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A double-blind, placebo-controlled interaction study between oxcarbazepine and carbamazepine, sodium valproate and phenytoin in epileptic patients

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1 The effect of carbamazepine (CBZ), sodium valproate (VPA) and phenytoin (PHT) on the pharmacokinetics of oxcarbazepine (OXC) was explored in three groups of 12 epileptic patients taking one of these drug as monotherapy.
2 Each patient took a single 600 mg dose of OXC followed 7 days later by 3 weeks' treatment with OXC 300 mg thrice daily and matched placebo in random order.
3 Seven untreated patients, acting as controls, were prescribed the single OXC dose and 3 weeks' active treatment only.
4 In those patients completing the study, the area under the concentration-time curve (AUC) at steady-state for hydroxycarbazepine (OHCZ), the active metabolite of OXC, was significantly lower in the CBZ-treated group than in controls ($P < 0.05$).
5 No other differences in AUCs or elimination half-lives for OHCZ were found between treated and untreated patients following single or multiple OXC dosing.
6 Median AUCs of CBZ, VPA and PHT during a dosage interval did not differ significantly after treatment with OXC and placebo.
7 Ten patients completing the study complained of side-effects during treatment with OXC compared with one taking placebo ($P < 0.01$).
8 There were no important changes in cognitive function testing during administration of OXC compared with placebo.
9 Standard doses of OXC can be given as add-on therapy in epileptic patients receiving CBZ, VPA or PHT without producing a clinically relevant pharmacokinetic interaction.

Keywords antiepileptic drug drug interaction epilepsy oxcarbazepine pharmacokinetics

Introduction

Oxcarbazepine (OXC), the 10-keto analogue of carbamazepine (CBZ), is an equally effective antiepileptic drug [1–4]. Despite structural similarity, their metabolic profiles differ. CBZ is oxidised down a number of pathways, in particular to the active metabolite, carbamazepine 10, 11 epoxide (CBZ-E), which is itself further transformed to the inert 10, 11 dihydrodiol [5]. OXC is rapidly and completely reduced to an active metabolite, 10 hydroxycarbazepine (OHCZ), most of which is eliminated as the glucuronide conjugate [6]. A smaller amount also reaches the urine as the trans-diol [7]. As OXC is present at low concentrations for just a few hours after dosing, OHCZ can be assumed to be responsible for the anticonvulsant effect.

This divergence in metabolic pathways holds out the possibility of clinical advantage for OXC over CBZ [8]. CBZ induces hepatic monooxygenase enzymes resulting in many unwanted drug interactions [9]. Autoinduction of its own metabolism, in addition, produces substantial intra- and inter-individual variation in circulating CBZ concentrations [10]. Drugs that influence oxidative enzymes, including the anticonvulsants, sodium valproate

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(VPA) and phenytoin (PHT), interfere with the metabolism of CBZ and CBZ–E producing clinically relevant adverse effects [11].

We undertook this study to explore the effects of CBZ, VPA and PHT on the pharmacokinetics of OXC in epileptic patients. In addition, any changes produced by additional OXC on concomitant antiepileptic drug concentrations could be identified, mirroring its clinical use in patients with refractory epilepsy.

Methods

Patients

The clinical characteristics of the 43 patients entering the study are displayed in Table 1. None had evidence of haematological, hepatic or renal disease and all were asked to refrain from alcohol throughout. The study had the approval of the local ethics committee and written informed consent was obtained from each patient.

Thirty-six patients were receiving treatment with a single antiepileptic drug. Although not seizure-free, all had been established on the same anticonvulsant regimen for at least 3 months prior to entry. Twelve took a mean dose (range) of 1025 mg (400–2000 mg) CBZ, 1541 mg (400–2800 mg) VPA, or 377 mg (250–500 mg) PHT at their usual timing throughout the study. Nine patients were receiving treatment with 14 other drugs, none of which was known to affect hepatic metabolic processes. Seven untreated patients acted as controls. They were either newly diagnosed after a second fit, or had relapsed off anti-epileptic treatment.

Protocol

The trial had a double-blind, random order, placebo-controlled, crossover design. After a 4 week baseline period, a single 600 mg oral dose of OXC was administered at 09.00 h with the patient's usual antiepileptic medication. Blood sampling via an indwelling catheter placed in a suitable antecubital vein was undertaken at 0, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48 and 72 h post-dose.

Following a 7-day washout period, the patient was randomised to additional OXC (300 mg thrice daily) or matched placebo. Untreated controls were given the active drug only. After 3 weeks' treatment, each patient underwent repeat venous sampling. Following a further 2-week washout period, the treated patients were crossed over to the alternative tablets and the procedure was repeated.

