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Effect of lamotrigine on the pharmacokinetics of carbamazepine and its active metabolite in dogs

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SUMMARY

The effect of lamotrigine (LTG) on the pharmacokinetics of carbamazepine (CBZ) and its active metabolite; carbamazepine-epoxine (CBZ-E), was investigated in dogs. Five male dogs received CBZ (2 x 200mg tab. p.o.) daily for a period of 1 week. After the end of this period, blood samples were collected serially for up to 24 hrs. After a wash-out period of 1 week, LTG (100 mg tab. p.o.) was coadministered with the CBZ dose (2 x 200 mg tab. p.o.) for 7 days. Blood samples were again serially collected and plasma levels of CBZ and CBZ-E were analysed by high performance liquid chromatography (HPLC). Concurrent administration of LTG with CBZ did not have any significant effect on the pharmacokinetic parameters of CBZ. There was also no significant difference between the plasma concentration ratio (CBZ-E to CBZ) vs time profiles in the two schedules of drug administration signifying the absence of pharmacokinetic interaction between LTG and CBZ or its active metabolite in this animal model.

INTRODUCTION

Lamotrigine [LTG, 3,5-diamino-6(2,3-dichlorophenyl)-1,2,4-triazine] is a relatively novel antiepileptic drug (AED) which most likely acts by inhibiting voltage-sensitive sodium channels leading to inhibition of excitatory neurotransmitter release, principally glutamate (1). It is widely used as both adjunctive and monotherapy in patients with partial and generalised tonic-clonic seizure (2).

In humans, LTG is rapidly and almost completely absorbed. After absorption, LTG is extensively metabolised to 2 N-glucuronide conjugate with only minor (10%) renal elimination of the unchanged drug. LTG does not induce mixed function oxidase enzymes in the liver and it is only 55% plasma-protein bound (3).

Carbamazepine (CBZ) is an older first-line AED in the treatment of simple or complex partial seizures and generalised tonic-clonic seizures. It is also used to treat trigeminal neuralgia and some psychiatric disorders (4).

CBZ is slowly and erratically absorbed with peak plasma levels occurring 4 to 8 hrs from oral administration. It is almost completely metabolised in the liver through microsomal cytochrome p-450 (CYP) enzymes, to an active metabolite, carbamazepine-10,11-epoxide (CBZ-E), with only less than 3% of a dose excreted unchanged. The elimination half-life of CBZ after single doses ranged between 25 and 65 hours (3). The CBZ-E metabolite is further inactivated by epoxide hydrolases yielding trans-10, 11-dihydroxy-10, 11-dihydro-CBZ (CBZ-D) which is partially conjugated with glucuronic acid prior to excretion in urine (5). The

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metabolism of CBZ may be altered by other drugs and by itself (autoinduction) especially after continued administration (6). It is moderately plasma-protein bound (75%), (5).

CBZ is frequently prescribed in polypharmacy with other AEDs such as LTG with the aim of enhancing benefit to epileptic patients. Studies relating to potential drug interaction between LTG and CBZ have not been conclusive. Warner et al (7) and Wolf (8) reported significant elevation of plasma levels of CBZ-E leading to neurotoxicity following coadministration of LTG with CBZ, but this finding was not substantiated by other investigators (9-12).

The present study examines the possibility of pharmacokinetic interaction between LTG and CBZ and its active metabolite, CBZ-E, in dogs.

MATERIALS AND METHODS

Materials

Pure CBZ powder was purchased from Sigma Chemical Co. (St. Louis, Mo, USA) while CBZ-E and LTG were gifts from Novartis (Basle, Switzerland) and Glaxo-Wellcome (UK), respectively. The commercial formulations of CBZ (Tegretol®, 200 mg tab.) and LTG (Lamictal®, 100 mg tab.) were locally purchased from a drug store. Methanol and acetonitrile were of HPLC-grade and other solvents and reagents used in this study were of analytical grade.

Animals

Five male beagle dogs (USA) weighing between 11-13 kg were used in this study. The animals were bred in the Experimental Animal Care Centre (College of Pharmacy, KSU, Riyadh, S.A.).

