The mechanism of the carbamazepine-valproate interaction in humans

I. Bernus, R. G. Dickinson, W. D. Hooper & M. J. Eadie

Department of Medicine, The University of Queensland, Royal Brisbane Hospital, Herston, Brisbane, Australia

Aims The study investigated the mechanism of the interaction between valproate and carbamazepine which causes raised plasma carbamazepine-10,11-epoxide concentrations with unchanged plasma carbamazepine concentrations. This interaction has usually been attributed to valproate inhibiting epoxide hydrolase, the enzyme that catalyses the biotransformation of carbamazepine-10,11-epoxide to carbamazepine-10,11-trans-diol.

Methods Clearances of plasma carbamazepine, carbamazepine-epoxide and carbamazepine-diol to relevant carbamazepine metabolites present in urine were measured under steady-state conditions in 17 adults receiving carbamazepine as anticonvulsant monotherapy, and in 10 adults taking the drug together with valproate.

Results Plasma carbamazepine-epoxide concentrations were higher, relative to carbamazepine dose, in the co-medicated patients. Plasma apparent clearances of carbamazepine, relative to drug dose, were similar whether or not valproate was taken. Formation clearances of carbamazepine-10,11-trans-diol conjugate, and probably of carbamazepine-10,11-trans-diol, were lower in subjects co-medicated with valproate, and a higher proportion of the carbamazepine dose was excreted in urine as carbamazepine-10,11-epoxide.

Conclusions Valproate appears to inhibit the glucuronidation of carbamazepine-10,11-trans-diol, and probably also inhibits the conversion of carbamazepine-10,11-epoxide to this trans-diol derivative, rather than simply inhibiting the latter reaction only.

Keywords: carbamazepine-valproate interaction, carbamazepine-trans-diol, carbamazepine-epoxide, epoxide hydrolase, glucuronidation

Introduction

Administration of the anticonvulsant valproate (VPA) to patients taking carbamazepine (CBZ) is associated with a rise in the plasma concentration of the CBZ metabolite carbamazepine-10,11-epoxide (CBZ-epoxide) without any appreciable change in the plasma concentration of CBZ itself [1–5]. This interaction may go unrecognised if plasma concentrations of CBZ alone are monitored. However, it may have clinical consequences, since CBZ-epoxide is a reasonably potent anticonvulsant and sedative in its own right. The usually accepted mechanism of the interaction is inhibition of CBZ-epoxide conversion to carbamazepine-10,11-trans-diol (CBZ-diol) [6]. This reaction is catalysed by microsomal epoxide hydrolase. However, certain published clinical and biochemical data are not entirely consistent with this belief. We have therefore attempted to determine the mechanism of the interaction in humans under therapeutic conditions, by studying steady-state clearances of CBZ to most of its recognised urinary metabolites in epileptic patients who received the drug either as anticonvulsant monotherapy, or in combination with valproate.

Correspondence Professor M. J. Eadie, Department of Medicine, The University of Queensland, Royal Brisbane Hospital, Herston, Brisbane, Australia.

Methods

Subjects

The study was carried out in two groups of informed consenting adult epileptic patients, 17 receiving carbamazepine alone (the CBZ group) and 10 receiving it with sodium valproate (the VPA-CBZ group). The characteristics of the 17 patients in the CBZ group have been described in another publication dealing with the mechanism of the dose-dependent clearance of CBZ [7]. The characteristics of the 10 VPA-CBZ comedicated patients are shown in Table 1. The CBZ group comprised 4 males and 13 females, and the VPA-CBZ group 5 males and 5 females (% male 23.5% *vs* 50%: difference = −26.5%: 95% C.I. = −63.4% to 10.5%). The mean ages of subjects were: CBZ group 60.6 ± s.d. 9.8 years; VPA-CBZ group 40.9 ± 15.8 years (difference = 19.7 years; 95% C.I. = 9.6 to 29.9 years). The mean daily CBZ doses in the two groups were reasonably similar: 9.22 ± s.d. 4.19 mg kg^{-1} *vs* 9.90 ± s.d. 3.08 mg kg^{-1}: difference = 0.69 mg kg^{-1}; 95% C.I. = −2.45 to 3.85 mg kg^{-1}.

