Epilepsy Research 158 (2019) 106218

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Pharmacokinetic interaction of brivaracetam on other antiepileptic drugs in adults with focal seizures: Pooled analysis of data from randomized clinical trials

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ARTICLE INFO

Keywords:
Epilepsy
SV2A
Carbamazepine
Carbamazepine-epoxide
Drug-drug interaction

ABSTRACT

Objective: To assess the effect of brivaracetam (BRV) on steady-state plasma concentrations of commonly prescribed antiepileptic drugs (AEDs).

Methods: Data were pooled from five randomized, double-blind, placebo-controlled efficacy studies (NCT00175929, NCT00175825, NCT00490035, NCT00464269, and NCT01261325) in which adults with refractory epilepsy, and receiving stable doses of 1–2 AEDs, initiated adjunctive treatment with BRV (or placebo) for up to 12 weeks, following a 4–8 week baseline period. Concentrations of carbamazepine, carbamazepine epoxide, clobazam, clonazepam, lacosamide, lamotrigine, levetiracetam, oxcarbazepine (MHD), phenobarbital, phenytoin, pregabalin, topiramate, valproic acid and zonisamide, were measured during baseline and during BRV or placebo evaluation periods. Log-transformed data for patients receiving BRV dosages of 50–200 mg/day (or placebo) were evaluated using repeated measures analysis of covariance. Geometric least-squares means ratios of respective AED concentrations (treatment vs baseline) and their 90% confidence intervals (CIs) were calculated. Relevant interaction of BRV on the respective AED was inferred if CIs were entirely outside of 0.80–1.25 limits.

Results: Within the population for analysis (n = 1402), relevant interaction was observed for carbamazepine epoxide alone which increased up to 2-fold from baseline due to inhibition of epoxide hydrolase by BRV, and the effect size was not influenced by concomitant valproic acid. Relevant interaction was not observed for other AEDs.

Conclusion: In adults with focal seizures, adjunctive BRV treatment does not affect plasma concentrations of the evaluated AEDs but increases carbamazepine epoxide metabolite. Carbamazepine dose reduction should be considered if tolerability issues arise.

1. Introduction

While approximately 60–70% of newly diagnosed patients are well-controlled with a single AED, and 50% of the remainder achieve seizure control by switching to an alternative AED, those with refractory epilepsy inevitably require polytherapy (Patsalos and Perucca, 2003; Patsalos, 2013). The large number of available AEDs widens the scope for exposure to different combinations and potential drug–drug interactions (DDIs) resulting from induction or inhibition of metabolic pathways (Zaccara and Perucca, 2014). A thorough understanding of potential DDIs is therefore essential for any new AED.

Brivaracetam (BRV) is a selective, high-affinity ligand of synaptic vesicle protein 2A (Gillard et al., 2011) and is approved for the treatment of focal seizures in patients 4 years of age and older. Fixed dosages of BRV from 5 to 200 mg/day have been evaluated in adults in a series of two Phase II (N01114, NCT00175929; N01193, NCT00175825) and three Phase III (N01252, NCT00490035; N01253, NCT00464269; N01358, NCT01261325) clinical trials, each randomized, double-blind and placebo-controlled (French et al., 2010; Van Paesschen et al., 2013; Biton et al., 2014; Ryvlin et al., 2014; Klein et al., 2015).

The pharmacokinetic properties of BRV include rapid and complete oral absorption, dose-proportional exposure across a wide dose range, low plasma protein binding (≤20%), distribution volume restricted to total body water, and elimination half-life of 9 h (Sargentini-Maier et al., 2007, 2008; Rolan et al., 2008; D'Souza and Perucca, 2016).

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https://doi.org/10.1016/j.eplepsyres.2019.106218
Received 19 June 2019; Received in revised form 9 October 2019; Accepted 13 October 2019
Available online 14 October 2019
0920-1211/

Extensive metabolism through several enzymatic pathways accounts for the majority of BRV clearance (Sargentini-Maier et al., 2008; Nicolas et al., 2012) primarily via amidase-mediated hydrolysis and secondarily via CYP2C19-mediated hydroxylation (D'Souza and Perucca, 2016; Stockis et al., 2016b).

Most in vitro data predict a low risk of DDIs with concomitant AEDs, including a lack of significant inhibition of cytochrome P-450 (CYP450) drug-metabolizing enzymes, amidases and active transporters (Chanteux et al., 2015). However, BRV exhibits a dose-dependent inhibition of epoxide hydrolase, for which CBZ-epoxide (CBZ-E), an active metabolite of CBZ, is a substrate (Stockis et al., 2015, 2016a).

The presented retrospective analysis, based on therapeutic drug monitoring data from Phase II and Phase III trials in adults, assessed the effect of BRV on steady-state plasma concentrations of a range of concomitant AEDs and/or their active metabolites, in turn informing the need for dose adjustment or AED monitoring when BRV and the tested AEDs are co-prescribed. The interaction of concomitant AEDs on BRV has been reported previously (Schoemaker et al., 2016).

