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Effect of valproic acid on the pharmacokinetic profile of oxcarbazepine in the rat

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Abstract

The pharmacokinetics of oxcarbazepine (30 mg kg^{-1}, po), administered for 1 week, was studied in rats pre-treated for 2 weeks with valproic acid (100 mg kg^{-1}, po). Oxcarbazepine (OXC) plasma levels were measured over a period of 24 h from dosing, using a sensitive HPLC method. No significant changes were observed in the mean values of OXC pharmacokinetic parameters (C_{max}, T_{max}, $t_{1/2}$ and $AUC_{0-\infty}$) between the control and the pre-treated groups. The findings of this study suggest that OXC metabolism in the rat is apparently not affected by valproic acid, and the lack of effect may be attributed to the different pathways of biotransformation of the two drugs.

Keywords: Oxcarbazepine; Valproic acid; Pharmacokinetic interaction; Rat

1. Introduction

Oxcarbazepine (OXC), the 10,11-dihydro-10-oxo-carbamazepine, is a new antiepileptic drug having the same anticonvulsant activity as carbamazepine (CBZ) but a completely different metabolic profile. In humans, OXC is rapidly reduced by a cytosolic aldo–keto reductase enzyme to the active metabolite, 10-hydroxy-carbazepine (MHD), Fig. 1 (Faigle and Menge, 1990). The bulk of this metabolite undergoes conjugation reaction with a glucuronyl moiety through the actions of microsomal glucuronyl-transferase prior to its excretion from the body, while a small fraction is further oxidized to an inactive 10,11-*trans*-dihydroxymetabolite (DHD) common to both OXC and CBZ (Lloyd et al., 1994). In rats, the reduction of OXC to MHD plays a minor role and oxidative reactions predominate (Wagner and Schmid, 1987). CBZ, on the other hand, is mainly oxidized in the liver to its active metabolite, carbamazepine-10-11-epoxide (CBZ-E) by microsomal mono-oxygenase oxidative enzymes of the cytochrome *P*-450 system (Eadie, 1991). The OXC metabolic profile suggests that it may have fewer drug interactions in man compared with CBZ.

During concomitant administration of valproic acid (VPA) with other antiepileptic drugs (AEDs), VPA has been observed to influence pharmacokinetics of phenobarbitone, phenytoin, ethosuximide and CBZ (Riva et al., 1996). Unlike the other AEDs, VPA is an inhibitor of hepatic oxidative metabolism. A cytochrome *P*-450 microsomal enzyme system appears to rapidly metabolize VPA in the liver. The drug undergoes oxidation reactions to metabolites which are finally conjugated for clearance from the body (Eadie, 1991). The coadministration of VPA with CBZ is very effective in the management of epilepsy; but it has been reported to precipitate CBZ toxicity (Ketter et al., 1991). In this regard VPA was shown in some studies not to have significant influence on plasma CBZ concentrations but it did increase the levels of the main

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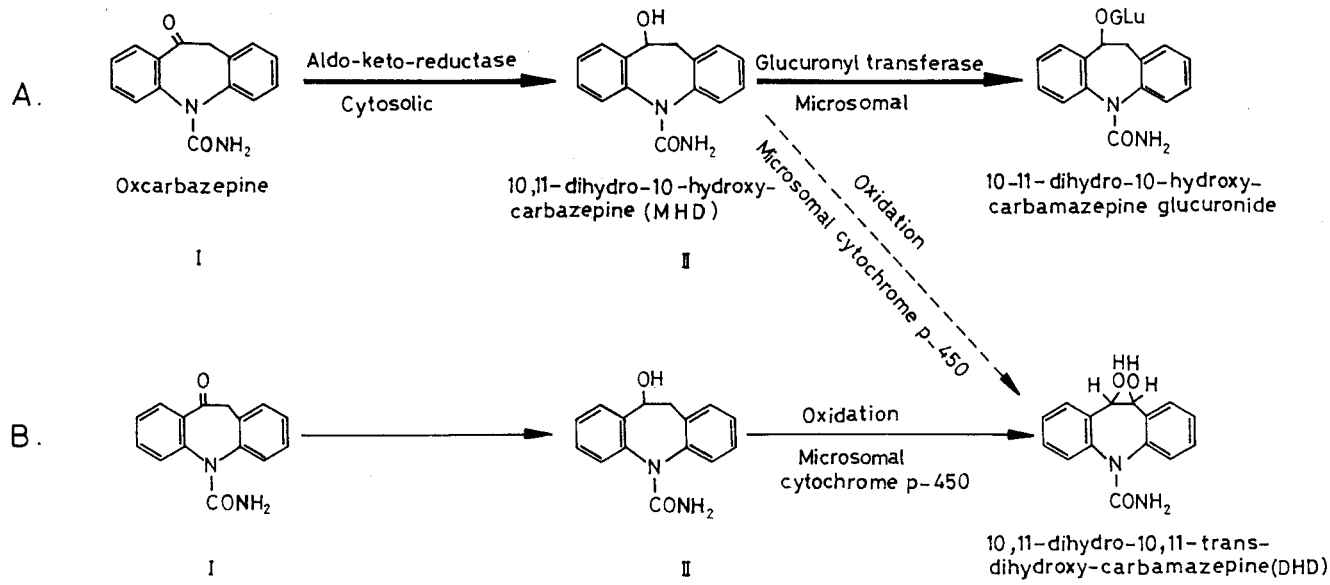

