Effect of valpromide on the pharmacokinetics of carbamazepine-10, 11-epoxide

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The single oral dose pharmacokinetics of carbamazepine-10, 11-epoxide (CBZ-E) were investigated in six normal volunteers during a control session and during concurrent treatment with valpromide (VPM) (300 mg twice daily for 8 days). VPM caused a prolongation of the CBZ-E half-life from 6.4 ± 1.4 to 20.5 ± 6.3 h and decreased CBZ-E clearance from 73.5 ± 20.0 to 23.5 ± 4.0 ml h^{-1} kg^{-1} ($P < 0.01$). These results suggest that the elevation of plasma CBZ-E levels in patients receiving carbamazepine and VPM in combination is due to inhibition of epoxide hydrolase in the liver.

Keywords valpromide carbamazepine-10, 11-epoxide epoxide hydrolase

Introduction

A clinically significant drug interaction has been described recently between valpromide (VPM), the amide derivative of valproic acid (VPA), and carbamazepine (CBZ) (Meijer *et al.*, 1985; Pisani *et al.*, 1986). When VPM is added to patients stabilized on CBZ, the plasma levels of the active carbamazepine-10,11-epoxide (CBZ-E) metabolite rise markedly leading to the development of clinical signs of intoxication. The serum levels and the plasma protein binding of unchanged CBZ are not affected by VPM (Pisani *et al.*, 1986).

Although the suggestion has been made that this interaction is mediated by inhibition of the CBZ-E metabolizing enzyme epoxide hydrolase (Pacifici *et al.*, 1985), the influence of VPM on the elimination of the epoxide has never been assessed directly. In this report we describe a three-fold decrease in CBZ-E clearance after direct administration of the metabolite in combination with VPM in normal subjects.

60 kg) took part in the study, which was approved by a local Ethics committee. Each subject received, after an overnight fast, a single 100 mg enteric-coated tablet of CBZ-E on two randomized occasions separated by an interval of at least 2 weeks. On one occasion CBZ-E was given alone, while on the other occasion it was given on the sixth day of treatment with VPM (300 mg twice daily for 8 days). The plasma concentration of CBZ-E was determined by h.p.l.c. (Kumps, 1984) in samples collected for up to 36 h after dosing. Plasma VPM and VPA levels in the same samples were assayed by gas liquid chromatography (Pisani *et al.*, 1979) and enzyme-immunoassay (EMIT), respectively.

Pharmacokinetic parameters for CBZ-E were determined by standard methods (estimates of clearance and volume of distribution are based on the assumption of complete bioavailability) (Spina *et al.*, 1988). Statistical comparisons were made by the Student's *t*-test for paired data.

Methods

Six normal volunteers (four females, two males) aged 18–45 years and weighing 40–71 kg (mean

Results

The plasma level profiles of CBZ-E on the two study occasions were strikingly different (Figure

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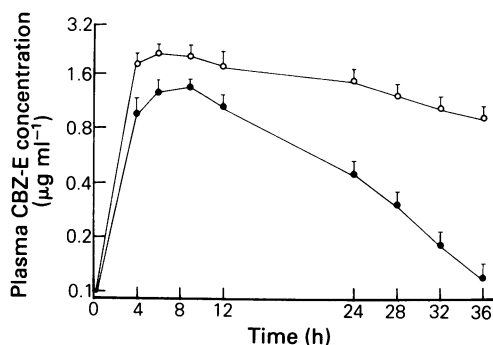
Figure 1   Plasma concentrations of CBZ-E (means ± s.d., $n = 6$) after intake of a 100 mg dose in a control session (●) and during concurrent treatment with VPM (○).

1). Concurrent treatment with VPM did not affect the time of peak CBZ-E concentration, but increased in all subjects the magnitude of the peak and reduced markedly the slope of the elimination phase.

Pharmacokinetic parameters are summarized in Table 1. During treatment with VPM, the half-life of CBZ-E increased from 6.4 ± 1.4 to 20.5 ± 6.3 h ($P < 0.01$), while clearance was reduced to 30% of the control value. The apparent volume of distribution was not affected by VPM.

Plasma VPM levels were below the limit of detection (1.0 μg ml⁻¹) in all samples. Plasma VPA levels in individual samples ranged from 35 to 72 μg ml⁻¹ (mean ± s.d: 50 ± 9 μg ml⁻¹).

Discussion

Since CBZ-E decomposes in gastric juice (Tomson *et al.*, 1983) we used a recently developed enteric-coated formulation which had been found to possess a high (>70%) absolute oral bioavailability (Spina *et al.*, 1988). The kinetic parameters of the epoxide in the control session are in good agreement with those reported after intake of the same formulation (Spina *et al.*, 1988), although in the present study a somewhat smaller volume of distribution was found.

The pronounced changes in CBZ-E half-life and clearance after administration of VPM clearly indicate that the interaction involves an inhibiting effect on the elimination of the epoxide. Since the latter is cleared virtually entirely by conversion to the corresponding diol by epoxide hydrolase (Tomson *et al.*, 1983; Bertilsson & Tomson, 1986), our data can be regarded as strong for evidence for the occurrence of *in vivo* inhibition of this enzyme. Such a mechanism of interaction is further supported by increased plasma levels of CBZ-E during combined therapy with CBZ and VPM (Meijer *et al.*, 1985; Pisani *et al.*, 1986) and by *in vitro* experiments showing that VPM is a powerful inhibitor of epoxide hydrolase in monkey (Pacifici *et al.*, 1985) and human (Pacifici *et al.*, 1986) liver microsomes.

Since VPM undergoes virtually complete first-pass conversion to VPA and only traces of unchanged amide are found in the blood of VPM-treated patients (Bialer *et al.*, 1984; Pisani *et al.*, 1981), the question arises of whether the interaction could be mediated by VPA itself. Although VPA does have a moderate elevating effect on plasma CBZ-E levels, we have recently shown that in epileptic patients treated with CBZ the magnitude of the interaction is much greater after administration of VPM than after intake of VPA doses producing equivalent or even higher VPA levels (Pisani *et al.*, 1986).

Table 1   Pharmacokinetic parameters (means ± s.d., $n = 6$) of CBZ-E in the control session and during treatment with valpromide.

	Control	Valpromide	P value
Peak concentration (μg ml⁻¹)	1.36 ± 0.40	2.10 ± 0.65	<0.01
Time of peak (h)	7.0 ± 1.5	6.2 ± 1.6	NS
Terminal half-life (h)	6.4 ± 1.4	20.5 ± 6.3	<0.01
AUC (μg ml⁻¹ h)	25.4 ± 8.9	77.5 ± 27.7	<0.01
Clearance (ml h⁻¹ kg⁻¹)	73.5 ± 20.1	23.5 ± 4.0	<0.01
Volume of distribution (l kg⁻¹)	0.66 ± 0.15	0.68 ± 0.13	NS

Moreover, substitution of VPA with VPM in patients treated with the CBZ-VPA combination still results in a marked elevation of plasma CBZ-E levels (Meijer *et al.*, 1985). Thus, it can be concluded that the interaction is due predominantly to VPM and that this drug possesses clinically relevant metabolic effects independent from those of its metabolite VPA. It cannot, however, be excluded that it is another VPM metabolite other than VPA, that causes the metabolic interaction.

In the light of the widespread role of epoxide hydrolase in the detoxication of various xenobiotics and reactive metabolites (Pacifici *et al.*, 1985), the clinical implications of the inhibiting effect of VPM treatment might extend far beyond the interaction described in this study.

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