2. Methods

2.1. Clinical studies

Data originated from patients who participated in any of the aforementioned Phase II and Phase III placebo-controlled studies, whose methodologies have been published previously (French et al., 2010; Van Paesschen et al., 2013; Biton et al., 2014; Ryvlin et al., 2014; Klein et al., 2015). The patient population included those of at least 16 years of age with refractory epilepsy and well-characterized focal seizures, receiving 1–2 concomitant AEDs. Each study included a prospective baseline period of 4–8 weeks, followed by a double-blind 7- to 12-week evaluation period in which patients were randomized to receive oral placebo or BRV twice daily (Fig. 1).

2.2. Study population

Patients from the original studies were included in this analysis subject to availability of AED concentrations at baseline and on at least one occasion during the treatment period. Per protocol, background AEDs could not be changed from baseline until the end of the treatment period. Patients taking hepatic enzyme inducing AEDs must have been taking a stable dosage for ≥1 month prior to study start, and maintained this dosage throughout the study. For the purpose of this analysis, evaluable patients needed a constant background AED dosage for ≥2 weeks during baseline and ≥2 weeks during the treatment period, and a constant dosage of BRV or placebo for ≥2 weeks. Patients taking more than one background AED (in addition to BRV or placebo) were counted once within each relevant AED category.

2.3. Therapeutic drug monitoring

The BRV dosing regimens, for the purposes of this pooled analysis, consisted of 50, 100, 150 or 200 mg/day in two divided doses. Doses below the lowest recommended dose of 50 mg/day, used in some of the trials, were ignored.

Plasma concentrations of concomitant AEDs and/or their metabolites were determined, including CBZ, CBZ-E, lacosamide (LCM), lamotrigine (LTG), levetiracetam (LEV), MHD (in patients treated with oxcarbazepine), phenobarbital (PB), pregabalin (PGN), phenytoin (PHT), topiramate (TPM), valproic acid (VPA) and zonisamide (ZNS). Plasma concentrations of clobazam (CLB) and clonazepam (CZP), were monitored in the last study (N01358) (Klein et al., 2015) and included in the analysis. Plasma concentrations of BRV were also measured and have been reported previously (Schoemaker et al., 2016). The visit and sampling schedule is depicted in Fig. 1. Blood samples for AED determinations were obtained at two baseline visits and two to four visits during evaluation. The BRV 200 mg/day dose was only included in study N01358 in which blood sampling was carried out at two evaluation visits. Timings of venipuncture were the same as for safety laboratory tests, immediately prior to the morning dose or at a similar time after dosing on each occasion.

2.4. Bioanalytical determinations

Plasma AED concentrations were determined by two distinct liquid chromatography-tandem mass spectrometry (LC–MS/MS) methods: Positive ionization was used for analysis of BRV and all background AEDs except VPA. All compounds were quantified using the respective deuterium-labelled internal standards. Sample extraction was performed using Waters Oasis HLB solid-phase extraction cartridges (Waters Inc, Milford, MA). Cartridges were preconditioned with 500 µL methanol followed by 500 µL acetic acid 0.1% (v:v) in water. Plasma samples (50 µL) were added to 50 µL of internal standards solution and 400 µL of acetic acid 0.1% (v:v) in water, and mixed for 1 min. Samples were transferred onto the cartridges and washed with 500 µL of acetic acid 0.1% (v:v) in water followed by 500 µL of acetic acid 0.1% (v:v) in water:methanol 95:5 (v:v). Analytes were eluted by 2 × 500 µL of methanol:water 90:10 (v:v) followed by 1 × 500 µL of methanol. Extracts were evaporated at 70 °C under a nitrogen stream and reconstituted with 400 µL of methanol:water 25:75 (v:v). Aliquots of 25 µL were analyzed by reversed-phase chromatography using an ACE C18 column (150 mm by 3 mm i.d.) (Advanced Chromatography Technologies Ltd, Aberdeen, UK) and a gradient mobile phase of ammonium formate 2.5 mM pH 9 and acetonitrile, with multiple reaction

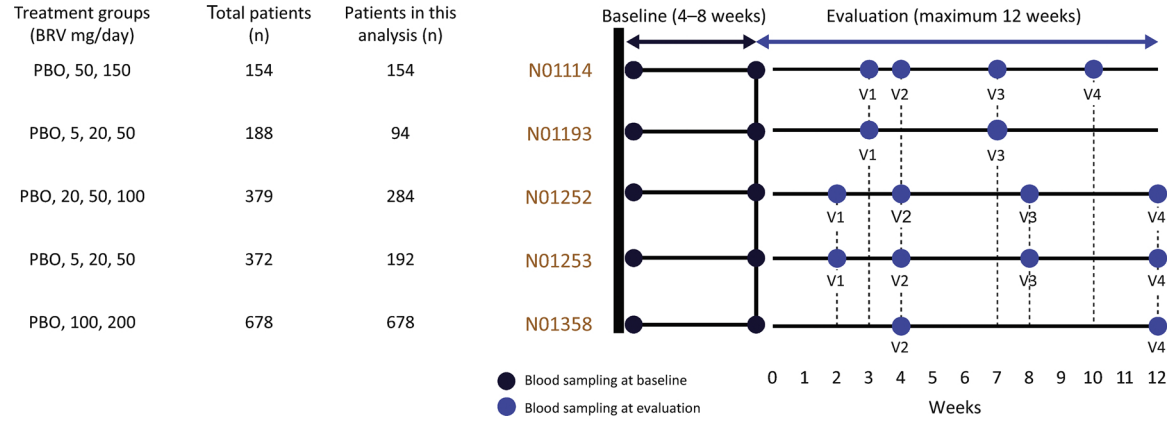

Fig. 1. Study design and blood sampling schedule.
Footnote: BRV, brivaracetam; PBO, placebo; V, visit

Table 1
Patient demographics and baseline characteristics.

