Effect of sodium valproate on carbamazepine disposition and psychomotor profile in man

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1 The effect of sodium valproate (VPA; 500 mg thrice daily for 7 days) and matched placebo on the disposition and psychomotor profile of a single dose of carbamazepine (CBZ; 10 mg kg⁻¹) was studied in eight healthy male subjects using a randomised balanced crossover design.

2 VPA alone had no effect on antipyrine clearance, urinary 6 β -hydroxycortisol excretion and a battery of psychomotor function tests after 3 days' treatment despite achieving a mean steady-state concentration (90 ± 6 mg l⁻¹) well within the target range (50–100 mg l⁻¹) for the drug.

3 VPA pre-treatment did not alter total CBZ area under the concentration-time curve (AUC 0–59 h) but did prolong CBZ elimination half life by 12% ($P < 0.01$). AUC 0–59 h for free plasma CBZ was 13% higher ($P < 0.02$) and half-life of unbound CBZ 16% longer ($P < 0.02$) during VPA treatment. CBZ-10,11 epoxide (CBZ-E) levels (52%) and CBZ-E/CBZ ratios (45%) were both elevated by concurrent VPA ($P < 0.05$) and free CBZ fraction was increased by 7% ($P < 0.02$).

4 The sole effect of VPA on the psychomotor profile of CBZ was prolongation of card sorting time ($P < 0.05$), although CBZ-related side effects were reported as more severe when VPA was also taken ($P < 0.01$).

5 These data suggest that VPA displaces CBZ from plasma protein binding sites and inhibits the metabolism of both the parent drug and its epoxide. The effect of VPA on the psychomotor profile of a large single dose of CBZ was minimal.

6 Further studies in epileptic patients receiving both these anticonvulsant drugs are warranted to appraise the extent and clinical relevance of their interaction.

Keywords carbamazepine sodium valproate epilepsy psychomotor function enzyme inhibition protein binding drug metabolism

Introduction

Sodium valproate (VPA), the sodium salt of valproic acid, is a broad spectrum anticonvulsant drug (Richens & Ahmed, 1975; Gram *et al.*, 1979; Covanis *et al.*, 1982; Callaghan *et al.*,

1982), which is now recognised as a first line agent for the management of partial and generalized seizures (Callaghan *et al.*, 1985; Turnbull *et al.*, 1985). Its branched chain fatty acid structure

bestows a pharmacokinetic profile that differs from other anticonvulsant drugs (Eadie, 1984). Saturable plasma protein binding is evident at clinically relevant concentrations (Bowdle *et al.*, 1980; Marty *et al.*, 1982), while VPA elimination proceeds via pathways of glucuronidation and fatty acid oxidation (Schobben, 1983). Pharmacokinetic interactions occur with older anticonvulsant drugs, for example, displacement of phenytoin from its binding sites on circulating albumin (Monks *et al.*, 1978; Cramer & Mattson, 1979; Levy & Koch, 1982) and inhibition of the metabolism of phenytoin (Bruni *et al.*, 1979; Perucca *et al.*, 1980), phenobarbitone (Kape-tanovic *et al.*, 1981) and ethosuximide (Mattson & Cramer, 1980; Pisani *et al.*, 1984a).

VPA is often used in combination with carbamazepine (CBZ), another first line anticonvulsant, in the treatment of intractable seizures. Like phenytoin, CBZ is recognised to accelerate VPA metabolism (Bowdle *et al.*, 1979; Levy & Koch, 1982), but the reciprocal effect of VPA on CBZ disposition is less clearly defined. The major active metabolite of CBZ is CBZ 10,11 epoxide (CBZ-E) (Frigerio & Morselli, 1975) and an increased CBZ-E/CBZ ratio has been reported in patients and healthy subjects receiving VPA and CBZ in combination (McKauge *et al.*, 1981; Brodie *et al.*, 1983; Levy *et al.*, 1984). Conversely total CBZ plasma concentrations have been noted to rise (Jeavons & Clark, 1974), decrease (Levy *et al.*, 1984) or show no change (Flachs *et al.*, 1979) when concurrent VPA is introduced. Lack of consensus among investigators may be partly related to the additional effect of VPA in displacing CBZ from the binding sites on circulating albumen (Mattson *et al.*, 1982; Levy *et al.*, 1984).

