological variables (table 2; see also table E-1 on the *Neurology* Web site at www.neurology.org) or in the intelligence test between and within any treatment groups.

Efficacy (per-protocol population). Approximately 58% of patients in the oxcarbazepine treatment group and 50% in the carbamazepine/valproate group were seizure free throughout the treatment phase.

Safety and tolerability (safety population). The most frequently reported treatment-emergent adverse events ($>10\%$) were fatigue and headache for oxcarbazepine, fatigue and rash for carbamazepine, and headache, in-

Figure. Results of the Computerized Visual Searching Task by treatment group in the per-protocol patient population (NS = no significant difference between oxcarbazepine and carbamazepine/valproate, $p = 0.195$; least square mean 1.1 seconds in favor of oxcarbazepine).

creased appetite, and alopecia for valproate. Possible drug-related adverse events occurred in 30.9% (oxcarbazepine), 28.6% (carbamazepine), and 44.8% (valproate) of patients. One serious adverse event, mild in severity and unrelated to the study drug, was reported for each treatment group.

Discussion. Oxcarbazepine did not differ from standard AED therapy (i.e., carbamazepine and valproate) as monotherapy over 6 months in cognitive function and intelligence in children or adolescents with newly diagnosed partial seizures. No impairment in cognitive function was observed in any treatment group over a 6-month period. This was a well-controlled study to investigate cognitive function in children receiving oxcarbazepine using a validated cognitive function test battery. The study was powered adequately to detect a clinically meaningful difference in the primary cognitive variable of mental processing speed (CVST). As standard AEDs are available for treatment initiation in children with partial epilepsy, an active-control design was chosen to evaluate the effects of oxcarbazepine relative to standard antiepileptic

monotherapy. This design was appropriate because the primary and secondary cognitive assessments were based on an objective measurement (computerized testing); it also facilitated recruitment into the study and contributed to the extremely low dropout rate observed. A 6-month treatment period was considered an appropriate length of time for the study to discover any possible cognitive change associated with AED therapy, but it is possible that some AED effects may be additive over a longer period. Overall, the relatively long duration of this study (6 months of treatment), the use of an untreated baseline in newly diagnosed patients, and the use of AEDs as monotherapy remain powerful factors in the design of this study. Seizures were well controlled throughout the study. All AEDs were well tolerated; the safety profile of oxcarbazepine was similar to that reported previously.^{9,10}

The open nature of the study may preclude the results from being considered as Class I evidence for clinical decision-making. However, the results remain important and clearly serve to highlight the lack of studies available examining cognitive outcomes in children following AED treatment.

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Table 2 Analysis of cognitive variables for comparison of oxcarbazepine with combined carbamazepine/valproate treatment (per-protocol population, $n = 97$)

	Psychomotor speed and alertness				Mental information processing speed and attention		Memory and learning			
	Finger-tapping task		Visual reaction time (msec)		BCRT	CVST	Recognition		Rey AVLT	
	Dominant hand	Nondominant hand	Dominant hand	Nondominant hand			Word	Figure	Immediate recall	Delayed recall
OXC-CBZ/VPA					Mean BCRT (msec)	CVST(s)				
LS mean	0.8	0.1	0.6	-15.3	14.1	1.1	-1.2	-0.7	1.1	0.4
(95% CI)	(-0.5 to 2.2)	(-1.2 to 1.4)	(-27.1 to 25.9)	(-46.2 to 15.6)	(-24.1 to 52.3)	(-0.6 to 2.9)	(-2.4 to 0.1)	(-2.0 to 0.6)	(-2.0 to 4.1)	(-0.5 to 1.4)
<i>p</i> value	0.231	0.895	0.966	0.328	0.464	0.195	0.067	0.298	0.483	0.389

OXC = oxcarbazepine; CBZ = carbamazepine; VPA = valproate; BCRT = binary choice reaction time; CVST = Computerized Visual Searching Task; AVLT = Auditory Verbal Learning Test; LS = least square; LS mean and *p* values based on analysis of covariance.

References

1. Motamedi G, Meador K. Epilepsy and cognition. *Epilepsy Behav* 2003;4 (suppl 2):S25–S38.
2. Devinsky O. Cognitive and behavioral effects of antiepileptic drugs. *Epilepsia* 1995;36(suppl 2):S46–S65.
3. Motamedi GK, Meador KJ. Antiepileptic drugs and memory. *Epilepsy Behav* 2004;5:435–439.
4. Aldenkamp AP, De Krom M, Reijs R. Newer antiepileptic drugs and cognitive issues. *Epilepsia* 2003;44(suppl 4):21–29.
5. Aldenkamp AP, Alpherts WCJ, Blennow G, et al. Withdrawal of antiepileptic medication – effects on cognitive function in children – the results of the multicentre ‘Holmfrid’ study. *Neurology* 1993;43: 41–51.
6. Beydoun A. Safety and efficacy of oxcarbazepine: results of randomized, double-blind trials. *Pharmacotherapy* 2000;20:152S–158S.
7. Glauser TA, Nigro M, Sachdeo R, et al. Adjunctive therapy with oxcarbazepine in children with partial seizures. *Neurology* 2000;54:2237–2244.
8. Lezak M. *Neuropsychological Assessment*, 3rd ed. New York: Oxford University Press, 1995.
9. Dam M, Ekberg R, Løyning Y, Waltimo O, Jakobsen K, The Scandinavian Oxcarbazepine Study Group. A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy. *Epilepsy Res* 1989;3:70–76.
10. Van Parys JA, Meinardi H. Survey of 260 epileptic patients treated with oxcarbazepine (Trileptal) on a named-patient basis. *Epilepsy Res* 1994;19:79–85.

NeuroImages

Migraine with urticaria

A. Fumal; J. Crémers; A. Ambrosini; J.-L. Grand; and J. Schoenen, Liège, Belgium, and Isernia, Italy

We report a patient with an unusual form of migraine without aura (code ICHD 1.1) since childhood. An urticarian chest eruption (figure) appears at the end of each migraine attack and outlasts the attack by 10 to 90 minutes. It is not related to any of the acute anti-migraine drugs nor to dietary components. Interictal histologic cutaneous examination is normal. Interictal blood values and the general clinical examination are normal. Such an association has been reported twice before.^{1,2} The common denominator between cutaneous lesions and migraine could be a systemic release of serotonin or other vasoactive substances like histamine, bradykinin, or nitric oxide.

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Figure. A maculo-papular urticarial, non-itching skin lesion on the anterior chest occurring during every attack in a 51-year-old man with migraine without aura since childhood.

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Address correspondence and reprint requests to Dr. Arnaud Fumal, University Department of Neurology, CHR de la Citadelle, Boulevard du XIIème de ligne 1, 4000 Liège, Belgium; e-mail: Arnaud.Fumal@ulg.ac.be

1. Unge G, Malmgren R, Olsson P, Theorell H, Tornling G. Effects of dietary-protein tryptophan restriction upon 5-HT uptake by platelets and clinical symptoms in migraine-like headache. *Cephalalgia* 1983;3: 213–218.
2. Kallos P, Kallos-Deffner L. Allergy and migraine. *Int Arch Allergy* 1955; 7:367–372.

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A. Fumal, J. Crémers, A. Ambrosini, et al.

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