	Placebo (n = 529)	Brivaracetam 50–200 mg/day (n = 873)
Age (years), mean (SD)	37.8 (12.7)	37.9 (12.9)[a]
Gender, male, n (%)	259 (49.0)	433 (49.6)
Race, n (%)		
White	395 (74.7)	661 (75.7)
Asian	64 (12.1)	124 (14.2)
Black	15 (2.8)	12 (1.4)
Other/mixed	55 (10.4)	76 (8.7)
Weight (kg), mean (SD)	74.0 (19.9)	73.1 (17.8)
BMI (kg/m^2), mean (SD)	26.2 (6.0)	25.9 (5.5)

BMI, body mass index; BRV, brivaracetam; SD, standard deviation.
[a] Although the inclusion criteria for all studies specified a minimum age of 16 years, a 14-year-old patient was enrolled in study N01253 and included in this analysis.

monitoring (MRM) detection on an API 3000 mass spectrometer (AB Sciex Llc, Framingham, MA, USA). Quantification ranges were as follows [lower–upper limit of quantification (ng/mL)]: CBZ 50–5000, CBZ-E 10–1000, CLB 5–500, CZP 0.5–50, LCM 50–1000, LTG 20–2000, LEV 200–4000, MHD 50–5000, PB 400–40,000, PGN 50–5000, PHT 800–40,000, TPM 100–10,000, ZNS 100–10,000. Samples above the upper limit of the range were reassayed after dilution.

Determination of plasma VPA was performed using LC–MS/MS with negative ionization. Plasma samples (75 µL) were added to 50 µL of deuterium-labelled internal standard, and mixed for approximately 1 min. Samples were transferred onto preconditioned extraction cartridges (same as above) and washed with 2 × 200 µL of water. Samples were then eluted with 2 × 200 µL of water + 1% ammonia:methanol 20:80 (v:v) followed by a 5-fold dilution with formic acid 0.2% in water. Aliquots of 5 µL were analyzed by reversed-phase chromatography using an Agilent Pursuit PFP column (50 mm by 2.1 mm i.d.) (Agilent Technologies, California, USA) and a gradient mobile phase of ammonium formate 2.5 mM pH 4.8 and acetonitrile, with MRM detection on a Quattro Ultima mass spectrometer (Waters). Quantification range was 25–500 µg/mL.

Both assays were validated in accordance with FDA and EMA guidelines and assay batch acceptance criteria also followed these guidelines. For all analytes, relative inaccuracy on quality control samples was < 15% compared to nominal concentration and relative imprecision was < 15% at each quality control level.

2.5. Statistical analysis

The AEDs investigated were those with data available for at least 10 patients in one of the treatment arms. For each AED, descriptive statistics included geometric mean plasma concentration and geometric coefficient of variation (CV%) at baseline and on treatment for each treatment group and for BRV overall (50–200 mg/day).

Log-transformed AED plasma concentrations were assessed by repeated measures analysis of covariance (ANCOVA) performed using the log-transformed arithmetic mean baseline (or the single baseline) concentration as a covariate (Littel et al., 1996). The model included visit, treatment (placebo and each BRV dose: 50, 100, 150 and 200 mg/day), and treatment-by-visit interaction as fixed effects and subject as random effect. An unstructured variance-covariance matrix was used to model the dependency among repeated measurements (visits within subject).

Geometric least-squares (LS) means ratios and associated 90% confidence intervals (CIs) were calculated for each visit, by treatment group and across BRV doses, to assess treatment effect. Geometric LS means ratios and 90% CIs were back-transformed, with the resultant adjusted geometric LS means ratios and 90% CIs of ratios to baseline forming the basis of a bioequivalence approach. Changes in AED concentration between evaluation and baseline were considered clinically relevant if the respective 90% CI fell entirely outside the conventional 0.80–1.25 limits.

Because VPA is also an inhibitor of epoxide hydrolase and can increase CBZ-E concentrations similarly to BRV, the effect of co-medication with VPA and BRV on CBZ-E concentrations was similarly assessed using ANCOVA on the log-transformed CBZ-E plasma concentrations. The analysis model included the following fixed effects: treatment (placebo, BRV dose), VPA status (VPA + or VPA −), and treatment by VPA interaction. Again an unstructured variance-covariance matrix was used. The log-transformed baseline CBZ-E concentration was inserted as covariate. LS means and 90% CIs were back-transformed to provide the adjusted geometric mean CBZ-E concentrations with their respective 90% CIs, for each BRV dose by VPA status.

All statistical analyses were performed using the SAS® software version 9.3 (SAS Institute, Cary, NC).

3. Results

3.1. Patient demographics and antiepileptic drug use

The overall population for analysis included 1402 patients (49%

Table 2
Summary of usage and daily doses of concomitant AEDs.