Study protocol

Subjects were studied under expected steady-state conditions for all drug therapies, employing a protocol approved by

Table 1 Personal details of the subjects in the VPA-CBZ group (details of the CBZ group have been published [7]).

Subject	Age (years)	Sex	Weight (kg)	CBZ dose (mg day^{-1})	VPA dose (mg day^{-1})	Co-medication
1	61	M	70	800	2500	Vigabatrin; captopril; digoxin; ranitidine
2	30	F	65	500	1000	
3	50	M	90	1200	5400	Naproxen; allopurinol; oxycodone; paracetamol; frusemide; methdilazine; nifedipine; simvastatin; orphenadrine
4	43	F	45	400	1000	
5	28	F	73	1000	1000	Folic acid
6	53	F	75	600	1200	
7	62	M	89	600	1000	Aspirin; temazepam; frusemide; salbutamol; paracetamol
8	20	M	70	600	1500	
9	43	F	65	400	1800	Cortisone; fludrocortisone; thyroxine
10	20	M	55	800	3000	Vigabatrin

the Royal Brisbane Hospital Institutional Ethics Committee. Studies were carried out over two consecutive 24 h periods in each subject. Subjects emptied their bladders at the start of the collection period; thereafter all urine passed was collected until each study concluded. Predose (trough) venous blood was collected at the mid-point of each study for estimation of plasma concentrations of CBZ, CBZ-epoxide and CBZ-diol. The following substances were measured in urine: CBZ, CBZ-epoxide, CBZ-diol, CBZ-acridan, 2-hydroxy-CBZ (2-OH-CBZ) and 3-hydroxy-CBZ (3-OH-CBZ). Except for CBZ and CBZ-epoxide, all the above substances were measured both before and after hydrolysis with β-glucuronidase (from *Helix pomatia*, type H-2, Sigma Chemical Co., St Louis, MO). Thus each unconjugated metabolite was measured directly, and its conjugated counterpart was measured by subtracting the value for the unconjugated metabolite from that for the corresponding total metabolite.

The h.p.l.c. assay methods used have been described previously [7, 8]. The intra-assay variability was $\leq 4\%$ and the inter-assay variability $\leq 6\%$ for CBZ, CBZ-epoxide, CBZ-acridan, 2-OH-CBZ and 3-OH-CBZ at concentrations of 2, 10 and 40 mg l^{-1}, and for CBZ-diol at concentrations of 5, 20 and 200 mg l^{-1}. Limits of quantification were 0.25 mg l^{-1} for CBZ and 0.05 mg l^{-1} for its metabolites.

Data analysis

Steady-state clearances were calculated as follows: for CBZ itself, CL/*F* as oral dose per day/mid-interval plasma concentration; for formation of each of the various metabolites studied, sum of the amount(s) of that metabolite and all measured substances derived from it excreted in urine per day/mid-interval plasma concentration of the metabolite, e.g. for CBZ-epoxide, sum of amounts of CBZ-epoxide, CBZ-diol (unconjugated) and CBZ-diol conjugate excreted in urine over 24 h/mid-interval plasma CBZ-epoxide concentration. Values for the CBZ and the VPA-CBZ groups, and for the outcomes of linear regression analyses carried out on the plasma concentration and clearance data, were compared by conventional statistical methods.

Results

Plasma concentration: dose relationships

The equations for the linear regressions for plasma concentration of (i) CBZ (ii) CBZ-epoxide (iii) unconjugated CBZ-diol and (iv) conjugated CBZ-diol, on carbamazepine daily dose per unit body weight, for the CBZ and the VPA-CBZ groups, are shown in Table 2. There was a statistically significant difference between the groups only for one pair of regressions, that for plasma CBZ-epoxide concentration on CBZ dose. The plasma CBZ-epoxide concentrations tended to be higher, relative to drug dose, in the patients comedicated with VPA, whereas the plasma concentrations of CBZ, and unconjugated and conjugated CBZ-diol, relative to CBZ dose, did not differ between the two sets of subjects. This confirmed the existence of the previously described CBZ-VPA interaction, which yields increased plasma CBZ-epoxide concentrations, in the co-medicated subjects studied.

