Br. J. clin. Pharmac. (1992), **34**, 85–87

Impairment of carbamazepine-10, 11-epoxide elimination by valnoctamide, a valpromide isomer, in healthy subjects

F. PISANI, A. FAZIO, C. ARTESI, G. OTERI, E. SPINA[3], T. TOMSON[2] & E. PERUCCA[1]
Institute of Neurological and Neurosurgical Sciences, University of Messina and [1]Clinical Pharmacology Unit, University of Pavia, Italy, [2]Department of Clinical Pharmacology at Karolinska Institute, Huddinge, Sweden and [3]Institute of Pharmacology, University of Messina, Messina, Italy

The effect of the valpromide isomer valnoctamide (VCD, 200 mg three times daily for 8 days), an over-the-counter tranquillizer, on the elimination kinetics of a single oral dose of carbamazepine-10, 11-epoxide (CBZ-E, 100 mg) was investigated in healthy subjects. During VCD treatment, the half-life of CBZ-E was prolonged significantly compared with control (19.7 ± 6.7 h *vs* 6.9 ± 2.0 h, means ± s.d., $P < 0.01$), and its oral clearance decreased four-fold (from 109.6 ± 30.7 to 28.8 ± 11.1 ml h^{-1} kg^{-1}, $P < 0.01$). These findings indicate that VCM, like valpromide, strongly inhibits epoxide hydrolase *in vivo*.

Keywords valnoctamide carbamazepine carbamazepine-10,11-epoxide drug interaction

Introduction

Valnoctamide (VCD, valmethamide, 2-ethyl-3-methyl-pentamide) is an isomer of valpromide (VPM), the amide derivative of valproic acid. Unlike VPM, which is used clinically as an antipileptic and an anti-psychotic drug, VCD has been commercially available for several decades as an over-the-counter tranquillizer (Stepansky, 1960). Recently, however, it has been shown that VCD also possesses anticonvulsant activity, suggesting its potential value in the management of seizure disorders (Chambon & Perio, 1980; Haj-Yehia & Bialer, 1990).

A problem associated with the use of VPM in epilepsy is its ability to inhibit epoxide hydrolase (Kerr *et al.*, 1989; Pacifici *et al.*, 1985; Pisani *et al.*, 1988), the enzyme responsible for the elimination of the active 10,11-epoxide metabolite of carbamazepine (CBZ). When VPM is given to patients stabilized on CBZ, the serum concentration of carbamazepine-10,11-epoxide (CBZ-E) increases dramatically, leading to clinical signs of intoxication (Meijer *et al.*, 1984; Pisani *et al.*, 1986).

Before designing clinical trials of VCD in patients with epilepsy, it is important to establish whether this compound causes a similar interaction. In the present report, we provide evidence that VCD is at least as potent as VPM in inhibiting the elimination of CBZ-E.

Methods

Six healthy subjects (four male, two female, age 20–50 years, body weight 50–74 kg) gave their informed consent to take part in the study, which was approved by a local Ethics Committee. Each subject received, after an overnight fast, a single oral dose of CBZ-E (1 × 100 mg enteric-coated tablet) on two occasions, (i) on a control day and (ii) on the 6th day of 8-day treatment with rac-VCD (Nirvanil, Midy, Milan, 1 × 200 mg tablet three times daily). The two CBZ-E dosing sessions were randomized, i.e. the control session either preceded or followed by at least 2 weeks the completion of VCD treatment. No food was allowed for 4 h after CBZ-E intake. Plasma samples for the measurement of CBZ-E by h.p.l.c. (Kumps, 1984) were obtained at 0, 4, 8, 12, 17, 24, 28, 32, 36, 48, 60 and 72 h after each dose.

Pharmacokinetic parameters of CBZ-E were calculated as described previously (Pisani *et al.*, 1990) and evaluated statistically using Student's *t*-test for paired data. Results are expressed as means ± s.d.

Results

Plasma CBZ-E concentrations in the two study sessions are shown in Figure 1, and pharmacokinetic parameters are compared in Table 1.