Concomitant AED	Placebo (n = 529)		Brivaracetam 50–200 mg/day (n = 873)	
	AED use, n (%)	Median dose (range), mg/day	AED use, n (%)	Median dose (range), mg/day
Carbamazepine	208 (39.3)	600 (200–2100)	351 (40.2)	600 (200–2400)
Clobazam	10 (1.9)	10 (5–30)	19 (2.2)	10 (10–50)
Clonazepam	9 (1.7)	1 (0.5–2)	13 (1.5)	2 (0.5–2.5)
Lacosamide	34 (6.4)	200 (100–400)	64 (7.3)	200 (100–400)
Lamotrigine	132 (25.0)	200 (50–900)	233 (26.7)	200 (25–1800)
Levetiracetam	54 (10.2)	2875 (500–5000)	84 (9.6)	3000 (500–5000)
Oxcarbazepine	75 (14.2)	900 (400–2700)	140 (16.0)	900 (300–3300)
Phenobarbital	24 (4.5)	100 (10–300)	59 (6.8)	100 (30–450)
Phenytoin	57 (10.8)	300 (100–550)	72 (8.2)	300 (25–2000[a])
Pregabalin	22 (4.2)	300 (50–800)	26 (3.0)	300 (100–600)
Topiramate	87 (16.4)	200 (25–1100)	102 (11.7)	200 (50–750)
Valproate	99 (18.7)	875 (200–2600)	180 (20.6)	1000 (100–3000)
Zonisamide	24 (4.5)	250 (100–600)	44 (5.0)	300 (100–650)

AED, antiepileptic drug; BRV, brivaracetam.
[a] 2000 is an outlier; the second highest value was 800 mg/day.

Table 3
Geometric mean (CV%) plasma concentration of concomitant antiepileptic drugs at baseline and on treatment, point estimate of ratio between treatment and baseline period and respective 90% confidence interval.

Concomitant antiepileptic drug	Statistic[a]	Placebo	Brivaracetam (mg/day)				
			50	100	150	200	50–200
Carbamazepine	n	208	121	127	20	83	351
	Baseline	8.60 (38)	9.10 (31)	8.41 (34)	8.47 (31)	9.06 (26)	8.80 (31)
	Treatment	9.03 (37)	8.84 (37)	8.35 (42)	7.71 (31)	8.09 (43)	8.48 (39)
	Ratio	1.01	0.98	0.96	0.94	0.89	0.94
	90% CI	0.98–1.03	0.95–1.01	0.92–0.99	0.86–1.03	0.86–0.93	0.92-0.96
Carbamazepine epoxide	n	205	121	126	20	83	350
	Baseline	1.66 (53)	1.85 (53)	1.48 (50)	1.63 (60)	1.61 (47)	1.64 (52)
	Treatment	1.76 (52)	2.53 (48)	2.57 (52)	2.73 (64)	3.25 (63)	2.66 (54)
	Ratio	0.99	1.37	1.62	1.77	1.98	1.63
	90% CI	0.97–1.02	1.33–1.42	1.56–1.68	1.61–1.94	1.89–2.08	1.58–1.67
Clobazam	n	10	0	8	0	11	19
	Baseline	0.207 (68)	–	0.163 (69)	–	0.228 (92)	0.198 (83)
	Treatment	0.172 (69)	–	0.144 (76)	–	0.203 (106)	0.176 (95)
	Ratio	0.94	–	NR	–	0.90	0.95
	90% CI	0.81–1.09	–	NR	–	0.78–1.03	0.85–1.05
Clonazepam	n	9	0	3	0	10	13
	Baseline	0.017 (37)	–	0.013 (67)	–	0.015 (83)	0.014 (77)
	Treatment	0.016 (51)	–	0.011 (47)	–	0.014 (76)	0.013 (69)
	Ratio	NR	–	NR	–	1.00	0.98
	90% CI	NR	–	NR	–	(0.86–1.15)	0.87–1.11
Lacosamide	n	34	0	29	0	35	64
	Baseline	8.38 (77)	–	7.25 (76)	–	8.06 (46)	7.68 (61)
	Treatment	9.16 (55)	–	6.85 (71)	–	7.58 (55)	7.24 (63)
	Ratio	1.09	–	0.94	–	0.95	0.96
	90% CI	1.01–1.18	–	0.87–1.02	–	0.89–1.03	0.90–1.01
Levetiracetam	n	54	54	18	12	0	84
	Baseline	28.8 (69)	29.0 (61)	25.4 (73)	40.6 (53)	–	29.6 (64)
	Treatment	29.7 (89)	32.5 (59)	25.1 (70)	41.1 (63)	–	31.5 (64)
	Ratio	0.98	1.13	0.96	1.04	–	1.06
	90% CI	0.91–1.04	1.06–1.21	0.86–1.07	0.89–1.21	–	0.99–1.13
Lamotrigine	n	132	82	80	18	53	233
	Baseline	6.27 (74)	6.40 (74)	5.69 (78)	6.73 (78)	5.49 (90	5.96 (79)
	Treatment	6.58 (77)	6.80 (73)	6.07 (78)	7.11 (84)	6.26 (86)	6.52 (78)
	Ratio	1.05	1.06	1.05	1.01	1.09	1.08
	90% CI	1.01–1.08	1.02–1.11	0.99–1.10	0.90–1.13	1.03–1.16	1.05–1.11
Oxcarbazepine MHD[b]	n	75	36	54	9	41	140
	Baseline	19.6 (48)	21.7 (43)	18.1 (46)	18.0 (40)	21.6 (32)	20.0 (42)
	Treatment	20.2 (46)	21.5 (36)	18.8 (46)	18.8 (43)	20.9 (32)	20.2 (40)
	Ratio	0.99	0.99	1.00	NR	1.00	1.01
	90% CI	0.95–1.03	0.94–1.05	0.95–1.05	NR	0.94–1.06	0.98–1.05
Phenobarbital	n	24	20	27	1	11	59
	Baseline	19.7 (66)	19.3 (45)	19.9 (55)	14.8	24.0 (39)	20.3 (48)
	Treatment	19.1 (70)	20.0 (45)	20.5 (54)	16.0	23.9 (43)	20.6 (49)
	Ratio	0.97	1.03	1.00	NR	1.02	1.02
	90% CI	0.92–1.03	0.97–1.09	0.95–1.06	NR	0.94–1.10	0.99–1.05
Pregabalin	n	22	7	11	2	6	26
	Baseline	5.31 (62)	4.61 (69)	3.32 (129)	2.98 (76)	2.74 (96)	3.44 (98)
	Treatment	5.61 (54)	5.17 (62)	3.82 (99)	3.32 (57)	3.98 (66)	4.21 (79)
	Ratio	1.05	NR	1.00	NR	NR	1.12
	90% CI	0.93–1.19	NR	0.82–1.22	NR	NR	0.99–1.27
Phenytoin	n	57	34	25	0	13	72
	Baseline	9.25 (96)	11.2 (79)	11.9 (90)	–	12.8 (80)	11.7 (82)
	Treatment	10.7 (85)	12.9 (92)	10.5 (71)	–	14.4 (123)	12.3 (90)
	Ratio	1.04	1.15	0.81	–	1.12	1.02
	90% CI	0.95–1.13	1.04–1.29	0.71–0.93	–	0.89–1.42	0.91–1.14
Topiramate	n	87	26	38	11	27	102
	Baseline	6.31 (72)	7.17 (67)	5.27 (68)	7.45 (72)	6.03 (51)	6.13 (65)
	Treatment	6.90 (69)	6.74 (68)	5.18 (71)	8.58 (64)	5.60 (44)	6.11 (67)
	Ratio	1.05	0.98	0.96	1.00	0.95	0.98
	90% CI	1.01–1.10	0.91–1.06	0.89–1.03	0.87–1.15	0.87–1.03	0.94–1.03
Valproate	n	99	66	64	14	36	180
	Baseline	66.7 (44)	65.2 (60)	70.3 (37)	69.9 (41)	58.8 (41)	65.9 (47)
	Treatment	66.0 (45)	65.3 (63)	71.7 (29)	66.5 (38)	62.4 (47)	67.1 (49)
	Ratio	1.01	0.98	1.04	0.98	1.00	1.00
	90% CI	0.96–1.05	0.93–1.04	0.98–1.10	0.87–1.11	0.93–1.08	0.97–1.03

