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Effect of eslicarbazepine acetate and oxcarbazepine on cognition and psychomotor function in healthy volunteers

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ABSTRACT

The results of two single-blind studies conducted to evaluate the cognitive and psychomotor effects of eslicarbazepine acetate and oxcarbazepine following single and repeated administration in healthy volunteers are reported. The cognitive and psychomotor evaluation consisted of several computerized and paper-and-pencil measures. Eslicarbazepine acetate and oxcarbazepine had similar overall cognitive profiles and did not cause clinically relevant cognitive impairment. The incidence of adverse events was lower with eslicarbazepine acetate than with oxcarbazepine.

1. Introduction

Antiepileptic drugs (AEDs) interact with neurotransmitter receptors or ion channels to decrease membrane excitability, thus contributing to a reduction in brain seizure activity. One pharmacological target is the voltage-gated sodium channel (VGSC) and its blockade is the proposed mechanism of action for several AEDs, such as carbamazepine (CBZ), oxcarbazepine (OXC), lamotrigine, and phenytoin [1].

Eslicarbazepine acetate (ESL) is a novel VGSC blocker [2,3] recently approved in Europe for use as adjunctive therapy for refractory partial-onset seizures. ESL is chemically related to CBZ and OXC. ESL shares with CBZ and OXC the dibenzazepine nucleus bearing the 5-carboxamide substitute, but is structurally different at the 10,11-position [3]. Following oral administration, ESL is rapidly and extensively metabolized to eslicarbazepine, the drug entity responsible for the pharmacological effect [4]. In randomized, double-blind, placebo-controlled phase III studies in adult patients with uncontrolled partial-onset seizures despite treatment with one or two concomitant AEDs [5,6] or one to three concomitant AEDs [7], ESL at once-daily doses of 800 and 1200 mg was generally well tolerated and significantly decreased seizure frequency compared with placebo.

AEDs usually exhibit a dose-dependent effect on cognitive functioning. Because AEDs are the major therapeutic modality for patients with epilepsy, comparison of the adverse cognitive effects of AEDs is important [8]. Despite effective anticonvulsant properties, OXC has been associated with several central nervous system-related adverse events including cognitive symptoms [9–11]. This study compared the pharmacodynamic effects of a single 900-mg oral dose of ESL or OXC and the effects of repeated administration of two oral doses of ESL (800 and 1200 mg administered once daily [QD]) and oral doses of OXC (300 and 600 mg administered twice daily [BID]).

2. Methods

2.1. Study design

Two single-blind studies were conducted to evaluate the cognitive and psychomotor effects of oral doses of ESL and OXC in healthy volunteers. Each study consisted of a single-dose phase (phase A) followed by a multiple-dose phase (phase B) comprising three periods (Fig. 1). In phase A, subjects were administered a single 900-mg dose of ESL or OXC (day 1). In phase B, subjects were administered: placebo in period 1 (days 2–8); ESL 800 mg QD or OXC 300 mg BID in period 2 (days 9–15); and ESL 1200 mg QD or OXC 600 mg BID in period 3 (days 16–22). The dosage regimens for the current study were defined according to the results of the ESL phase III studies [5–7] and the recommended dosage of OXC [10,12] as adjunctive therapy for

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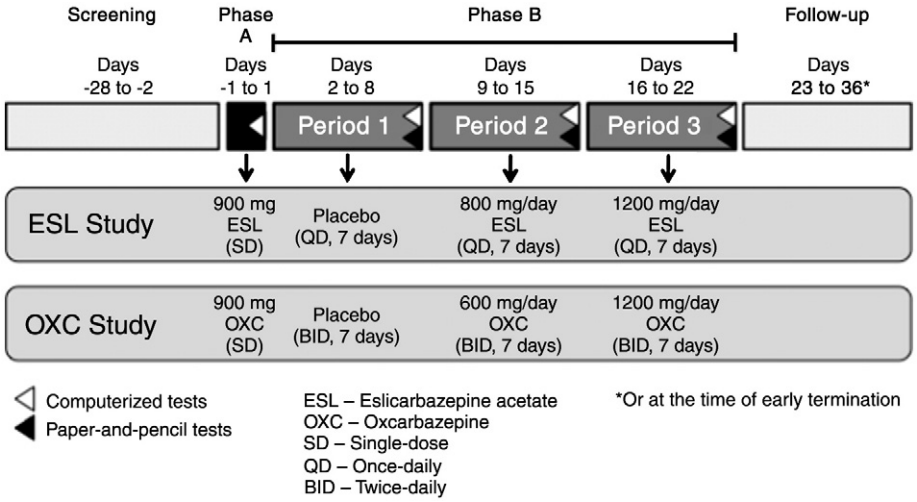

Fig. 1. Study design summary.

partial-onset seizures. ESL was administered QD, in the morning, whereas OXC was administered every 12 hours, in the morning and the evening. A follow-up visit was scheduled 7 to 14 days after the last dose.