Phase I:

The dogs received an oral dose of CBZ (2 x 200 mg tab) for a period of 1 week. At the end of this period, the animals were fasted overnight (water given *ad libitum*) and then each dog was placed in an upright position in a restrainer cage. The leg was shaven and a cannula (18-guage) placed in the femoral vein. Blood samples (Ca 0.5 ml) were collected through the cannula just before and at 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hr following CBZ administration. Heparinised saline was flushed in after each sample withdrawal to maintain haemodynamics and prevent blockage of the cannula. The blood samples were immediately centrifuged at 1000 x g for 5 min and the resulting plasma samples were stored at -20°C pending analysis.

Phase II:

After a wash-out period of 1 week, the animals from Phase I were started on oral daily doses of CBZ (2 x 200 mg tab) and LTG (100 mg tab) for 7 days. The LTG was given 1 hr after CBZ administration. At the end of the 7-day period, the animals were fasted overnight, given the drug doses and plasma samples were collected as in Phase I.

Drug Analysis:

Plasma concentrations of CBZ and its active metabolite, CBZ-E were measured by a previously reported high performance liquid chromatographic (HPLC) method (13). Briefly, to a 100 µl of plasma sample, 20 µl of internal standard (9-hydroxymethyl-10-carbamyl acridan; 50 mg/l) was added and extracted with 100 µl of diethyl ether. The mixture was vortex-mixed for 30 sec, shaken on a rotary mixer for 5 min and then centrifuged at 1000 x g for 10 min. The organic layer was separated and evaporated to dryness. The residue was redissolved in 100 µl mobile phase and then 20 µl of the resultant solution was injected onto the chromatograph.

Chromatography was performed on a reverse phase Supelcosil LC-18 (Supelco Inc, USA) stainless steel column (5 µm, 150 mm x 4.6 mm ID). The mobile phase consisted of potassium phosphate buffer (0.01 M)-methanol-acetonitrile (65:18:17, v/v/v) and the pH adjusted to 7.5. The flow rate was 1.0 ml/min and ultraviolet detection was set at 220 nm. The retention times for CBZ-E, CBZ and internal standard were 4.48, 10.20 and 5.82 min., respectively. The method was capable of detecting plasma levels of CBZ and CBZ-E to as low as 0.2 µg/ml. The inter-assay coefficients of variation (% CV) for CBZ and CBZ-E ranged between 2.62 to 4.50 and from 1.90 to 5.49, respectively.

Pharmacokinetic and Statistical Analysis

Pharmacokinetic parameters of CBZ and CBZ-E were determined by non-compartmental method. Area under the plasma concentration-time curve and area under the first moment of the plasma concentration-time curve (AUMC) were calculated using the linear trapezoidal method with extrapolation to time infinity. Mean residence time (MRT) was calculated as MRT = $AUMC_{0-\infty}/AUC_{0-\infty}$. First order elimination rate

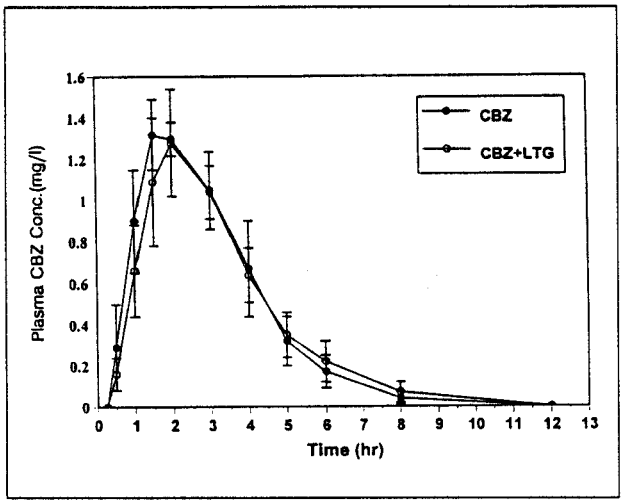

Fig. 1 : Mean (± SEM) plasma concentration-time profile of CBZ administered alone (●) and after coadministration with LTG (O) in dogs, (n=5)