Plasma CBZ apparent clearance (CL/F)

The plasma apparent clearance (CL/*F*) of CBZ is dose-dependent [7]. Regressions for CL/*F* on CBZ dose did not differ significantly between the CBZ group (CL/*F* = 35.20 ± 6.265 CBZ dose/wt; mean value = 92.8 ± 33.1 l day^{-1}; $r^2 = 0.6316$; $P < 0.0001$) and the VPA-CBZ group (CL/*F* = 62.57 ± 3.539 CBZ dose/wt; mean value = 97.6 ± 29.2 l day^{-1}; $r^2 = 0.1395$; $P = 0.288$) in respect to the slopes of the regression lines (difference = 2.726; $F = 0.8594$, df = 1,23, $P = 0.364$) or to the height difference (separation) between the lines (difference = −0.86 l day^{-1}; $F = 0.0070$; df 1,14; $P = 0.8685$)—(Figure 1a).

Table 2 Equations for linear regressions ($y = a + bx$) for plasma concentration ($mg\,l^{-1}$) of CBZ, CBZ-epoxide and unconjugated and conjugated CBZ-diol on CBZ dose/weight (x) for the CBZ group and the CBZ-VPA group.

	CBZ group	*CBZ-VPA group*	*Difference*	*95% C.I.*
Plasma CBZ				
a	4.67	3.12		
b	0.42	0.410	−0.168	−0.664 to 0.328
mean *y* (s.d.)	6.89 (2.22)	7.18 (2.06)		
line separation			−0.093	−1.68 to 1.49
Plasma CBZ-epoxide				
a	0.918	−0.256		
b	0.043	0.199	−0.155	−0.253 to −0.058*
mean *y* (s.d.)	1.32 (0.38)	1.72 (0.74)		
line separation			−0.341	−0.716 to 0.034
Plasma unconjugated CBZ-diol				
a	0.536	−0.667		
b	0.228	0.364	−0.136	−0.350 to 0.077
mean *y* (s.d.)	2.64 (1.23)	2.93 (1.41)		
line separation			−0.116	−0.818 to 0.586
Plasma conjugated CBZ-diol				
a	0.094	0.172		
b	0.027	0.006	0.021	−0.032 to 0.073
mean *y* (s.d.)	0.339 (0.250)	0.231 (0.134)		
line separation			0.123	−0.044 to 0.291

* = $P < 0.05$.

Metabolite excretions in urine

The mean percentages of the CBZ dose recovered in urine as parent substance plus derived metabolites were very similar for the CBZ group and the VPA-CBZ group ($48.6 \pm 14.8\%$ and $46.4 \pm 11.3\%$ respectively: difference 2.2%; 95% CI = −9.0% to 13.4%).

Percentages of the CBZ dose excreted in urine as the various metabolites studied in the two patient groups are shown in Table 3. The only statistically significant differences between the groups were: (i) a higher mean percentage of the CBZ dose was excreted as CBZ-epoxide in the CBZ-VPA subjects (1.59% *vs* 1.07%) and (ii) a lower mean percentage of the dose was excreted as CBZ-diol conjugate in this group (7.13% *vs* 9.78%).

Formation clearances of CBZ metabolites

The calculated values of the formation clearances of the various CBZ metabolites studied in the CBZ group and the CBZ-VPA group are compared in Table 4, where the comparisons are also shown after exclusion of one outlying subject, who had a very aberrant CBZ-diol conjugate formation clearance. There were no statistically significant differences in mean formation clearance for any metabolite before exclusion of the outlier: after exclusion, mean formation clearance of CBZ-diol conjugate was statistically significantly lower in the CBZ-VPA group (17.58 ± 4.80 *vs* $24.14 \pm 5.81\ l\ day^{-1}$).