(*continued on next page*)

Table 3 (*continued*)

Concomitant antiepileptic drug	Statistic[a]	Placebo	Brivaracetam (mg/day)				
			50	100	150	200	50–200
Zonisamide	n	24	12	16	0	16	44
	Baseline	19.6 (68)	24.0 (80)	18.3 (56)	–	15.7 (61)	18.6 (66)
	Treatment	20.5 (66)	24.7 (66)	19.3 (37)	–	16.0 (65)	20.2 (61)
	Ratio	1.01	1.03	1.13	–	0.96	1.01
	90% CI	0.95–1.07	0.95–1.11	1.02–1.24	–	0.86–1.06	0.95–1.07

NR, not reported.

[a] n, number of patients; Baseline, geometric mean (geometric CV%) plasma concentration (μg/mL) during baseline; Treatment, geometric mean (geometric CV%) plasma concentration (μg/mL) during treatment; Ratio, geometric least squares means ratio between treatment and baseline periods; 90% CI, 90% confidence interval around the ratio, derived from linear mixed-effect model.

[b] Mono Hydroxy Derivative, active circulating metabolite of oxcarbazepine.

male; mean age 37 years), of whom 62.3% were randomized to receive BRV and 37.7% to receive placebo. Patient demographics were well balanced across the groups (Table 1).

Median daily doses of each concomitant AED were also comparable between BRV and placebo arms (Table 2). The most commonly prescribed concomitant AED was CBZ, with 39.3% of the placebo group and 40.2% of the BRV group receiving this medication (Table 2). Usage of other individual AEDs ranged from 2.7% to 25.1% in both groups. The overall proportion of concentration values per AED that were either missing or excluded due to dose changes or missing information was 18.7%; percentages of patients with AED dose changes were generally low for all AEDs (from 0.0% to 11.6%) and similar between BRV and placebo groups.

3.2. Antiepileptic drug plasma concentrations

In total, 7322 valid AED plasma concentration values were available during the baseline and treatment (evaluation) phases of the contributing studies for the placebo and BRV 50–200 mg/day groups. Geometric mean (CV%) plasma concentrations and geometric LS means ratios of AED concentrations between the treatment and baseline periods are presented in Table 3.

For all AEDs but three, the treatment to baseline ratios remained close to 1 across treatment groups without visible trends for BRV dose-related changes (Table 3), and the respective 90% CIs were fully enclosed within the 0.80–1.25 limits (Fig. 2).