Seizure numbers were recorded throughout the study on standard charts with which the patients were familiar. At each hospital visit, a tablet count was made as a check on compliance. Cognitive function tests, as described previously [12], were performed 2 and 6 h after administration of the last dose of both treatments.

Assays

Blood samples were centrifuged immediately after withdrawal and the sera stored at −20° C for batch analysis. Concentrations of OXC and its active metabolite were determined using the high performance liquid chromatographic (h.p.l.c.) method of Kumps [13].

The limit of determination was 0.2 mg l^{-1} for OXC and 0.25 mg l^{-1} for OHCZ. OXC concentrations were negligible and are not presented. The intra-assay coefficients of variation for OHCZ at 0.25 mg l^{-1}, 5 mg l^{-1} and 10 mg l^{-1} were 4.2%, 6.8% and 3.5% respectively. CBZ, VPA and PHT were measured by enzyme immunoassay (Emit, Syva, Palo Alto, USA), while CBZ–E was measured by h.p.l.c. using 5-(*p* methylphenyl)- 5-phenyl hydantoin as internal standard [14].

Analyses

The areas under the concentration-time curve (AUC) for OHCZ, CBZ, CBZ–E, VPA and PHT were calculated using the trapezoidal rule. AUC to infinity was obtained for the single OXC dose using an estimation based on the half-life calculated from the 72 h reading to infinity. AUC 0–*t* used data to eight hours for multiple dosing periods. For comparison with chronic dosing, the AUC data following the single dose were corrected for a 300 mg OXC dose by simple division assuming linear kinetics [15]. The ratio of logarithmic mean OHCZ AUC between control and treated patients was calculated after single and repeated OXC dosing. Subtraction of this value from unity provided an indication of the percentage difference in AUC between treated patients and controls. The AUCs for CBZ, CBZ–E, VPA and PHT were calculated from the dosage intervals (Table 1) of the individual patients (once daily: AUC (0, 24 h), twice daily: AUC (0, 12), thrice daily: AUC (0, 8), four times daily: AUC (0, 6 h)). Elimination half-lives for OHCZ were obtained by log linear regression.

Statistics

The Mann Whitney test for unmatched samples was used to explore intra- and inter-group differences in AUCs and elimination half-lives and for comparing seizure numbers. Reports of side-effects were examined with the chi-square test. Comparisons of cognitive function following active drug and placebo were made with Student's *t*-test for paired values using the Bonferroni correction for multiple testing.

Results

Eight treated patients did not complete the study. Three were taking CBZ, three VPA and two PHT. One patient developed an erythematous rash after the single OXC dose. Four patients dropped out because of side-effects while on chronic OXC (two nausea and vomiting, one headache, one confusion). One patient reported an intolerable headache while taking placebo. A further patient became mildly anaemic on placebo and one did not comply correctly with the protocol.

Concentration time-curves for OHCZ in all treated groups and in controls following the single OXC dose and on chronic dosing are presented in Figure 1. The ratios of logarithmic mean AUCs for OHCZ between control and treated groups (treated/control) were lower

at steady-state (CBZ 0.60, VPA 0.82, PHT 0.71) than after the single OXC dose (CBZ 0.85, VPA 0.94, PHT 0.95). There were no significant differences in AUCs for OHCZ among treated and untreated patients following administration of the single OXC dose (Table 2). At steady-state, OHCZ AUCs were lower in all treated groups *vs* controls, particularly in patients receiving CBZ (40% lower) and PHT (29% lower). This was statistically significant ($P < 0.05$) for the CBZ-treated group. Within group comparisons after the single OXC dose and at steady-state did not reveal any important differences in OHCZ AUCs (Table 2).

Table 1 Demographic characteristics (mean ± s.d.) of 43 epileptic patients

Treatment	*Carbamazepine*	*Sodium valproate*	*Phenytoin*	*Untreated*
Patient numbers	12	12	12	7
Male:female	3:9	4:8	6:6	5:2
Age (years)	34 ± 10	39 ± 14	36 ± 11	37 ± 13
Height (cm)	162 ± 11	168 ± 9	165 ± 13	172 ± 12
Weight (kg)	73 ± 16	70 ± 15	61 ± 13	67 ± 11
Duration (years)	15 ± 7	16 ± 16	16 ± 11	5 ± 7
GTCS:CPS:PSG	6:5:1	4:5:3	4:7:1	5:0:2
Daily dose (mg)	1025	1541	377	—
Dosage range (mg)	400–2000	400–2800	250–500	—
Dosage interval (24 h, 12 h, 8 h, 6 h)	0, 11, 0, 1	1, 11, 0, 0	7, 4, 1, 0	—
Other drugs	Prochlorperazine Pizotifen Folic acid	Thyroxine Bendrofluazide Flurbiprofen Atenolol	Hydrocortisone Thyroxine Sustanon Simvastatin Disopyramide	Dihydrocodeine Aspirin

GTCS = generalised tonic clonic seizures.
CPS = complex partial seizures.
PSG = partial seizures with secondary generalisation.