Steady-state plasma apparent clearance of CBZ is known to be dose-dependent [7]. Hence some of the formation clearances of CBZ metabolites might also be dose-dependent. This proved to be the case for the formation clearances of CBZ-epoxide and CBZ-diol, but not for those of the other metabolites. Therefore the regressions for formation clearance on CBZ dose for CBZ-epoxide and CBZ-diol were compared for the CBZ group and the CBZ-VPA group (Figure 1b and 1c, where the regression equations are shown in the legend and, purely for comparison, similar data are shown for CBZ-diol conjugate—Figure 1d). With the outlier excluded, the regressions for CBZ-epoxide formation clearance did not differ between the two Groups (slopes: $F = 0.7623$; df = 1,22; $P = 0.392$: line separations: $F = 0.1831$; df = 1,23; $P = 0.623$). The regressions for CBZ-diol formation clearance did differ (slopes: $F = 3.498$; df = 1,22; $P = 0.075$: line separation: $F = 4.541$; df = 1,23; $P = 0.044$). Thus in subjects co-medicated with VPA, the regression analysis suggested a statistically significantly lower formation clearance of CBZ-diol. A lower formation clearance of CBZ-diol conjugate had also been found, so that two consecutive stages in the epoxide-diol pathway appeared to be inhibited by VPA.

Discussion

It is generally accepted that biological oxidation of CBZ to its epoxide, followed successively by hydration of CBZ-epoxide to CBZ-diol, and then conjugation of the diol with glucuronic acid, comprises the main metabolic pathway of the drug in humans [9]. Recognition of the existence of the valproate-carbamazepine interaction has usually depended on simultaneous measurement of plasma CBZ and CBZ-epoxide concentrations. These measurements have repeatedly shown higher plasma levels of the epoxide in the presence of relatively unchanged levels of the parent drug i.e. raised CBZ-epoxide/CBZ ratios, when CBZ and VPA are taken together [1, 10–14]. Inhibition of microsomal epoxide hydrolase activity would suffice to account for this