We report a placebo controlled prospective study of the effect of VPA on the disposition of a single large CBZ dose in healthy subjects. A battery of psychomotor function tests have been incorporated to attempt to quantify any dynamic interaction.

Methods

Subjects

Eight healthy male Caucasian subjects aged 21–45 years were studied. None had clinical or laboratory evidence of hepatic, renal or haematological abnormality and only one smoked cigarettes. No other drugs were ingested in the month preceding the study or during the experimental period. Subjects were also invited to refrain from alcohol. The study had the approval

of the Western Infirmary Ethics Committee and written informed consent was obtained from all participants.

Protocol

The study had a randomised, balanced, double-blind, cross-over design. Each subject was asked to ingest VPA 500 mg thrice daily and placebo at 08.00 h, 16.00 h and 00.00 h for 1 week. A single oral dose of CBZ (10 mg kg⁻¹) was administered at 22.00 h on day 4 of both treatment schedules. Drug free interval between the two arms of the study was at least 2 weeks.

Venous blood sampling was performed at 08.00 h, 12.00 h and 16.00 h on days 3, 5 and 6 for circulating VPA levels, and 10, 12, 14, 16, 18, 35, 38, 42 and 59 h after each dose of CBZ for total and free CBZ and CBZ-E concentrations.

Antipyrine kinetics and 24 h urinary 6 β -hydroxycortisol excretion were measured at baseline prior to each arm, on day 3 of VPA or placebo treatment and after each dose of CBZ. Antipyrine 600 mg was administered orally at 09.00 h and saliva collected for assay at 3, 5, 8, 12, 24 and 36 h after dosing. Twenty-four hour urine was collected for measurement of steroid excretion.

Psychomotor function tests

Subjects were pre-trained prior to entry and completed a battery of psychomotor function tests and side effect scores at 08.00 h, 12.00 h and 16.00 h on three study days during each arm. These were at baseline prior to drug ingestion, on the 3rd day of treatment with VPA or placebo and again on day 5 following CBZ ingestion. The tests employed had previously been shown to detect psychomotor impairment at comparable CBZ dosing (Macphee *et al.*, 1986a).

Critical flicker fusion threshold (CFFT), recognition (CRT1) and total choice reaction (CRT2) times, card sorting ability, finger tapping rate, and visual analogue sedation scoring were performed as previously described (Macphee *et al.*, 1986a). CFFT response was determined by the mean of three ascending and three descending frequencies of flicker and CRT was recorded as the mean time to extinguish 30 stimulus presentations, both tests using the Leeds psychomotor tester (Hindmarch, 1980). Card sorting ability was estimated by noting the time taken to sort a pack of conventional playing cards into 13 congruent sets. Finger tapping rate with the index finger of the dominant hand on a calculator keyboard was timed over 60 s.

Sedation was assessed using a 10 cm visual

analogue scale with end-points of 'wide-awake' and 'nearly asleep'. Subjects were also asked to report any side effects experienced from a list of those recognised to be associated with both drugs together with a number of 'dummy' symptoms such as pruritus, facial pain, constipation, dyspnoea and cough. They were graded on 10 cm visual analogue scales with higher scores representing increased severity.

Analyses

Blood samples were taken into heparinised tubes, immediately centrifuged and the plasma stored at -20°C until analysis which was performed within 1 week of freezing. Total VPA ($\text{mg l}^{-1} \times 6.98 = \mu\text{mol l}^{-1}$) and CBZ ($\text{mg l}^{-1} \times 4.23 = \mu\text{mol l}^{-1}$) concentrations were obtained by enzyme immunoassay (Emit, Syva) and free CBZ levels were determined by equilibrium dialysis and enzyme immunoassay as previously described (Macphee *et al.*, 1986a). CBZ-E ($\text{mg l}^{-1} \times 3.96 = \mu\text{mol l}^{-1}$) and antipyrine concentrations were assayed by h.p.l.c. methodology (Macphee *et al.*, 1984). 6 β -hydroxycortisol was measured by a sensitive, specific radioimmunoassay (Park, 1978).