Fig. 1. Metabolic pathways of oxcarbazepine in man (A) and rat (B).

metabolite, CBZ-E (Robbins et al., 1990). The purpose of this study was to investigate the possible influence of repeated doses of VPA on the pharmacokinetics of OXC, a drug closely related to CBZ, in rats.

2. Materials and methods

2.1. Materials

OXC, 10-OH-CBZ and 10-11-epoxycarbamazepine were kindly supplied by Ciba-Geigy (Basle, Switzerland). Sodium valproate, 40 mg ml^{-1} syrup (Epilim®) was from Sanofi Pharma (Manchester, UK). Carboxymethylcellulose (CMC) was purchased from BDH Chemicals (Poole, UK). Acetonitrile (HPLC grade) was purchased from E. Merck (Darmstadt, Germany). HPLC water was prepared using a Milli-Q Water System (Millipore, Bedford, MA, USA). All other reagents were of analytical grade.

2.2. Subjects and experimental procedure

Adult male Sprague–Dawley rats weighing 250–300 g were used in this study. Animals were randomly divided into two (treatment and control) groups. OXC solutions were freshly prepared in 1% carboxymethylcellulose (CMC), and sodium valproate was used as the commercial preparation, 40 mg ml^{-1} syrup (Epilim®), and were administered orally with a feeding needle.

The treatment group ($n = 12$), received VPA (100 mg kg^{-1}, po) daily for 7 days and then in combination with OXC (30 mg kg^{-1}, po) for another week. On the other hand, the control group ($n = 12$) received 1% CMC for 1 week and then OXC (30 mg kg^{-1}, po) was given daily for another week. At the end of the 14-day treatment period, the animals were fasted overnight (water given ad libitum), and cannulation of the left femoral artery with polythene tubing (0.50 mm I.D., 1.0 mm O.D., Portex, Hythe, Kent, UK), was carried out under light ether anesthesia. The other end of the tubing was passed under the emerging at the back of the neck. After flushing it with heparinized saline, the open end of the cannula was closed with a pin plug. Following the surgical procedure, the animals were kept in individual cages and allowed to recover from anesthesia.

After recovery, the animals were given oral doses of OXC (30 mg kg^{-1}, po) alone or in combination with VPA, (100 mg kg^{-1}, po) and returned to their restraining cages. During the subsequent serial sampling of blood, a few drops of blood were routinely discarded to avoid potential contamination and/or dilution with the heparinized saline filling the length of the cannula. In this manner, blood samples (ca. 0.3 ml) for the measurement of OXC were drawn through the indwelling cannula into small plastic centrifuge tubes (LIP, Yorkshire, UK) just before and 0.5, 1, 2, 4, 6, 9, 12, 24 and 36 h after OXC dosing. The cannula was flushed with an equal volume of normal saline to maintain the circulatory volume in the animal. The blood samples were then immediately centrifuged at 3000 rpm for 5 min, and aliquotes 100 μl of plasma samples were stored at −20°C until assay.

2.3. Drug analysis

OXC was determined using a previously described HPLC method (Matar et al., 1995). Briefly, to 0.1 ml of rat plasma, 20 μl of 10,11-epoxycarbamazepine as internal standard (2 μg ml^{-1}) and 0.5 ml of dichloromethane were added.

Chromatography was performed on a reverse phase Novapak C_{18} column (4 μm, 150 mm × 3.9 mm I.D.). The mobile phase consisted of a mixture of 20% v/v acetonitrile in water and the pump (M 501) flow rate was 1.5 ml/min. The effluent was monitored at 215 nm with a variable wavelength UV detector (M 481).

The lower limit of detection of OXC was 50 ng/ml. The interday coefficient of variation ranged between 6.3 to 8.3%.

2.4. Pharmacokinetic and statistical analysis

Pharmacokinetic parameters for OXC were calculated. These included maximum plasma concentration (C_{max}) and time to attain the maximum concentration (T_{max}) which were directly determined from the resulting concentration–time profiles. The elimination rate constant (K_{el}) was calculated from log-linear least-squares regression of the terminal phase data points.

The elimination half-life ($t_{1/2}$) was calculated as 0.693 divided by the elimination rate constant. Non-compartmental model was applied to calculate the area under the plasma concentration–time curve (AUC), which was determined by the linear trapezoidal rule. The area from the last point to infinity was determined by dividing the last plasma concentration by the elimination rate constant. The programme used for the determination of the OXC pharmacokinetic parameters was Kinetica software 2.0.1, 1996–2006 (MicroPharm International, USA). Pharmacokinetic parameters are presented as (mean ± S.E.M.).

