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Pharmacokinetic interaction of brivaracetam on carbamazepine in adult patients with epilepsy, with and without valproate co-administration

Armel Stockis [a,*], Maria L. Sargentini-Maier [a,1], Martin J. Brodie [b]

[a] UCB Pharma, Braine l'Alleud, Belgium
[b] Epilepsy Unit West Glasgow, ACH-Yorkhill, Glasgow, Scotland, UK

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ABSTRACT

Objective: This Phase I, open-label, dose-escalation study investigated the effects of steady-state brivaracetam on the pharmacokinetics of carbamazepine in patients with epilepsy, with and without valproate co-administration. Valproate and brivaracetam inhibit epoxide hydrolase and increase carbamazepine epoxide levels.

Methods: Adult patients with epilepsy being chronically treated with carbamazepine alone (n = 9) or with carbamazepine and valproate (n = 9) received brivaracetam during successive 1-week periods at doses of 50 mg, 100 mg, 200 mg, and 100 mg twice daily (bid). Doses of carbamazepine and valproate must have been stable for at least 3 months. Trough plasma concentrations of carbamazepine, carbamazepine epoxide, and diol metabolites were determined on Days 1, 8, 15, 22, and 29, and at the end of study visit (ESV, 2–3 weeks later).

Results: Eighteen patients with median (range) age of 45 (20–62) years and body weight of 74 (59–124) kg were enrolled and completed the study. In patients treated with carbamazepine alone, brivaracetam dose-dependently increased mean trough levels of carbamazepine epoxide from 1.38 μg/mL on Day 1 predose to 2.16 μg/mL (+57%) on Day 8 (50 mg bid), 2.72 μg/mL (+97%) on Day 15 (100 mg bid), 3.02 μg/mL (+119%) on Day 22 (200 mg bid), 2.67 μg/mL (+94%) on Day 29 (100 mg bid), and 1.22 μg/mL (−12%) at ESV, respectively. In patients on carbamazepine and valproate, carbamazepine epoxide increased from 1.98 μg/mL at baseline to 2.72 μg/mL (+37%), 3.70 μg/mL (+87%), 4.43 μg/mL (+124%), 3.11 μg/mL (+57%), and 1.94 μg/mL (−2%), respectively. There was no trend for change in carbamazepine, carbamazepine diol or valproate levels. Brivaracetam levels increased linearly with dose. Brivaracetam was well tolerated.

Conclusions: Carbamazepine epoxide plasma concentrations were approximately doubled by brivaracetam 100 or 200 mg bid. Data are consistent with a dose-dependent and reversible inhibition of epoxide hydrolase by brivaracetam. Carbamazepine epoxide was approximately 0.7 μg/mL higher in presence of valproate. There is no need to limit brivaracetam dosing when used concomitantly with carbamazepine.

1. Introduction

An estimated 70 million people in the world have epilepsy (Ngugi et al., 2010). Although the majority of patients achieve lasting remission with currently available antiepileptic drugs (AEDs), many patients remain resistant to treatment and continue to experience seizures (Schmidt and Schachter, 2014). A recent analysis which identified distinct patterns of response to AEDs in patients with newly diagnosed epilepsy demonstrated that 25% of patients continued to have persistent seizures despite repeated trials of different medications, used singly or in combination (Brodie et al., 2012), while a further 16% had a 'remitting–relapsing' course fluctuating between periods of seizure freedom and recurrence (Brodie et al., 2012). Thus, effective treatment of all patients with epilepsy remains an important unmet clinical need. Brivaracetam is a selective, high-affinity ligand for synaptic vesicle protein 2A (SV2A) (Gillard et al., 2011; Kenda et al., 2004). The efficacy of brivaracetam was established in three fixed-dose, randomized, double-blind, placebo-controlled confirmatory studies (Biton et al., 2014; Klein et al., 2015; Ryvlin et al., 2014), which included 1567 randomized

* Corresponding author at: UCB Pharma, Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium.
E-mail address: Armel.Stockis@ucb.com (A. Stockis).
[1] Current affiliation: Ablynx, Zwijnaarde, Belgium.

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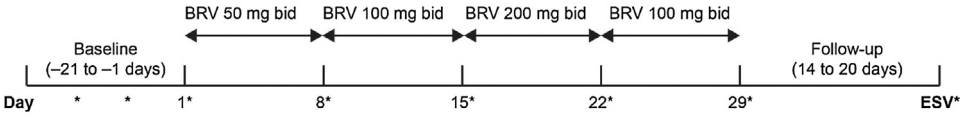

*Trough plasma sample for drug level determination (brivaracetam [except at baseline and ESV], carbamazepine and metabolites, and valproate).

bid, twice daily; BRV, brivaracetam; ESV, end of study visit.

Fig. 1. Study design.

patients. Brivaracetam 50–200 mg/day was recently approved as adjunctive therapy in the treatment of focal (partial-onset) seizures in patients 16 years of age and older with epilepsy.