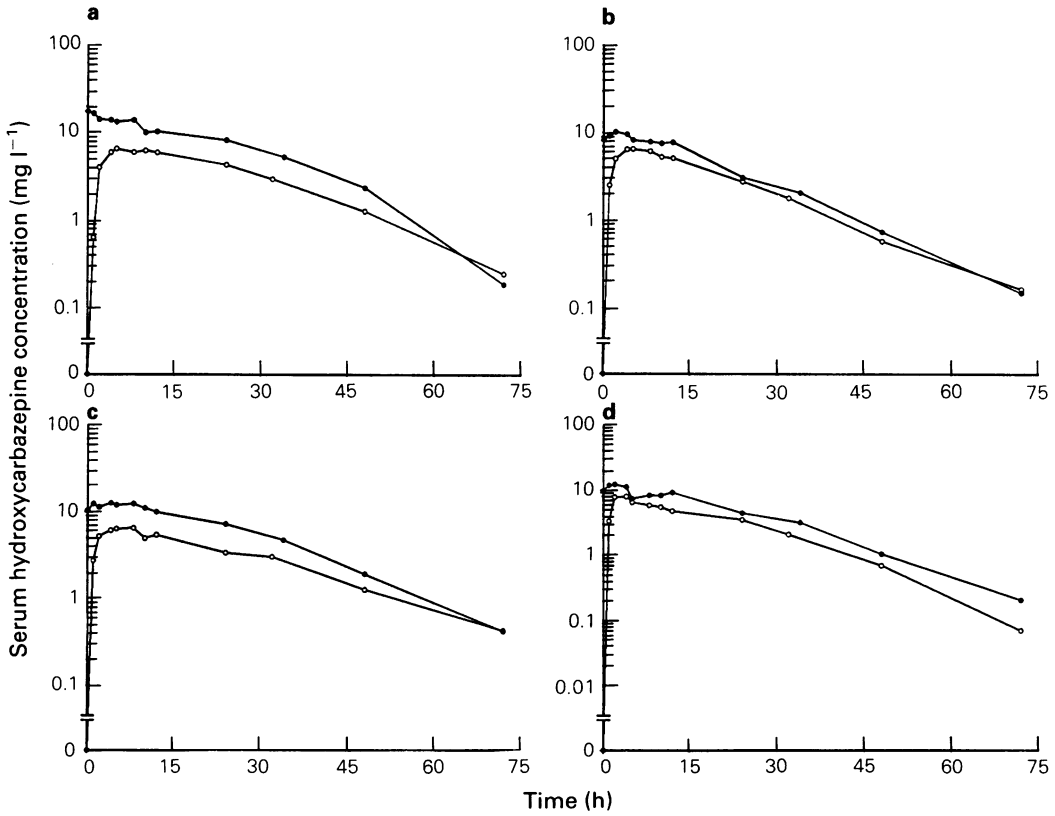

Figure 1 Concentration-time curves for hydroxycarbazepine among patients taking b) carbamazepine, c) sodium valproate or d) phenytoin as monotherapy and a) in untreated controls after a single 600 mg dose of oxcarbazepine (corrected to 300 mg, ○) and at steady-state (300 mg thrice daily for 3 weeks, ●).

The median elimination half-life of OHCZ in patients taking VPA was significantly prolonged following administration of the single OXC dose compared with that at steady-state. The elimination half-life in VPA treated patients *vs* controls was also longer after a single OXC dose, but this failed to reach statistical significance ($P = 0.1$). No such differences were apparent among the other treatment groups or the controls. No differences in AUCs for concomitant antiepileptic drugs or CBZ–E were observed during treatment with OXC at steady-state compared with those calculated for the placebo phase (Table 3).