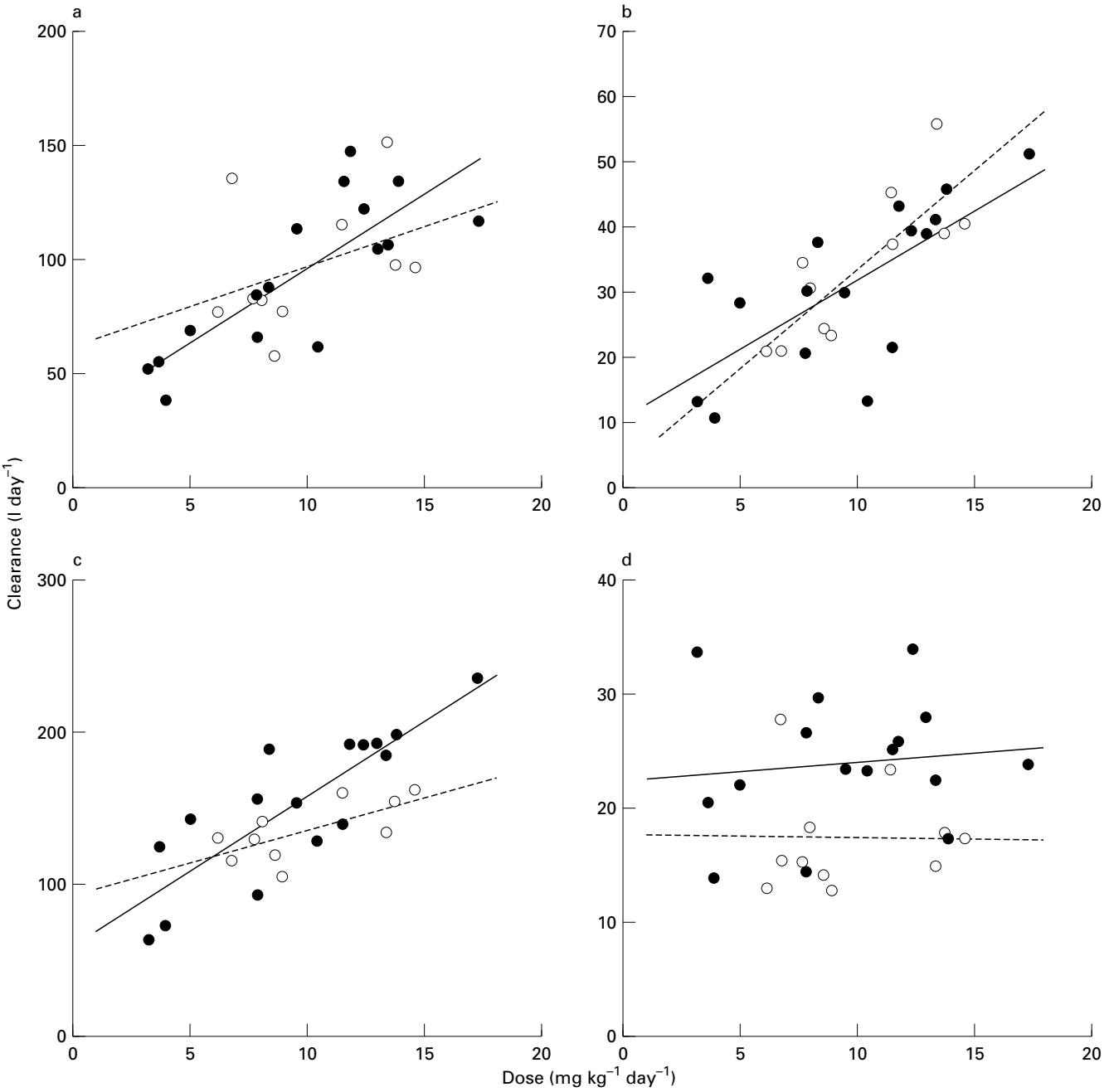

Figure 1 a) Linear regressions for plasma CBZ apparent clearance (CL/*F*) on CBZ dose for the CBZ group (solid circles and continuous line: y = 35.20 + 6.27 dose/wt: $r^2 = 0.6313$, $P < 0.0001$) and the CBZ-VPA group (open circles, broken line: y = 62.57 + 3.54 dose/wt: $r^2 = 0.1395$, $P = 0.2878$). b) Linear regressions for CBZ-epoxide formation clearance on CBZ dose for the CBZ group (solid circles and continuous line: y = 10.69 + 2.15 dose/wt: $r^2 = 0.5053$, $P = 0.002$) and the CBZ-VPA group (open circles and broken line: y = 3.04 + 3.08 dose/wt: $r^2 = 0.6498$, $P = 0.005$). c) Linear regressions for unconjugated CBZ-diol formation clearance on CBZ dose for the CBZ group (solid circles and continuous line: y = 59.57 + 9.90 dose/wt: $r^2 = 0.6997$, $P < 0.0001$) and the CBZ-VPA group (open circles and broken line: y = 92.70 + 4.32 dose/wt: $r^2 = 0.4663$, $P = 0.030$). d) Linear regressions for CBZ-diol conjugate formation clearance on CBZ dose for the CBZ group (solid circles and continuous line: y = 39.91 − 1.210 dose/wt: $r^2 = 0.0650$, $P = 0.3233$) and the CBZ-VPA group (open circles and broken line: y = 17.85 − 0.027 dose/wt: $r^2 = 0.0003$, $P = 0.962$). Neither regression is statistically significant and the regression lines are drawn only to permit comparison with the other graphs.

finding, though it is not the only theoretical possibility. Published attempts to define the mechanisms of the interaction experimentally have led to somewhat ambiguous outcomes. Thus, in humans, Levy *et al.* [10] found valproate comedication caused a fall in plasma carbamazepine concentration, but they gave VPA for only 6 days, which may not have been long enough for a new CBZ steady state to develop. Subsequently, under probable steady-state conditions in humans, this group of workers obtained evidence that valproate intake led to a decreased formation clearance of CBZ-diol [5]. Pisani *et al.* [15] found a decreased plasma clearance of a single dose of CBZ-epoxide given to persons taking valproate, consistent with decreased microsomal epoxide hydrolase activity or a decrease in metabolism further along the epoxide-diol pathway. Mattson *et al.* [16] showed that VPA reduced the plasma protein binding of

Table 3 Mean percentages of the carbamazepine dose excreted in urine as various carbamazepine metabolites.