In phase A, subjects completed five computerized tests (Choice Reaction Time, Divided Attention Test, Sternberg Short-Term Memory Test, Digit Vigilance Test, and Digit Symbol Substitution Test). In periods 1, 2, and 3 of phase B, subjects completed the same computerized tests in addition to three paper-and-pencil tests (Rey Auditory–Verbal Learning Test, Controlled Oral Word Associates Test, and Trail Making Test).

For phase A, subjects were admitted to the clinical research unit on day –1 (the day before dosing), where they underwent a training session for the computerized tests. On the morning of day 1, subjects were administered the investigational drug (ESL 900 mg or OXC 900 mg). A refresher training session occurred at –1.5 hours predose and the computerized tests were completed at –1 hours predose and then 3, 6, and 10 hours postdose. Subjects were discharged on day 2 after having received the first placebo dose in period 1 of phase B.

For phase B, subjects were requested to return to the clinic once daily (ESL study) or twice daily (OXC study) for 21 consecutive days.

In period 1 (days 3–8), a training session for all computerized and paper-and-pencil tests was carried out after the morning dose on day 6. On the morning of day 8, a refresher training session for computerized tests only was given prior to dosing, and all computerized and paper-and-pencil tests were completed 1 hour postdose.

On day 9 (start of period 2) and day 16 (start of period 3), subjects were admitted to the clinic in the morning and received the first dose of the investigational drug corresponding to that period (ESL 800 mg or OXC 300 mg in period 2, and ESL 1200 mg or OXC 600 mg in period 3). Subjects were discharged the day after and continued on an outpatient basis during days 11 to 15 (period 2) and days 18 to 22 (period 3). On the mornings of day 15 in period 2 and day 22 in period 3, a refresher training session for computerized tests only was given prior to dosing, and all computerized and paper-and-pencil tests were completed 1 hour postdose.

Both studies followed Good Clinical Practice recommendations and were conducted according to the principles of the Declaration of Helsinki. The study protocols and subject information were reviewed and approved by an independent ethics committee. Written informed consent was obtained from each subject prior to study enrollment.

2.2. Subjects

Because of the exploratory nature of this clinical trial, the sample size was not determined on the basis of a statistical hypothesis test. On the basis of previous studies of similar design [13], it was determined that a minimum of 20 subjects was an appropriate sample size.

A total of 56 healthy male and female subjects 18 to 45 years of age were recruited and tested by a single center in Canada (Kendle Early Stage, Toronto, ON, Canada). Twenty-six subjects were enrolled in the ESL study and 30 subjects were enrolled in the OXC study. Subjects satisfied the following main inclusion criteria: they were native speakers of English language or had learned English before 12 years of age; had completed at least high school level education; had a body mass index (BMI) between 18 and 30 kg/m^2; and were "healthy" as determined by medical history, vital signs, physical examination, 12-lead ECG, and clinical laboratory evaluation.

2.3. Safety evaluation

The safety evaluation included monitoring of: adverse events (elicited using a nonleading question); vital signs (blood pressure, heart rate, respiratory rate, and oral temperature); plasma biochemistry, hematology, and urinalysis; 12-lead ECG; and physical neurological examination (conducted at screening and follow-up visits). The Safety Population included all subjects who took at least one dose of study medication (ESL, OXC, or placebo), and was used for the analysis and presentation of the safety parameters. The adverse events were coded by preferred term (PT), using the *Medical Dictionary for Regulatory Activities* (MedDRA).

2.4. Evaluable population for the cognition and psychomotor function assessments

The Evaluable Population included all subjects in the Safety Population who completed at least period 2 of phase B, who did not have major protocol violations, and who had valid pharmacodynamic data. This definition was determined at the time of the protocol development. The Evaluable Population was used for the analysis and presentation of the pharmacodynamic parameters.

2.5. Cognitive and psychomotor evaluation

The main outcome measures included in the analyses were as follows:

2.5.1. Computerized measures (in both phase A and phase B)

2.5.1.1. Choice Reaction Time. Choice Reaction Time (CRT) provides a measure of psychomotor speed [14], using a numeric keypad that is