A small fall in seizure numbers (mean ± s.e. mean, $n = 29$) was observed during the 3 weeks of OXC administration compared with placebo, which just failed to reach statistical significance (OXC 5.7 ± 1.7, placebo 7.3 ± 2.1, NS, 95% CI −3 to 0). Tablet counts were consistent with good compliance throughout. Ten patients completing the study complained of side-effects during treatment with OXC compared with one on placebo ($P < 0.01$). Three were taking concomitant CBZ, two VPA and five PHT. A total of 17 complaints were made on OXC compared with 3 on placebo ($P < 0.01$). The most common symptoms associated with OXC therapy were nausea ($n = 5$), dizziness ($n = 4$) and sedation ($n = 3$). Other problems were vomiting (2) and one each of blurred vision, headache and confusion. Sedation, dizziness and headache were also noted by a single patient during the placebo phase. Treatment with OXC had little impact on cognitive function (Table 4).

Discussion

CBZ, PHT and VPA are eliminated by oxidative metabolic processes mediated by the hepatic P-450 monoxygenase system. These enzymes are highly

Table 2 Median (range) areas under the concentration-time curve (AUC, mg l^{-1} h) and elimination half-lives (h) for hydroxycarbazepine in treated and control patients

AUC	n	*Single dose (SD)*	n	*Steady-state (SS)*	P	95% CI for *difference (SD–SS)*
Carbamazepine	12	95 (50–181)	9	72* (43–137)	NS	−44 to +12
Sodium valproate	12	104 (39–157)	9	97 (58–201)	NS	−38 to +33
Phenytoin	12	89 (72–181)	11	76 (42–160)	NS	−40 to +35
Untreated	7	102 (80–135)	7	111* (88–183)	NS	−13 to +49
Half-life						
Carbamazepine	12	13.0 (8.1–16.2)	9	11.3 (8.1–19.1)	NS	−4 to +2
Sodium valproate	11	15.1 (10.4–19.1)	9	13.6 (5.5–15.3)	< 0.05	−5.5 to −0.3
Phenytoin	12	11.3 (6.2–19.2)	10	10.6 (7.5–15.8)	NS	−4.2 to +2.7
Untreated	7	13.4 (9.5–32.8)	7	13.0 (10.0–22.9)	NS	−3.9 to +6.6

Single dose data were corrected for a 300 mg oxcarbazepine dose.
*$P < 0.05$.
95% CI for difference +15 to +80.

Table 3 Median (range) areas under the concentration-time curve (mg l^{-1} h) during a dosage interval for concomitant antiepileptic drugs and carbamazepine epoxide following single and steady-state oxcarbazepine dosing

Treatment group	n	*Single dose*	n	*Steady-state (SS)*	n	*Placebo (PL)*	95% CI for *difference (SS–PL)*
Carbamazepine	12	107 (53–178)	9	84 (75–160)	10	92 (39–185)	−44 to +22
Sodium valproate	12	976 (326–2207)	9	1118 (413–2290)	9	1114 (727–2525)	−313 to +433
Phenytoin	12	271 (157–477)	11	344 (147–555)	10	314 (185–509)	−50 to +126
Carbamazepine epoxide	12	17.9 (5.9–32.0)	9	16.9 (7.2–41.0)	10	12.7 (4.0–33.1)	−12.9 to +6

susceptible to induction and inhibition. OXC, however, undergoes reduction by cytosolic enzymes to the active OHCZ metabolite. The keto-reductase enzyme responsible for this conversion is not inducible [16]. Further metabolism to the glucuronide conjugate is mediated by microsomal transferases, which are less susceptible to metabolic interference than oxidative enzymes [17].

Treatment with OXC has not resulted in autoinduction of metabolism [18, 19], nor has it altered the markers of enzyme induction, such as antipyrine clearance and urinary 6-β hydroxycortisol excretion [19]. In patients changed from CBZ to OXC, an observed rise in concomitant antiepileptic drug concentrations supported less powerful induction with the new agent [1, 2]. In this study, consistent elimination half-lives of OHCZ following single and multiple OXC dosing in the untreated patients confirms a lack of autoinduction of metabolism with this drug.

Volunteer studies have suggested that OXC does not interfere with warfarin metabolism [20], nor does cimetidine [21] or dextropropoxyphene [22] inhibit OXC breakdown, as in the case with CBZ [11]. However, an inconsistent decrease in the bioavailability of the oral contraceptive pill has been noted during treatment with OXC [23]. In addition, the AUC of the calcium antagonist felodipine was reduced by 28% following its introduction [24], compared with a 90% reduction with CBZ, PHT and phenobarbitone [25, 26]. It has been suggested that at high doses OXC can act as an enzyme inducer [27]. An alternative hypothesis is that OXC selectively induces a single isoform of cytochrome P450, namely P450 3A [15].