Metabolite	*CBZ alone*	*CBZ-VPA*	*Difference*	*95% C.I.*
CBZ-epoxide	1.07 ± 0.39	1.59 ± 0.72	0.52	0.08 to 0.95†
Unconjugated CBZ-diol	22.69 ± 8.01	26.38 ± 7.74	3.69	−2.81 to 10.19
Conjugated CBZ-diol*	9.78 ± 2.87	7.13 ± 1.54	2.65	0.60 to 4.69†
CBZ-acridan	0.19 ± 0.22	0.17 ± 0.10	0.03	−0.13 to 0.18
CBZ-acridan conjugate	4.00 ± 1.39	3.57 ± 1.41	0.43	−0.72 to 1.57
2-OH-CBZ	0.05 ± 0.03	0.04 ± 0.02	0.01	−0.02 to 0.03
2-OH-CBZ conjugate	3.01 ± 1.12	2.79 ± 0.71	0.22	−0.59 to 1.03
3-OH-CBZ	0.10 ± 0.10	0.11 ± 0.06	0.01	−0.08 to 0.06
3-OH-CBZ conjugate	4.07 ± 1.83	3.70 ± 1.58	0.37	−1.06 to 1.79

*one grossly outlying value excluded.
†$P < 0.05$.

Table 4. Mean formation clearances ($l\ day^{-1}$) of various carbamazepine metabolites. Values in [ ] apply when one outlying carbamazepine-diol conjugate value is omitted.

Substance	*CBZ alone*	*CBZ-VPA*	*Difference*	*95% C.I.*
CBZ-epoxide	33.09 ± 14.52	33.50 ± 11.76	0.410	−10.7 to 11.6
	[31.13 ± 11.47]	[33.50 ± 11.76]	[1.40]	−7.79 to 12.5
Unconjugated	159.0 ± 51.9	135.5 ± 19.49	23.5	−11.9 to 58.9
CBZ-diol	[153.8 ± 48.83]	[135.5 ± 19.49]	[18.3]	−15.3 to 51.9
Conjugated	28.76 ± 19.86	17.58 ± 4.80	11.18	−2.07 to 24.4
CBZ-diol	[24.14 ± 5.81]	[17.58 ± 4.80]	[6.56]	2.05 to 11.10*
CBZ acridan	3.70 ± 0.35	3.38 ± 0.28	0.33	−0.71 to 1.36
2-OH-CBZ	2.51 ± 0.20	2.72 ± 0.31	0.21	−0.53 to 0.94
3-OH-CBZ	3.49 ± 0.28	3.77 ± 0.49	0.28	−0.79 to 1.36

* = $P < 0.05$.

CBZ, *in vitro*. In monkeys, Levy *et al.* [10] showed that VPA decreased the plasma protein binding of both CBZ and its epoxide, and decreased the elimination clearance of CBZ-epoxide, again consistent with decreased epoxide hydrolase activity (or with decreased glucuronidation of CBZ-diol). Subsequently Chang & Levy [17, 18] in the isolated perfused rat liver found that VPA decreased the formation clearance of CBZ-epoxide and the intrinsic clearances of CBZ, but also the clearance of CBZ-epoxide, again consistent with inhibition of epoxide hydrolase or of diol glucuronidation. However, the *in vitro* biochemical studies of Pacifici *et al.* [19] failed to show inhibition of epoxide hydrolase activity by CBZ, a finding which deterred acceptance of the hypothesis that VPA raised plasma CBZ-epoxide concentrations by inhibiting the enzyme responsible for its further metabolism. Later Kerr *et al.* [5] showed that VPA (at 100 μM, but not at the more therapeutically relevant concentration of 10 μM) did inhibit microsomal epoxide hydrolase. Since the publication of this result the mechanism of the interaction seems to have been generally accepted, at least tacitly, to be microsomal epoxide hydrolase inhibition. However, discordant observations continued to appear. Thus Miller *et al.* [20] noted that, unexpectedly, CBZ clearance fell in humans when VPA was withdrawn from CBZ-VPA combination therapy. This should not have occurred if microsomal epoxide hydrolase activity or CBZ-diol conjugation had become disinhibited after VPA was no longer present, and was more suggestive of decreased activation of CBZ oxidation. Omtzigt *et al.* [21] found that, in pregnant women, VPA co-medication led to lowered plasma CBZ levels, slightly raised CBZ-epoxide levels and to a decreased proportion of the CBZ dose being excreted in urine as CBZ-diol (unconjugated plus conjugated). While pregnancy itself is known to alter CBZ metabolism [8], this finding was not consistent with microsomal epoxide hydrolase inhibition as the sole metabolic alteration present in the valproate comedicated subjects. Svinarov & Pippenger [22] measured plasma (unconjugated) CBZ-diol levels as well as simultaneous CBZ and CBZ-epoxide levels. In those taking VPA plus CBZ there were raised plasma levels of CBZ and of both of its metabolites (though CBZ levels were increased only in children). On this basis they concluded that VPA was a general inhibitor of the epoxide-diol pathway, and not purely an inhibitor of the epoxide hydrolase catalysed stage.