For PHT and PGN, the 90% CIs exceeded the 0.80 or the 1.25 limit of the acceptance interval without being completely outside of this interval. This inconclusive effect did not exhibit a dose dependency. For BRV 50–200 mg/day doses combined, the 90% CI was within the limits for PHT (0.91–1.14) and was marginally above for PGN (0.99–1.27). The number of patients who received both BRV and PGN was small (n = 26). High inter-individual variability of PHT and PGN plasma concentrations was noted for all treatment groups.

Regarding CBZ, a BRV dose-dependent decrease from baseline was observed with a treatment to baseline ratio reaching 0.89 (90%CI: 0.86–0.93) for BRV 200 mg/day; the change was significant as the upper 90% confidence limit was < 1.00 but was not clinically relevant as the lower limit was > 0.80.

A BRV dose-dependent increase in the metabolite CBZ-E was observed which was clinically relevant across the 50–200 mg/day dose range and also fell outside the 0.80–1.25 limits in the combined BRV group (Fig. 2). A mean change of +37%, +62%, +77%, +98% and −1% was observed for BRV 50, 100, 150 and 200 mg/day and placebo groups respectively (Table 3). This change from baseline corresponded to CBZ-E geometric mean concentrations of 2.53, 2.57, 2.73, and 3.25 μg/mL with BRV 50, 100, 150 and 200 mg/day respectively (geometric coefficients of variation between 48 to 64%) compared with 1.76 μg/mL in those receiving placebo. Few samples contained CBZ-E concentrations above 6 μg/mL (BRV 50 mg/day 9/406, 2.2%; 100 mg/day 4/304, 1.3%; 150 mg/day 3/62, 4.8%; 200 mg/day 11/152, 7.2%; placebo 0/562, 0%). Two samples had a CBZ-E concentration above

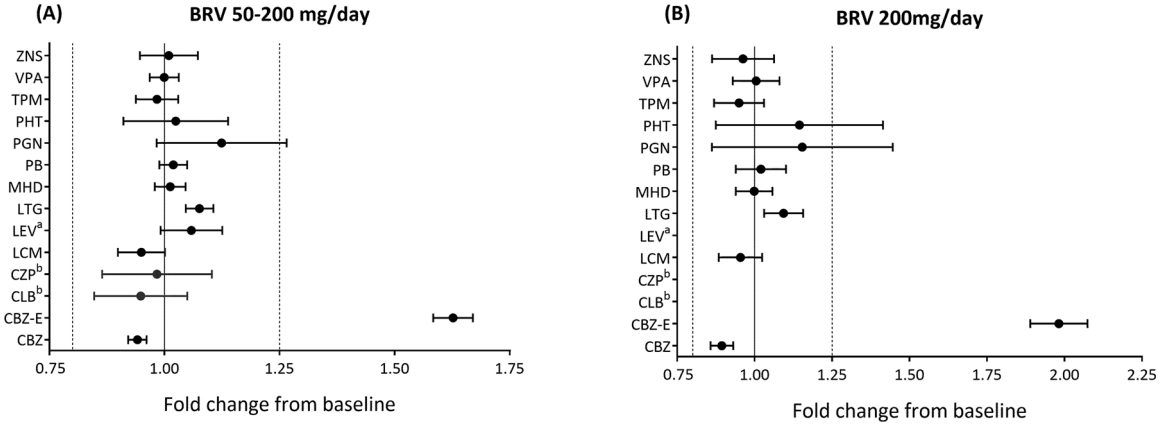

Fig. 2. Fold change from baseline of each antiepileptic drug when co-administered with brivaracetam 50–200 mg/day (A) or 200 mg/day (B).
Footnotes: [a]Concomitant LEV was excluded in study N01358. [b]CZP and CLB were not evaluated in the BRV 200 mg/day group (right panel) due to insufficient patient numbers (< 10).
BRV, brivaracetam; CBZ, carbamazepine; CBZ-E, carbamazepine-10,11-epoxide; CLB, clobazam; CZP, clonazepam; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; MHD, mono-hydroxy derivative of oxcarbazepine (OXC); PB, phenobarbital; PGN, pregabalin; PHT, phenytoin; TPM, topiramate; VPA, valproate; ZNS, zonisamide.

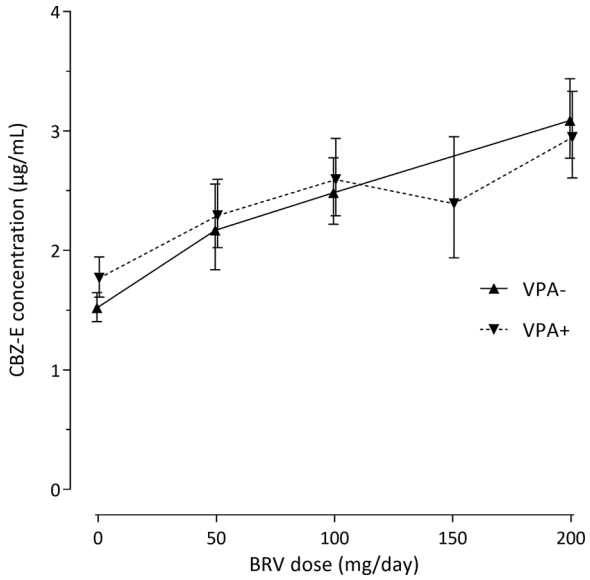

Fig. 3. Carbamazepine epoxide geometric least squares mean concentration (90% CI) vs. brivaracetam daily dose in patients taking carbamazepine without valproate (VPA−, n = 88) or with valproate (VPA+, n = 78).
Footnote: BRV, brivaracetam; CBZ-E, carbamazepine-10,11-epoxide; CI, confidence interval; VPA, valproic acid.