Studies exploring the interaction of OXC with other anticonvulsants in patients have mainly compared it with CBZ. Substituting OXC for CBZ in epileptic patients taking anticonvulsant polytherapy was associated with a 20–30% rise in steady-state plasma concentrations of PHT and VPA [1, 2]. The AUCs of CBZ, VPA and PHT in the present study were not significantly altered by OXC suggesting an absence of metabolic interference with these first-line antiepileptic drugs.

Patients taking CBZ or PHT had lower OHCZ concentrations at steady-state compared with controls, which was statistically significant for the CBZ-treated group. Possible explanations include a small induction effect by these drugs on the breakdown of this metabolite or acceleration of an alternative pathway of OXC biodegradation. This would have little clinical relevance when OXC was being prescribed in patients not fully controlled with CBZ or PHT monotherapy, as titration of the OXC dose would be the normal course of events. However, withdrawal of CBZ or PHT might produce a rise in OHCZ concentrations which could, theoretically, result in concentration-dependent toxicity.

The elimination half-life of OHCZ after the single OXC dose was prolonged compared with steady-state in patients taking VPA. This is likely to be a chance observation. VPA is known to produce enzyme inhibition [28], in particular of the breakdown of CBZ–E [29]. That the OHCZ half-lives at steady-state did not differ from those in controls, however, argues against a consistent interaction. Furthermore, as the AUCs of OHCZ after the single OXC dose and at steady-state were similar in VPA treated patients and controls, any interaction between OXC and VPA, if it exists, is not likely to be clinically relevant.

Our study provides some small support for the view that OXC compares favourably with the other major antiepileptic drugs in its relative lack of effect on formal cognitive function testing [30]. Although sensitive to the deleterious effects of CBZ and PHT [31], it is, however, possible that our battery of tests would not register cognitive impairment with OXC at the dosage used in this study. Side-effects were observed largely when OXC was taken in combination with other antiepileptic drugs. Untreated patients tolerated the drug well. This is in keeping with results from double-blind clinical trials that have hinted at superior tolerability of OXC over CBZ in newly diagnosed epileptic patients [4] and in those with refractory epilepsy [3].

OXC is a new anticonvulsant with similar efficacy and, possibly, superior tolerability to CBZ [15]. No

Table 4 Mean (s.d.) cognitive function test scores 2 and 6 h after 3 weeks' treatment with 300 mg oxcarbazepine thrice daily and matched placebo

	Oxcarbazepine		*Placebo*	
Test	*2 h*	*6 h*	*2 h*	*6 h*
Decision time (s)*	0.57 (0.2)	0.54 (0.2)	0.53 (0.1)	0.52 (0.1)
Movement time (s)*	0.29 (0.1)	0.31 (0.1)	0.29 (0.1)	0.30 (0.1)
Finger tapping (per min)	75.9 (24.0)	74.7 (22.3)	73.7 (21.4)	77.2 (22.7)
Forward digit span	6.0 (1.5)	6.3 (1.5)	6.5 (1.6)	6.2 (1.6)
Backward digit span	4.2 (1.2)	4.2 (1.5)	4.3 (1.3)	4.5 (1.6)
Verbal learning*	12.4 (4.4)	13.3 (4.1)	13.3 (4.2)	12.6 (3.8)
Tracking test	16.0 (8.3)	17.5 (8.9)	16.5 (8.9)	17.6 (9.0)
Threshold detection (frame units)*	2.0 (0.9)	2.0 (1.0)	1.7 (0.9)	1.8 (0.7)
Sedation score*	4.1 (3.1)	4.6 (3.4)	2.8 (2.2)	3.9 (3.0)
Side-effect score*	10.6 (9.1)	10.0 (7.8)	9.9 (10.1)	8.4 (5.9)

*Denotes test where low score is better than high score.

clinically relevant pharmacokinetic interactions were noted when patients receiving monotherapy with CBZ, VPA or PHT were given an additional 900 mg OXC daily for 3 weeks. This study was not designed to measure efficacy nor was the OXC dose titrated optimally. Nevertheless, it was sufficient to produce a small reduction in seizure numbers and a significant incidence in side-effects compared with placebo. In addition, 600–1200 mg OXC per day is regarded as standard dosing with the drug [15]. OXC, therefore, can be used as adjunctive therapy in treated epileptic patients, including those taking CBZ, without producing clinically relevant pharmacokinetic interactions.

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