Antipyrine kinetics and total and free CBZ elimination half-lives were calculated by linear regression using the method of least squares. Areas under the concentration-time curves (AUC 0–59 h) were calculated for total and free CBZ and CBZ-E concentrations, CBZ-E/CBZ ratios and free CBZ fractions using the trapezoidal rule.

Statistics were performed on parameters of CBZ disposition, antipyrine kinetics and 6 β -hydroxycortisol excretion using Student's *t*-test for paired values. Psychomotor function data were examined by repeated measure analysis of variance, except for sedation and side effect visual analogue scores which were compared using the Wilcoxon rank sum test. Correlations between mean daily total VPA concentrations and changes in CBZ disposition were explored using Kendall's rank correlation.

Results

Mean ($\pm$ s.e. mean) plasma VPA concentrations on days 3, 5 and 6 were $90 \pm 6 \text{ mg l}^{-1}$, $91 \pm 8 \text{ mg l}^{-1}$ and $79 \pm 10 \text{ mg l}^{-1}$ respectively, indicating that the drug had reached steady-state by day 5 when CBZ was administered. Total and free plasma CBZ elimination half-lives during both treatments are shown in Figure 1. Total CBZ half-lives were prolonged by a mean of 12% ($P <$

Figure 1 Elimination half-lives (mean $\pm$ s.e. mean) for total and free plasma carbamazepine (CBZ) following a single oral dose of 10 mg kg^{-1} in eight subjects receiving sodium valproate 500 mg thrice daily and matched placebo. Statistics were obtained by Student's *t*-test for paired values.

0.01), and free CBZ half lives by 16% ($P < 0.02$) during VPA therapy. Other changes in CBZ disposition associated with combined treatment are shown in Table 1. AUC 0–59 h for free CBZ was increased by 13% ($P < 0.02$), but significant differences in total circulating CBZ AUC 0–59 h were not detected. AUC 0–59 h for CBZ free fraction was 7% higher during VPA treatment ($P < 0.05$). CBZ-E concentrations and CBZ-E/CBZ ratios during both arms are shown in Figure 2. Overall, CBZ-E AUC 0–59 h was increased by 52% ($P < 0.05$) and CBZ-E/CBZ AUC by 45% ($P < 0.05$) in the VPA arm of the study. No significant relationships were detected between individual mean VPA concentrations and changes in CBZ free concentration, CBZ free fraction, CBZ-E concentrations or CBZ-E/CBZ ratio expressed as the difference in AUC 0–59 h between the two treatment arms.

Antipyrine metabolism was unaffected by VPA treatment. Mean ($\pm$ s.e. mean) apparent clearance values were similar on day 3 (VPA: $0.98 \pm 0.16 \text{ ml min}^{-1} \text{ kg}^{-1}$; placebo: $1.04 \pm 0.14 \text{ ml min}^{-1} \text{ kg}^{-1}$) and day 5 (VPA: $1.10 \pm 0.2 \text{ ml min}^{-1} \text{ kg}^{-1}$; placebo: $1.06 \pm 0.13 \text{ ml min}^{-1} \text{ kg}^{-1}$). Daily urinary 6 β -hydroxycortisol excretion did not demonstrate any significant alteration on day 3 (VPA: $468 \pm 111 \mu\text{g } 24 \text{ h}^{-1}$; placebo $327 \pm 53 \mu\text{g } 24 \text{ h}^{-1}$) or on day 5 (VPA: $303 \pm 52 \mu\text{g}$