Co-administration of VCD was associated with a marked increase in the plasma concentrations of CBZ-E. During VCD treatment, the half-life of CBZ-E increased from 6.9 ± 2.0 to 19.7 ± 6.7 h ($P < 0.01$), and its oral clearance decreased from 10 ± 31 to 29 ± 11 ml h^{-1} kg^{-1} ($P < 0.01$).

Correspondence: Dr F. Pisani, Clinica Neurologica, Policlinico Universitario, 98013 Contesse, Messina, Italy

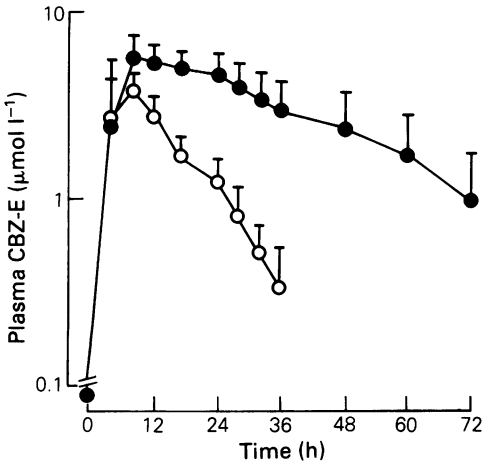

Figure 1 Plasma concentrations of CBZ-E (means ± s.d., $n = 6$) after a single oral dose of the compound (100 mg) in a control session (○) and during treatment with VCD (●) (200 mg three times daily for 8 days).

Table 1 Pharmacokinetic parameters of CBZ-E (means ± s.d., $n = 6$) after a single oral dose of the compound (100 mg) in a control session and during co-administration of VCD (200 mg three times daily for 8 days)

	Control	*VCD*	P *value*
C_{max} (μmol l^{-1})	5.2 ± 2.4	6.0 ± 1.5	NS
t_{max} (h)	7.3 ± 3.0	12.0 ± 6.2	NS
Elimination half-life (h)	6.9 ± 2.0	19.7 ± 6.7	< 0.01
AUC (μmol ml^{-1} h)	63.8 ± 22.5	252.7 ± 103.5	< 0.01
Oral clearance (ml h^{-1} kg^{-1})	110 ± 31	29 ± 11	< 0.01

Discussion

Since CBZ-E is eliminated virtually entirely by conversion to the corresponding diol by epoxide hydrolase (Bertilsson & Tomson, 1986), our findings provide strong evidence for an inhibitory effect of VCD on epoxide hydrolase *in vivo* as predicted by *in vitro* studies with human liver microsomes (Levy, R. H., personal communication).

The magnitude of the interaction caused by VCD was comparable with that observed in a similar study after administration of its isomer VPM at the same dosage (600 mg) (Pisani *et al.*, 1988). Valproic acid also inhibits epoxide hydrolase (Kerr *et al.*, 1989) and impairs the elimination of CBZ-E (Pisani *et al.*, 1990; Robbins *et al.*, 1990), albeit to a much lesser extent compared with either VPM or VCD. The observation that VPM and VCD are much more potent than valproic acid in inhibiting epoxide hydrolase both *in vitro* and *in vivo* strongly suggests that the primary amide group facilitates blockade of enzyme activity. In this respect, it is of interest that, unlike VPM which is extensively deaminated to valproic acid during first pass through the liver (Bialer *et al.*, 1984), VCM undergoes little presystemic conversion to the corresponding acid and is found in the circulation largely in unchanged form (Bialer *et al.*, 1990).

In a preliminary investigation addition of VCM to the therapeutic regimen of epileptic patients stabilized on CBZ was found to cause a 1.5 to 6-fold elevation in serum CBZ-E concentrations, and this was associated in many cases with clinical signs of CBZ intoxication (Pisani *et al.*, unpublished data). Since VCD is widely available as an over-the-counter drug, this interaction may not be easily recognized by medical practitioners. Finally, it should be mentioned that epoxide hydrolases play a vital role in the detoxication of many endogenous reactive metabolites (Pacifici *et al.*, 1985). Therefore, as pointed out for VPM (Pisani *et al.*, 1988), blockade of enzyme activity by VCD could have important and widespread adverse clinical consequences beyond the impairment of CBZ metabolism.