The studies described in the present paper have gone further than previous published work in humans, by measuring not only the plasma concentrations of all known metabolites on the epoxide-diol pathway, but the simultaneous urinary excretions of these metabolites and also the excretions of the drug's acridan and phenolic metabolites. The studies also related the clearances to the CBZ dose,

where some of the clearances proved to be dose dependent. Since the apparent clearance of oral CBZ in the present study exceeded the sum of the formation clearances of the CBZ derivatives measured in urine, it is possible that the oral bioavailability of CBZ was incomplete and/or that the interaction between CBZ and VPA may have involved CBZ metabolites other than those studied, as well as those investigated.

In the present study the plasma concentrations of CBZ and its epoxide-diol pathway metabolites behaved as described by Svinarov & Pippenger [22] for adults and by Omzigt *et al.* [21] for pregnant women when VPA was co-administered. Assuming that the oral bioavailability of CBZ did not change when VPA was co-administered, the proportion of the CBZ dose excreted into urine as CBZ-epoxide was higher, and the proportion excreted as CBZ-diol conjugate was lower, when the CBZ-VPA interaction was present, whereas the proportions of the dose excreted as the remaining epoxide-diol pathway metabolite CBZ-diol, and as acridan and phenolic derivatives, were unaltered. These findings, and the behaviour of the CBZ metabolite formation clearances in the presence of VPA, were consistent with unaltered oxidation of CBZ to CBZ-epoxide, but probable decreased conversion of CBZ-epoxide to CBZ-diol and decreased conjugation of the CBZ-diol. Inhibition of these consecutive stages of the epoxide-diol pathway would be consonant with raised plasma CBZ-epoxide concentrations in the presence of unaltered plasma concentrations of CBZ itself and its diol and diol-conjugate derivatives, and with an increased proportion of the CBZ dose appearing in urine as CBZ-epoxide, and a decreased proportion as CBZ-diol conjugate.

The present study has thus defined the mechanism of the CBZ-VPA interaction in humans in greater detail than hitherto, and shown that VPA probably inhibits not one but two consecutive stages of the CBZ-epoxide-diol pathway. The first stage is catalysed by microsomal epoxide hydrolase, and the second by a UDP-glucuronyl transferase. Glucuronidation is a major pathway of VPA elimination in humans, and instances of VPA co-administration inhibiting drug or drug metabolite glucuronidations are known e.g. zidovudine [23], lamotrigine [24], *p*-hydroxyphenobarbitone [25, 26]. Thus there are recognised precedents to the suggestion that VPA inhibits CBZ-diol glucuronidation. Indeed the question might be asked as to whether VPA (or a VPA metabolite) acts separately to inhibit two consecutive stages of the epoxide-diol pathway, or whether inhibition of CBZ-diol glucuronidation leads to inhibition of microsomal epoxide hydrolase activity via a product inhibition mechanism.

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(*Received 8 July 1996, accepted 6 February 1997*)