Table 1 Areas under the concentration-time curve (AUC 0–59 h) and elimination half-lives ($t_{1/2}$) for total and free plasma carbamazepine (CBZ) concentrations and AUC for CBZ 10,11 epoxide concentrations (CBZ-E), CBZ-E/CBZ ratios and free CBZ fractions in eight healthy subjects following treatment with sodium valproate and placebo

Treatment	Total CBZ		Free CBZ		CBZ-E	CBZ-E/CBZ	Free CBZ fractions
	AUC ($\text{mg l}^{-1} \text{ h}$)	$t_{1/2}$ (h)	AUC ($\text{mg l}^{-1} \text{ h}$)	$t_{1/2}$ (h)	AUC ($\text{mg l}^{-1} \text{ h}$)	AUC (% h^{-1})	AUC (% h^{-1})
Valproate	319 $\pm$ 22 $P = 0.5$	29.3 $\pm$ 2.1 $P < 0.01$	86 $\pm$ 4 $P < 0.02$	37.1 $\pm$ 2.8 $P < 0.02$	35 $\pm$ 3 $P < 0.05$	679 $\pm$ 48 $P < 0.05$	1481 $\pm$ 58 $P < 0.05$
Placebo	305 $\pm$ 22	26.2 $\pm$ 1.6	76 $\pm$ 5	31.9 $\pm$ 2.1	23 $\pm$ 3	467 $\pm$ 59	1382 $\pm$ 39

Values are mean $\pm$ s.e. mean

CBZ $\text{mg l}^{-1} \times 4.23 \mu\text{mol l}^{-1}$, CBZ-E $\text{mg l}^{-1} \times 3.96 = \mu\text{mol l}^{-1}$.

Statistics by Student's paired t -test.

Figure 2 Serial mean ($\pm$ s.e. mean) plasma concentrations of carbamazepine 10,11 epoxide (CBZ-E) and CBZ-E/CBZ ratios following a single oral dose of 10 mg kg^{-1} CBZ in eight subjects receiving sodium valproate 500 mg thrice daily ($\bullet$) and matched placebo ($\circ$).

24 h^{-1} ; placebo: 403 $\pm$ 86 $\mu\text{g 24 h}^{-1}$). There were no significant changes in either measure of hepatic monooxygenase activity when comparing pre-treatment values with those obtained 3 or 5 days later.

Total CBZ concentrations were similar during both treatment arms immediately following each psychomotor test session (Table 2). Although free CBZ and CBZ-E levels tended to be higher

during VPA administration, these differences were not statistically significant when considered at each discrete time point. Psychomotor function was similar at baseline prior to entry of each study arm excluding any carry-over effect. The data obtained before and after CBZ administration during both phases are shown in Table 3. VPA alone did not produce a decrement in performance in any of the tests. VPA treatment was, however, associated with a small increase in card sorting time ($P < 0.05$) during CBZ treatment. The other objective measures of psychomotor function did not differ, although a trend to longer reaction times and sedation scores was apparent. Total side effects scores of symptoms recognised to be associated with CBZ neurotoxicity are shown in Table 4. These were significantly elevated at all time points during the VPA arm of the study ($P < 0.01$). None of the dummy symptoms was similarly affected.

Discussion

CBZ is a lipid-soluble drug, around 75% of which is bound to albumen in the circulation (Pynnonen, 1979). Its major pathway of elimination is via the formation of CBZ 10,11 epoxide, although hydroxylation and direct N-glucuronidation also take place (Eichelbaum *et al.*, 1985). CBZ displays dose-dependent hetero- and auto-induction (Rapeport *et al.*, 1983), which may result in temporary loss of seizure control in some patients (Macphée & Brodie, 1985). Neurotoxic side effects such as diplopia, ataxia, dizziness and headache may manifest over a wide range of plasma concentrations (Hoppener *et al.*, 1980; Blennow, 1983; Tomson, 1984; Macphée *et al.*, 1986c). The disposition of CBZ may be affected by a variety of drugs including enzyme inducing anticonvulsants such as phenytoin which accelerate its metabolism (Christiansen