The significance level chosen was $P < 0.05$ using a two-tailed unpaired Student's t-test for comparing two means. Evaluation was performed using STAT100 software, version 1.24, 1995–1996 (Biosoft, Cambridge, UK).

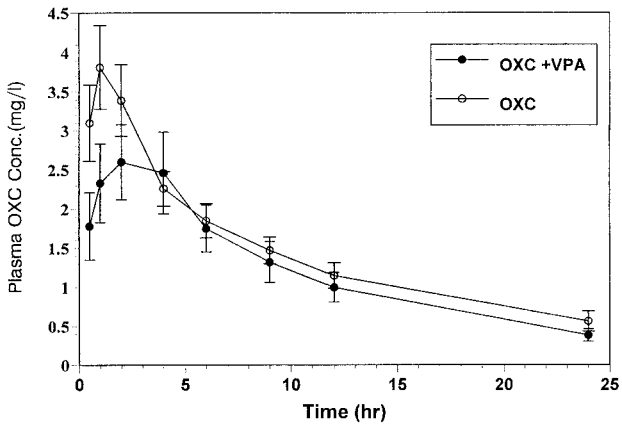

Fig. 2. Mean (±S.E.M.) plasma concentration–time profile of oxcarbazepine (o) when administered alone (30 mg kg^{-1}, po) and after pre-treatment with (100 mg kg^{-1}) valproic acid (•) in rats ($n = 12$).

Table 1
Pharmacokinetic parameters (mean ± S.E.M) for OXC (30 mg kg^{-1}, po) administered alone and in combination with VPA (100 mg kg^{-1}, po) in rats ($n = 12$)

Pharmacokinetic parameter	OXC alone	OXC with VPA
C_{max} (μg ml^{-1})	4.36 ± 0.43	3.21 ± 0.52 *
T_{max} (h)	1.94 ± 0.37	2.53 ± 0.34 *
$t_{1/2}$ (h)	11.74 ± 2.00	9.75 ± 1.76 *
$AUC_{0-\infty}$ (μg h ml^{-1})	46.99 ± 6.65	36.46 ± 5.70 *

* Student's t-test, $P > 0.05$.

3. Results

The mean plasma concentration–time profiles of OXC after oral administration of OXC (30 mg kg^{-1})both alone or in combinations with VPA (100 mg kg^{-1}, po) are shown in Fig. 2. The computed pharmacokinetic parameters are presented in Table 1. VPA did not produce any significant effect on the mean value of OXC pharmacokinetic parameters. Slight but not statistically significant decrease was observed in the maximum plasma concentration during pre-treatment with VPA.

4. Discussion

OXC is chemically related to CBZ but it has completely different metabolic profile. In humans, OXC is rapidly and almost completely reduced to its active metabolite (MHD) with only a minimal amount of the parent drug being found in the blood. This metabolite may partially undergo a further reduction to the DHD form prior to its systemic clearance as a glucuronide conjugate (Lloyd et al., 1994). Therefore, the pharmacokinetics of OXC and MHD are completely controlled by two non-oxidative enzymatic processes (reduction and conjugation). In rats, this reductive biotransformation plays a minor role and levels of the parent drug greatly exceed MHD concentration in plasma (Wagner and Schmid, 1987). The dependent conversion of MHD to DHD plays a minor role in humans, but it

constitutes a major metabolic pathway in rats. By contrast, the principal metabolic route for the structurally related drug, CBZ, involves a microsomal oxidation to its active metabolite (CBZ-E), and subsequent hydrolysis of the latter to an inactive metabolite, *trans*-10,11-dihydroxy-10-11- dihydrocarbamazepine (CBZ-diol).

The metabolic route for VPA involves initial oxidation by the microsomal cytochrome *P*-450 system followed by conjugation to glucuronic acid derivative. Rembeck et al. (1987) reported a decrease in CBZ levels when VPA was concomitantly used with CBZ. Another study reported a significant increase in CBZ-E levels due to inhibition of epoxide hydrolase by VPA (Robbins et al., 1990).

The objective of this study was to find the potential interaction of VPA with OXC, a drug closely related to CBZ. Despite its close structural similarity to CBZ, OXC exhibits a completely different metabolic profile to that of CBZ in both human and laboratory animals. The results of the present study indicate that pre-treatment with VPA did not significantly alter the pharmacokinetics of OXC in the rat. In addition to that, the plasma levels of MHD had not been followed because most of its levels were below the detection limit (20 ng ml^{-1}). This finding is in a good agreement with an earlier report on the interaction of OXC with VPA in healthy subjects and epileptic patients (Tartara et al., 1993). This lack of change in plasma OXC levels in rats pretreated with VPA could be explained on the different metabolic pathways of OXC, which is mainly reduction while VPA undergoes oxidation with a microsomal *P*-450 system.

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