Brivaracetam is characterized by a mono-compartmental, linear, and dose-proportional pharmacokinetic profile with low inter-individual variability (Rolan et al., 2008; Sargentini-Maier et al., 2007). It is rapidly and completely absorbed following oral administration, and has a plasma half-life of approximately 9 h (Stockis et al., 2016a).

The major metabolic pathway of brivaracetam involves hydrolysis of the acetamide group by non-cytochrome P450 (CYP)-dependent amidase to form a carboxylic acid derivative, while a second pathway involves CYP2C19-mediated hydroxylation of the propyl side chain to form the hydroxy brivaracetam metabolite (Sargentini-Maier et al., 2008; Stockis et al., 2014b, 2016b). A third metabolite is formed by a combination of both pathways (Sargentini-Maier et al., 2008). All three metabolites are pharmacologically inactive.

When used as an adjunctive treatment, brivaracetam is likely to be co-administered with carbamazepine, one of the most frequently prescribed AEDs in the treatment of focal seizures.

Carbamazepine metabolism involves oxidation, primarily by CYP3A4, to a pharmacologically active metabolite, carbamazepine-10-11-epoxide (carbamazepine epoxide). Carbamazepine epoxide, in turn, undergoes hydrolysis *via* microsomal epoxide hydrolase to inactive carbamazepine-10-11-*trans*-diol (carbamazepine diol) (Patsalos et al., 2008; Theodore et al., 1989). As a result of its widespread use, carbamazepine is frequently prescribed in combination with other AEDs, such as valproate. Valproate appears to increase carbamazepine epoxide levels by inhibiting epoxide hydrolase and uridine diphosphate-glucuronyl transferase (Bernus et al., 1997).

A recent bilateral pharmacokinetic interaction study in healthy participants indicated that brivaracetam 200 mg twice daily (bid) did not modify exposure to carbamazepine but did result in a 2.6-fold increase in carbamazepine epoxide. This effect was due to competitive inhibition of epoxide hydrolase by brivaracetam, as shown by *in vitro* experiments. As an enzyme inducer, carbamazepine decreased exposure to brivaracetam by 29% and increased plasma levels of the brivaracetam hydroxy metabolite by 17% (Stockis et al., 2015). Study participants received a stable carbamazepine dosage of 600 mg/day (in the lower part of the therapeutic dose range) for a limited period of 2 weeks, together with a supra-therapeutic dosage of brivaracetam 400 mg/day; the potential additive effect of valproate was not included in the study design. The current investigation was required to explore the pharmacokinetic interactions of steady-state brivaracetam on long-term treatment with higher carbamazepine dosages (with or without valproate) in patients with epilepsy.

2. Methods

2.1. Study design

This open-label, unilateral pharmacokinetic interaction study was conducted in the United Kingdom (two centers) and Poland (one center). Brivaracetam was administered bid to adult patients with epilepsy being chronically treated with carbamazepine alone (n = 9) or in combination with valproate (n = 9). Following screening and baseline, patients received during four successive 7-day periods brivaracetam 50 mg bid, 100 mg bid, and 200 mg bid, and then 100 mg bid in the final week. After brivaracetam was discontinued, patients were followed-up for a period of 14–20 days (Fig. 1). Trough plasma concentrations of brivaracetam, carbamazepine, carbamazepine epoxide, carbamazepine diol, and valproate were determined on two occasions during baseline, on Days 1, 8, 15, 22, and 29, and at the end of study visit (ESV, 2–3 weeks later). Safety and tolerability were assessed by monitoring of adverse events, laboratory values, and vital signs throughout the study.

The study was conducted in compliance with the ethical principles originating from the Declaration of Helsinki and the Good Clinical Practice guidelines. The study protocol was reviewed and approved by an independent medical ethics committee. All participants provided their informed consent in writing prior to the start of any study procedure.

2.2. Study population

This study was conducted in adult patients aged 18–65 years with a diagnosis of well-characterized epileptic syndrome according to the International League Against Epilepsy classification (International League Against Epilepsy, 1989). Patients were to be receiving ≥600 mg/day carbamazepine in twice daily intake, either alone (n = 9) or in combination with ≥500 mg/day valproate (n = 9), at stable doses over a period of at least 3 months. Plasma concentrations of carbamazepine, carbamazepine epoxide, and valproate at study entry were to be within the range of 4–12 μg/mL, ≤4 μg/mL, and 40–100 μg/mL, respectively.

Key exclusion criteria included a history or presence of status epilepticus during the year preceding the study, history of multiple or severe drug allergies, suicide attempt, suicidal ideation, or other psychiatric disorders in the past 5 years. Patients with impaired hepatic function or any medication that may significantly influence brivaracetam metabolism (unless stable for ≥3 months) were not eligible for this study. Other exclusion criteria included clinically significant electrocardiogram (ECG) abnormalities, treatment with central nervous system (CNS) drugs other than carbamazepine and valproate, or alcohol, tobacco or drug addiction.