8 µg/mL: 9.82 µg/mL in a patient receiving BRV 200 mg/day + CBZ 400 mg/day + CLB 10 mg/day, and 8.25 µg/mL in a patient receiving BRV 200 mg/day + CBZ 300 mg/day + ZNS 100 mg/day + CZP at unknown dose.

The influence of background treatment with VPA on the relationship between CBZ-E concentration and BRV dosage was explored in patients treated with CBZ alone (Fig. 3). At BRV 50 mg/day, geometric mean CBZ-E values were 2.29 µg/mL (VPA+) vs. 2.17 µg/mL (VPA−), at BRV 100 mg/day 2.59 vs. 2.48 µg/mL, at BRV 150 mg/day 2.39 vs. 1.59 µg/mL and at BRV 200 mg/day 2.95 vs. 3.09 µg/mL. In the placebo group, geometric mean CBZ-E concentrations were 1.77 vs. 1.52 µg/mL, respectively for VPA+ and VPA−.

4. Discussion

Further to recent work focusing on potential interactions with CBZ (Stockis et al., 2016a), the primary objective of the reported pooled analyses was to determine the effect of BRV on steady-state plasma concentrations of a range of concomitant AEDs and assess the potential for DDIs. Notably, BRV did not substantially modify concentrations of CBZ, CLB, CZP, LCM, LTG, LEV, MHD, PB, PGN, PHT, TPM, VPA or ZNS in adult patients with refractory focal epilepsy. This is particularly relevant to the use of BRV as adjunctive therapy alongside these agents. Although 90% CIs for PHT and PGN exceeded one of the pre-defined limits at some dose levels, the ratio of geometric LS means of drug concentrations during adjunctive BRV and at baseline did not suggest relevant interaction as the mean changes were less than 20% (1.02 or +2% for PHT, and 1.12 or +12% for PGN) and did not appear to be correlated with the BRV dose. A 20% increase in PHT concentration was reported at the BRV supratherapeutic dose of 400 mg/day (Moseley et al., 2016). The numbers of patients receiving PGN were too small to permit meaningful assessment with three dose groups involving fewer than 10 patients.

While the changes in CBZ concentration were significant but not clinically relevant (Treatment to Baseline ratio remained fully enclosed within 0.80–1.25 limits), BRV did, however, effect a large dose-dependent increase in the concentration of CBZ-E, the active metabolite of CBZ, reaching a 2-fold increase at BRV 200 mg/day. This is consistent with findings from a Phase I open-label study in healthy volunteers where BRV 400 mg/day dosing for 2 weeks was associated with a 2.6-fold mean increase in CBZ-E (Stockis et al., 2015) and a Phase I study in patients with epilepsy in which BRV 200 mg/day similarly resulted in a 2-fold increase (Stockis et al., 2016a). The raised CBZ-E level is due to inhibition of epoxide hydrolase; in vitro studies have demonstrated that BRV inhibits enzymatic CBZ-E hydrolysis dose-dependently with a mean IC_{50} of 8.20 µM (Stockis et al., 2015). This IC_{50} value was used to predict that BRV 400 mg/day would increase CBZ-E plasma concentrations by 2.3-fold, in close agreement with the observed 2.6-fold increase.

Background therapy with VPA, which is also an epoxide hydrolase inhibitor and a very widely prescribed AED often used in combination therapy (Potter and Donnelly, 1998), may be predicted to potentiate this interaction. However, in our analysis, the increase in CBZ-E concentration upon addition of BRV therapy does not appear to be consistently affected by the presence or absence of concomitant VPA. Equally, co-administration of CBZ with BRV and a CYP3A4 enzyme-inducing drug could potentially raise the CBZ-E levels above a critical threshold; however, this was not explored in the present analysis.