This study was supported by a grant from the Italian Ministry for University and Scientific and Techological Research (40% Project 'Epilessia e Neuromodulatori').

References

Bertilsson, L. & Tomson, T. (1986). Clinical pharmacokinetics and effects of carbamazepine and carbamazepine-10,11-epoxide. An update. *Clin. Pharmacokin.*, **11**, 177–198.

Bialer, M., Rubinstein, A., Dubrovsky, J., Raz, I. & Abramsky, O. (1984). Pharmacokinetics of valpromide after oral administration of a solution and a tablet to healthy volunteers. *Eur. J. clin. Pharmac.*, **27**, 501–503.

Bialer, M., Haj-Yehia, A., Barzaghi, N., Pisani, F. & Perucca, E. (1990). Pharmacokinetics of a valpromide isomer, valnoctamide, in healthy subjects. *Eur. J. clin. Pharmac.*, **38**, 289–291.

Chambon, J. P. & Perio, A. (1980). Valnoctamide: Pharmacological data suggesting an antiepileptic activity. *Neurosci. Lett.*, **5** (Suppl.), S327.

Haj-Yehia, A. & Bialer, M. (1990). Structure pharmacokinetic relationships in a series of short fatty acid amides that possess anticonvulsant activity. *J. pharm. Sci.*, **79**, 719–724.

Kerr, B. M., Rettie, A. E., Eddy, A. C., Loiseau, P., Guyot, M., Wilensky, A. J. & Levy, R. H. (1989). Inhibition of human liver microsomal epoxide hydrolase by valproate and valpromide: *In vitro/in vivo* correlation. *Clin. Pharmac. Ther.*, **46**, 82–93.

Kumps, A. (1984). Simultaneous determination of oxcabazepine, carbamazepine and their metabolites in serum. *J. liquid Chromatogr.*, **7**, 1235–1241.

Meijer, J. W. A., Binnie, C. D., Debets, R. M. C., Van Parys, J. A. P. & De Beer-Pawlikowsky, N. K. B. (1984). Possible hazard of valpromide-carbamazepine combination treatment in epilepsy. *Lancet*, **i**, 802.

Pacifici, G. M., Thomson, T., Bertilsson, L. & Rane, A. (1985). Valpromide/carbamazepine and risk of teratogenicity. *Lancet*, **ii**, 397–398.

Pisani, F., Fazio, A., Oteri, G., Ruello, G., Gitto, C., Russo, F. & Perucca, E. (1986). Sodium valproate and valpromide: Differential interactions with carbamazepine in epileptic patients. *Epilepsia*, **27**, 548–552.

Pisani, F., Fazio, A., Oteri, G., Spina, E., Perucca, E. & Bertilsson, L. (1988). Effect of valpromide on the pharmacokinetics of carbamazepine-10,11-epoxide. *Br. J. clin. Pharmac.*, **25**, 611–613.

Pisani, F., Caputo, M., Fazio, A., Oteri, G., Russo, M., Spina, E., Perucca, E. & Bertilsson, L. (1990). Interaction of carbamazepine-10,11-epoxide, an active metabolite of carbamazepine, with valproate: A pharmacokinetic study. *Epilepsia*, **31**, 339–342.

Robbins, D. K., Wedlund, P. J., Kuhn, R., Baumann, R. J., Levy, R. H. & Chang, S. L. (1990). Inhibition of epoxide hydrolase by valproic acid in epileptic patients receiving carbamazepine. *Br. J. clin. Pharmac.*, **29**, 759–762.

Stepansky, W. (1960). A clinical study on the use of valmethamide, an anxiety reducing drug. *Curr. Ther. Res.*, **2**, 144–149.

(*Received 14 October 1991, accepted 13 February 1992*)