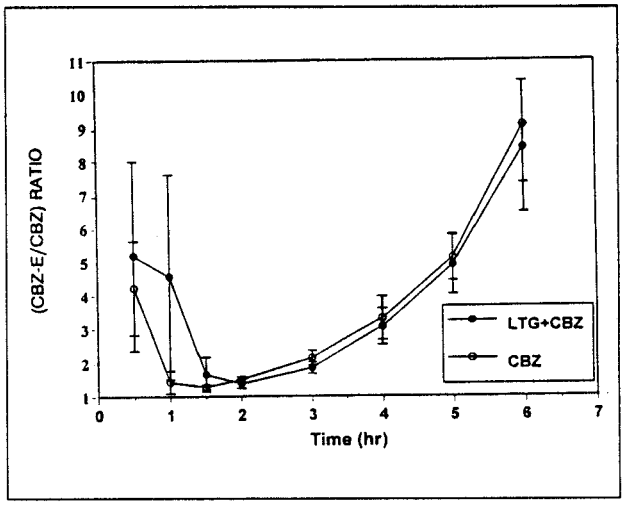

Fig. 2 : Mean (± SEM) ratio of the plasma concentration of CBZ-E to CBZ versus time during administration of CBZ alone (O) and after coadministration with (●) in dogs, (n = 5).

Table I: Mean (±SD) pharmacokinetic parameters of CBZ (2 x 200 - mg tab, p.o.) in dogs before and after LTG (100 mg tab, p.o.) administration, (n=5)

Parameter	**Before**	**After**	***p*-value***
C_{max} (mg/l)	1.51 ± 0.26	1.44 ± 0.52	0.847
t_{max} (hr)	2.21 ± 0.75	2.21 ± 0.52	0.997
$t_{1/2el}$ (hr)	0.96 ± 0.25	1.21 ± 0.56	0.445
$AUC_{0-\infty}$ (mg hr/l)	4.63 ± 1.25	4.60 ± 1.76	0.983
MRT (hr)	273 ± 0.71	3.21 ± 0.81	0.298

* Significantly different from baseline (before) using paired t-test ($p \leq 0.05$)

constant (K_{el}) was determined from the slope of the best long-linear fit of the terminal phase by least-squares linear regression analysis. The elimination half-life ($t_{1/2}$) was calculated as Ln 2 divided by K_{el}. Oral clearance (Cl/F) was calculated as Cl/F = Dose/$AUC_{0-\infty}$ and the volume of distribution (V_d/F) was obtained from the relationship, Vd/F = (Cl/F)/K_{el}, where F was the absolute bioavailibility. Values for the maximum plasma concentration (C_{max}) and time to attain the maximum concentration (t_{max}) were directly extracted from plasma concentration-time curves. The pharmacokinetic parameters are presented as mean ± SD. The Student's t-test for paired data was used for statistical evaluation with $p \leq 0.05$ as the level of significance (STAT 100, version 1.24, 1995, Biosoft, Cambridge, UK).

RESULTS

Mean plasma CBZ concentration-time profile before and after LTG administration is presented in Fig. 1. The corresponding computed pharmacokinetic parameters and the results of their statistical camparisons is shown in Table I. The mean concentration ratio of CBZ-E to CBZ versus time before and after LTG combination is shown in Fig. 2.

In dogs, CBZ appears to be rapidly absorbed with peak plasma levels being attained after 2.20 ± 0.75 hr from dosing. This is a considerably shorter period than that reported for humans (4 to 8 hrs). Moreover, CBZ is rapidly eliminated from the dog's body with a mean elimination half-life of 0.96 ± 0.25 hr. In humans, the reported elimination half-life ranges from 25 to 65 hrs.

Comparison of the principal pharmacokinetic parameters of CBZ during single and coadministratiion with LTG did not show any significant differences (Table I). Similarly, there were no significant differences in the mean plasma concentration ratio (CBZ-E/CBZ) *vs* time profiles between the two treatment schedules (Fig. 2).