Table 2 Mean ($\pm$ s.e. mean) carbamazepine (CBZ) and CBZ 10,11 epoxide (CBZ-E) concentrations immediately following each psychomotor testing session

		08.00 h	12.00 h	16.00 h
Total CBZ (mg l ⁻¹)	Valproate	8.9 $\pm$ 0.6	8.3 $\pm$ 0.5	7.6 $\pm$ 0.5
	Placebo	8.7 $\pm$ 0.6	8.3 $\pm$ 0.4	7.4 $\pm$ 0.5
Free CBZ (ml l ⁻¹)	Valproate	2.23 $\pm$ 0.1	2.0 $\pm$ 0.12	1.99 $\pm$ 0.1
	Placebo	2.13 $\pm$ 0.2	2.0 $\pm$ 0.14	1.78 $\pm$ 0.1
Total CBZ-E (mg l ⁻¹)	Valproate	0.48 $\pm$ 0.06	0.57 $\pm$ 0.06	0.68 $\pm$ 0.05
	Placebo	0.46 $\pm$ 0.08	0.50 $\pm$ 0.06	0.48 $\pm$ 0.06

CBZ mg l⁻¹ $\times$ 4.23 = μ mol l⁻¹, CBZ-E mg l⁻¹ $\times$ 3.96 = μ mol l⁻¹.

Table 3 Card sorting time (CS), recognition (CRT1) and total choice reaction time (CRT2), critical flicker fusion threshold (CFFT), finger tapping rate (FT) and sedation score (SS) following sodium valproate or placebo (Day 3) and carbamazepine/valproate or carbamazepine/placebo (Day 5) in eight subjects

Test	Treatment	Day 3			Day 5		
		08.00 h	12.00 h	16.00 h	08.00 h	12.00 h	16.00 h
CS (s)	Valproate	52.3 $\pm$ 3	51 $\pm$ 3	53.9 $\pm$ 3	58.6 $\pm$ 3*	55.6 $\pm$ 3*	57.2 $\pm$ 3*
	Placebo	54.1 $\pm$ 4	52 $\pm$ 3	49.5 $\pm$ 2	54.6 $\pm$ 3	52 $\pm$ 2	52.8 $\pm$ 2
CRT1 (ms)	Valproate	368 $\pm$ 12	377 $\pm$ 16	379 $\pm$ 17	395 $\pm$ 12	391 $\pm$ 13	397 $\pm$ 13
	Placebo	375 $\pm$ 9	389 $\pm$ 10	384 $\pm$ 14	387 $\pm$ 11	380 $\pm$ 12	386 $\pm$ 15
CRT2 (ms)	Valproate	535 $\pm$ 19	543 $\pm$ 19	549 $\pm$ 22	584 $\pm$ 14	564 $\pm$ 24	576 $\pm$ 20
	Placebo	533 $\pm$ 14	598 $\pm$ 18	530 $\pm$ 19	547 $\pm$ 15	533 $\pm$ 18	536 $\pm$ 19
CFFT (Hz)	Valproate	30.8 $\pm$ 0.6	30.5 $\pm$ 0.7	30.1 $\pm$ 0.5	27.4 $\pm$ 0.2	28.4 $\pm$ 0.4	27.9 $\pm$ 0.4
	Placebo	29.5 $\pm$ 0.3	29.6 $\pm$ 0.5	29.5 $\pm$ 0.4	28.5 $\pm$ 0.5	28.2 $\pm$ 0.5	28.8 $\pm$ 0.7
FT (number min ⁻¹)	Valproate	358 $\pm$ 6	364 $\pm$ 5	361 $\pm$ 7	339 $\pm$ 8	345 $\pm$ 8	345 $\pm$ 7
	Placebo	353 $\pm$ 8	353 $\pm$ 8	356 $\pm$ 7	347 $\pm$ 8	349 $\pm$ 7	356 $\pm$ 9
SS (cm)	Valproate	12.8 $\pm$ 3	9.8 $\pm$ 3	12 $\pm$ 4	38.2 $\pm$ 7	32 $\pm$ 7	24.4 $\pm$ 5
	Placebo	11.1 $\pm$ 4	10 $\pm$ 3	11.4 $\pm$ 3	35.7 $\pm$ 6	24 $\pm$ 4	20.5 $\pm$ 9

Values are mean $\pm$ s.e. mean. Statistics obtained by repeated measures analysis of variance for CS, CRT1, CRT2, CFFT, FT and Wilcoxon rank sum test for SS, * P < 0.05.