CBZ is a first-line option for the treatment of focal seizures (Iyer and Marson, 2014) and remains among the most frequently used AEDs in combination therapy. Approximately 80% of total CBZ clearance at steady-state occurs via the sequential epoxide-diol pathway (Svinarov and Pippenger, 1996). There remains a lack of clear consensus regarding the clinical toxicity of elevated CBZ-E although 8 µg/mL has been cited (Patsalos et al., 2008) as a typical threshold for emergence of transient adverse events (AEs). In this analysis, values of CBZ-E above 8 µg/mL were recorded in very few (2/924) plasma samples from BRV-treated patients. Even in patients taking the highest approved dose of BRV (200 mg/day), the mean concentration of CBZ-E was 3.25 µg/mL, or less than 50% of that threshold. Similarity to the parent drug has been reported with respect to both anticonvulsant and neurotoxic effects (Pisani et al., 1990). However, most of the published literature originates from limited case reports or open-label studies. Furthermore, in most studies CBZ-E levels have not been quantified (Patsalos et al., 2008), and this lack of data limits the derivation of a strong correlation. Mean CBZ-E concentrations with concomitant BRV 50–200 mg/day administration observed in the present study (2.53–3.25 µg/mL) are consistent with Phase I results, in which BRV 400 mg/day in combination with CBZ 600 mg/day was associated with a peak CBZ-E concentration of 3.0 µg/mL (Stockis et al., 2015). Pooled analysis of data from the three double-blind, placebo-controlled, fixed-dose, Phase III studies does not support an association between CBZ-E levels and toxicity (Brodie et al., 2018). Among patients treated with BRV 50–200 mg/day, completion rates were similar in CBZ+ (92.7%) and CBZ− (88.7%) groups, as was the incidence of TEAEs commonly recognized as potentially associated with CBZ-E toxicity, including ataxia, diplopia, dizziness, nystagmus and somnolence (CBZ+ 24.4% vs CBZ− 24.2%). However, serious AEs and discontinuations due to TEAEs were more frequent in the CBZ− group than in the CBZ+ group (3.9% vs 1.6% and 9.2% vs 2.9%, respectively). Such data suggests the rise in CBZ-E is unlikely to be clinically significant in most patients, and does not support special monitoring or automatic dose adjustments of CBZ when BRV is prescribed adjunctively.

With the exception of raised CBZ-E, the findings for BRV are similar to those observed for LEV. The latter does not influence steady-state concentrations of CBZ, PHT, VPA, LTG, PB, gabapentin, primidone or vigabatrin in adults (Gidal et al., 2005), or of CBZ, VPA, LTG or TPM in children (Otoul et al., 2007). For example, in adults, 90% CIs for geometric LS mean concentration ratios between LEV treatment and baseline encompassed unity for all AEDs except CBZ and VPA, where upper limits were 0.99 and 0.97, respectively (Gidal et al., 2005). However, the magnitude of changes upon introduction of LEV treatment (2% and 6%) was not deemed to be clinically relevant (Gidal et al., 2005). Similar to the case for co-administration of BRV with PHT and PGN, addition of LEV to vigabatrin resulted in 90% CIs for

geometric mean ratios exceeding the 0.80–1.25 limits due to a small number of observations (Gidal et al., 2005).

DDIs have been reported with other second- and third-generation AEDs. For example, eslicarbazepine has been shown to increase CBZ, LTG and TPM clearance and therefore decrease plasma concentrations by 12–13%, 25% and 16%, respectively (Patsalos, 2013). Eslicarbazepine, however, has been reported to increase PHT maximum plasma concentration (C_{max}) and area under the plasma concentration versus time curve (AUC) values by 30–35% and has demonstrated inconsistent effects on VPA pharmacokinetics (Patsalos, 2013). LCM 400 mg/day has been shown to decrease concentrations of MHD by 15% in patients co-prescribed oxcarbazepine, while a dosage of 200 mg/day was without effect (Patsalos, 2013). Furthermore, perampanel displays modest pharmacokinetic interactions with several AEDs. Plasma concentrations of CBZ, CLB, LTG and VPA are each decreased by < 10% in its presence (Patsalos, 2013).

The present data are limited by the retrospective nature of the analysis, the small numbers of patients exposed to some of the concomitant drugs, and methodological differences in the individual trials, particularly relating to the schedule of study visits and associated blood sampling.

5. Conclusions

Our findings suggest that adjunctive BRV does not relevantly affect the plasma concentrations of concomitantly administered AEDs, with the exception of a dose-dependent increase in the CBZ metabolite CBZ-E, attributable to inhibition of epoxide hydrolase. Pooled analysis of safety data from the three pivotal Phase III studies does not support an association between CBZ-E levels and symptoms of toxicity; therefore, there is currently no evidence to suggest that BRV dose adjustment or additional drug or metabolite monitoring is required when used with concomitant CBZ or any of the other tested AEDs. However, because of increased exposure to CBZ-E, CBZ dose reduction should be considered if tolerability issues arise in patients on concomitant BRV (Briviact, 2018).

Disclosures

Brian D. Moseley has served as a paid consultant for UCB Pharma, Eisai, and Validus Pharmaceuticals. He also serves on speakers bureaus for UCB Pharma, Eisai, and LivaNova. He has received research support from Nonin Medical, Inc, GW Pharma, Sunovion, and LivaNova. Christian Otoul, Ludovicus Staelens, and Armel Stockis are employed by UCB Pharma. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Funding

UCB Pharma was responsible for the design and conduct of the original Phase III studies, and the collection, management, and analysis of the data. The post-hoc analyses reported here were sponsored by UCB Pharma. Editorial assistance was provided by Shelley Morris, MSc, QXV Communications (an Ashfield Business, Macclesfield, UK) and was funded by UCB Pharma. UCB Pharma was involved in the writing of the manuscript. The authors made the final decision to submit the manuscript for publication.

Data sharing statement

Qualified researchers whose proposed use of the data has been approved by an independent review panel will be given access to anonymized individual participant data and redacted study documents. Additional information is available on www.clinicalstudydatarequest.com.

Acknowledgements

The authors thank the patients and their caregivers, in addition to the investigators and their teams, who contributed to the original studies. The authors acknowledge Barbara Pelgrims, PhD (UCB Pharma, Brussels, Belgium) for coordination of the publication.

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