DISCUSSION

CBZ is known to induce its own metabolism (autoinduction) with prolonged usage (6). Full CBZ autoinduction usually takes place in 2 to 4 weeks (14). Because of CBZ autoinduction, the design of our study involved CBZ administration for 1 week followed by a wash-out period of 1 week and thereafter coadministration with LTG for 1 week. Moreover, LTG was administerd 1 hr after CBZ since the metabolite (CBZ-E) and LTG would achieve maximum concentrations in plasma and potential interactive effects of LTG with either CBZ or CBZ-E would be evident at this period.

The results of the present study indicate that LTG had no apparent effect on the kinetics of both CBZ and CBZ-E. Very few reports confirmed interaction between LTG and CBZ resulting in increased serum levels of CBZ-E and development of neurotoxicity (7,8). Warner et al (7) studied the effect of LTG on CBZ pharmacokinetics in 9 epileptic patients. After LTG was added to CBZ therapy, the plasma levels of CBZ-E increased by 45% and the CBZ-E: CBZ ratio increased by 19%. In 4 patients, these increases were clinically significant, leading to neurotoxicity. Similarly, Wolf (8) studied the effect of addition of LTG to CBZ in 9 patients and found that 8 of them developed neurotoxicity. In all the patients studied, a small and inconsistent but statistically significant increase in CBZ-E concentration was found. Wolf (8) proposed a different mechanism of interaction; pharmacodynamic rather than pharmacokinetic which was also advanced by Warner et al (7). Buchanan (15) also observed adverse effects when LTG was coadministered with CBZ but he did not correlate these effects with plasma levels of either CBZ or CBZ-E.

On the other hand, other investigators (9, 11, 12, 16, 17) assessed the effect of LTG on CBZ and/or its active metabolite and reported a lack of pharmacokinetic interaction between LTG and either CBZ or its active metabolite, CBZ-E. Schapel et al (9) found clinically insignificant alterations in plasma CBZ-E levels during addition of LTG to CBZ treatment of 13 patients. Pisani et al (10) also found that LTG had no effect on CBZ-E levels. They compared the pharmacokinetics of a single oral dose of CBZ-E (100mg) in 10 epileptic patients on chronic monotherapy with LTG (200-300 mg/day) and 10 healthy control individuals. The CBZ-E pharmacokinetic parameters were similar for the two groups, suggesting lack of LTG effect on the metabolic disposition of CBZ-E. Eriksson and Boreus (11) reported similar results. They studied the effect of LTG on CBZ in 11 children and 3 adolescents and found that LTG had no effect on the plasma concentrations of either CBZ or CBZ-E. However, their observation of neurotoxicity in some patients was attributed to the occurrence of a pharmacodynamic rather than a pharmacokinetic interaction between LTG and CBZ.

Moreover, Gidal et al (17) assessed the potential interaction of LTG with CBZ and CBZ-E by evaluating the oral clearance of CBZ and the steady-state CBZ-E/CBZ serum concentration ratios in 9 epileptic patients. They found that the CBZ oral clearance and CBZ-E: CBZ ratios were not significantly different before and after concurrent administration of LTG and subsequently concluded that there was no pharmacokinetic interaction between LTG and CBZ or CBZ-E. More recently, Besag et al (12) investigated whether the neurotoxicity reported in some epileptic patients when LTG was added to ongoing treatment with CBZ was a reflection of pharmacokinetic or pharmacodynamic interaction. They studied this effect in 47 epileptic patients on CBZ therapy by introducing increasing doses of LTG. They observed neurotoxicity in 9 patients without apparent changes in serum levels of either CBZ or CBZ-E and concluded that the observed adverse effect was essentially a consequence of pharmacodynamic interaction.

Our results are in agreement with the latter observations and indicate that LTG when coadministered with CBZ doesn't significantly modify the pharmacokinetics of either CBZ or CBZ-E. Equally, the CBZ-E/CBZ plasma concentration ratio does not appear to be significantly different for the two treatment schedules. This ratio reflects the ability of the concomitant drug(s) to induce or inhibit the cytochrome p-450 isoenzymes (CYP3A4, CYP2C9, CYP2C19) or drugs such as LTG, which inhibit epoxide hydrolase (10).

It is clear from the present data that LTG does not exhibit pharmacokinetic interaction with CBZ or its active metabolite during their concurrent administration.

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