Table 4 Side effect scores in eight subjects at 10–18 h following a dose of carbamazepine (10 mg kg⁻¹) with sodium valproate (VPA) and placebo (P)

Side effect	08.00 h		12.00 h		16.00 h	
	VPA	P	VPA	P	VPA	P
Diplopia (2)	13 (0–25)	16 (0–32)	0 (0–0)	7 (0–13)	0 (0–0)	0 (0–0)
Ataxia (7)	31 (4–65)	23 (0–62)	15 (0–38)	7 (0–33)	22 (0–34)	4 (0–11)
Headache (3)	23 (0–35)	0 (0–0)	15 (3–22)	4 (0–12)	6 (0–19)	14 (0–41)
Nausea (4)	49 (15–80)	25 (0–86)	36 (9–80)	8 (0–33)	26 (3–52)	0 (0–0)
Dry mouth (5)	36 (5–86)	27 (0–85)	35 (3–82)	12 (0–39)	18 (0–34)	10 (0–51)
Mean	152	91	101	38	52	28
	< P 0.01		P < 0.01		P < 0.01	

Values are mean (range) in cm in subjects reporting side effects.

Figures in parenthesis following side effect are number of subjects reporting individual side effects. Statistics were obtained by Wilcoxon rank sum test on cumulative data between VPA and P phases.

& Dam, 1973) or by inhibiting drugs which reduce its clearance. Inhibitory interactions have been reported with cimetidine (Macphee *et al.*, 1984), diltiazem (Brodie & Macphee, 1986), erythromycin (Wong *et al.*, 1983), isoniazid (Wright *et al.*, 1982), verapamil (Macphee *et al.*, 1986b), viloxazine (Pisani *et al.*, 1984b) and danazol (Kramer *et al.*, 1986).

The average increase of 7% in CBZ free fraction observed during VPA treatment in our subjects is almost identical to that reported *in vitro* (Mattson *et al.*, 1982) and previously in healthy volunteers (Levy *et al.*, 1984). While the *in vitro* investigation demonstrated a concentration-dependent increase in CBZ displacement, such a correlation between subjects was not demonstrable in our study. This may be explained by the relatively narrow range of plasma VPA concentrations achieved and the considerable intra dose fluctuation that occurs in unbound VPA levels (Marty *et al.*, 1982).

This study has confirmed the increase in CBZ-E concentrations and ratio of CBZ-E/CBZ previously reported at a single time point during concurrent CBZ and VPA treatment (McKauge *et al.*, 1981; Brodie *et al.*, 1983; Levy *et al.*, 1984). Although phenytoin and phenobarbitone also elevate concentrations of CBZ-E during combination therapy (McKauge *et al.*, 1981) this is considered to arise through induction of the epoxide-diol pathway, a mechanism unlikely to account for the changes observed in this study. The effect of CBZ-E metabolism by VPA would best be explained by inhibition of its metabolism as has been previously reported in the Rhesus monkey and in man (Levy *et al.*, 1984) and demonstrated in isolated perfused rat liver (Chang & Levy, 1985).

The prolonged elimination half-life and increased AUC for free plasma CBZ in the face of such small changes in total CBZ suggests that VPA-mediated inhibition of parent drug and epoxide metabolism may occur concurrently. This is supported by data from Chang & Levy (1985) using perfused rat liver. The considerable variation in CBZ concentrations during a dosage interval (Hoppener *et al.*, 1980; Blennow, 1983; Paxton *et al.*, 1983; Macphee *et al.*, 1987) may obscure small rises in circulating CBZ. Alternatively any inhibitory effect on parent drug metabolism may be offset by an increase in auto-induction during chronic CBZ therapy. Interestingly, VPA did not inhibit antipyrine metabolism significantly at relatively high concentrations of the drug unlike other enzyme inhibiting drugs that modify CBZ disposition, such as cimetidine (Macphee *et al.*, 1984) and verapamil (Rumiantsev *et al.*, 1986).

Psychomotor tests were performed to identify a possible synergistic effect of VPA on the neurotoxic profile of CBZ. The tests selected had previously been found to be sensitive to CBZ administration (Macphee *et al.*, 1986a). The day 3 comparison with placebo suggests that VPA alone has no important acute effect on psychomotor function. This is in general agreement with previous studies which have reported, at worst, only isolated decrements in cognitive function with the drug (Harding & Pullan, 1977; Sommerbeck *et al.*, 1977; Thompson & Trimble, 1981). VPA treatment had a minor effect on the objective psychomotor test profile of CBZ. Interestingly, subjective side-effect monitoring appeared more sensitive to possible VPA influences.

A small increase in the free fraction of CBZ following addition of VPA is unlikely to provoke sustained toxicity, although transient accentuation of side effects may be anticipated. However, if inhibition of CBZ metabolism persists during chronic therapy then significant elevations in free CBZ concentration may accrue. The increase in CBZ-E concentrations during VPA treatment may also contribute, as both in animal models (Frigerio & Morselli, 1975) and in patients with trigeminal neuralgia (Tomson & Bertilsson, 1984), CBZ and CBZ-E appear to have equipotent pharmacological activity. CBZ-E may itself provoke neurotoxic symptoms similar to CBZ (Patsalos *et al.*, 1985). Patients receiving large doses of CBZ may be particularly susceptible to such toxicity because of pre-existent high concentration of CBZ-E due to autoinduction of the epoxide-diol pathway (Brodie *et al.*, 1983; Bertilsson *et al.*, 1986). Appropriate use of this anticonvulsant combination may require monitoring of CBZ-E as well as the parent drug to optimise treatment schedules. Similarly, alterations in CBZ or VPA concentrations may become apparent in patients taking both drugs if one or other is withdrawn.

The interaction between CBZ and VPA is reciprocal and complex. This emphasises the desirability of anticonvulsant monotherapy wherever possible. Unfortunately nearly 25% of all epileptic patients remain uncontrolled despite 'optimal treatment' with one anticonvulsant drug (Reynolds *et al.*, 1983). Hence, a combination of first line agents such as CBZ and VPA is frequently prescribed. Further studies in such patients are required to ascertain the extent and clinical relevance of their interaction.

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References

- Bertilsson, L., Tomson, T. & Tybring, G. (1986). Pharmacokinetics: Time-dependent changes—autoinduction of carbamazepine epoxidation. *J. clin. Pharmacol.*, **26**, 459–462.
- Blennow, G. (1983). Adverse effects from the circadian fluctuations of carbamazepine plasma levels. *Acta Paediatr. Scand.*, **72**, 397–401.
- Bowdle, T. A., Levy, R. H. & Cutler, R. E. (1979). Effects of carbamazepine on valproic acid kinetics in normal subjects. *Clin. Pharmacol. Ther.*, **26**, 629–634.
- Bowdle, T. A., Patel, I. H., Levy, R. H. & Wilensky, A. J. (1980). Valproic acid dosage and plasma protein binding and clearance. *Clin. Pharmacol. Ther.*, **28**, 486–492.
- Brodie, M. J., Forrest, G. & Rapeport, W. G. (1983). Carbamazepine 10,11 epoxide concentrations in epileptics on carbamazepine alone and in combination with other anticonvulsants. *Br. J. clin. Pharmacol.*, **16**, 747–750.
- Brodie, M. J. & Macphee, G. J. A. (1986). Carbamazepine neurotoxicity precipitated by diltiazem. *Br. med. J.*, **292**, 1170–1171.
- Bruni, J., Wilder, B. J., Willmore, I. J. & Barbour, B. (1979). Valproic acid and plasma levels of serum phenytoin. *Neurology*, **29**, 904–905.
- Callaghan, N., O'Hare, J., O'Driscoll, D., O'Neill, B. & Daly, M. (1982). Comparative study of ethosuximide and sodium valproate in the treatment of typical absence seizures (petit mal). *Dev. Med. Child Neurol.*, **24**, 830–836.
- Callaghan, N., Kenny, R. A., O'Neill, B., Crowley, M. & Goggin, T. (1985). A prospective study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy. *J. Neurol. Neurosurg. Psychiatr.*, **48**, 639–644.
- Chang, S. L. & Levy, R. H. (1985). Inhibition of epoxidation of carbamazepine by valproic acid in the isolated perfused rat liver. *J. Pharmacokin. Biopharm.*, **5**, 453–466.
- Christiansen, J. & Dam, M. (1973). Influence of phenobarbital and dephenylhydantoin on plasma carbamazepine levels in patients with epilepsy. *Acta Neurol. Scand.*, **49**, 543–546.
- Covanis, A., Gupta, A. K. & Jeavons, P. M. (1982). Sodium valproate: monotherapy and polytherapy. *Epilepsia*, **23**, 693–720.
- Cramer, J. A. & Mattson, R. H. (1979). Valproic acid: *in vitro* plasma protein binding and interactions with phenytoin. *Ther. Drug Monit.*, **1**, 105–116.
- Eadie, M. J. (1984). Anticonvulsant drugs. *Drugs*, **27**, 328–363.
- Eichelbaum, M., Tomson, T., Tybring, G. & Bertilsson, L. (1985). Carbamazepine metabolism in man: induction and pharmacogenetic aspects. *Clin. Pharmacokin.*, **10**, 80–90.
- Flachs, H., Gram, L., Wurtz-Jorgensen, A. & Parnes, J. (1979). Drug levels of other antiepileptic drugs during concomitant treatment with sodium valproate. *Epilepsia*, **20**, 187.
- Frigerio, A. & Morselli, P. L. (1975). Carbamazepine: Biotransformation. In *Advances in Neurology*, Vol 11, eds. Penry, J. K. & Daly, D. D., pp. 295–308. New York: Raven Press.
- Gram, L., Flachs, H., Wurtz-Jorgensen, A. Parnes, J. & Anderson, B. (1979). Sodium valproate, serum levels and clinical effect: A controlled study. *Epilepsia*, **20**, 303–312.
- Harding, G. F. A. & Pullan, J. J. (1977). The effect of sodium valproate on the EEG, the photosensitive range, the CNV and reaction-time. *Electroenceph. clin. Neurophysiol.*, **43**, 465.
- Hindmarch, I. (1980). Psychomotor function and psychoactive drugs. *Br. J. clin. Pharmacol.*, **10**, 189–209.
- Hoppener, R. J., Kuyser, A., Meijer, J. W. A. & Hulsman, J. (1980). Correlation between daily fluctuations of carbamazepine serum levels and intermittent side effects. *Epilepsia*, **21**, 341–350.
- Jeavons, P. M. & Clark, J. E. (1974). Sodium valproate in the treatment of epilepsy. *Br. med. J.*, **2**, 584–586.
- Kapetanovic, I. M., Kupferberg, H. J., Porter, R. J., Theodore, W., Schulman, E. & Penry, J. K. (1981). Mechanism of valproate-phenobarbital interaction in epileptic patients. *Clin. Pharmacol. Ther.*, **29**, 480–486.
- Kramer, G., Theisohn, F., Von Unruh, G. E. & Eichelbaum, M. (1986). Carbamazepine-danazol drug interaction: Its mechanism examined by a stable isotope technique. *Ther. Drug Monit.*, **8**, 387–392.
- Levy, R. H. & Koch, K. M. (1982). Drug interactions with valproic acid. *Drugs*, **24**, 543–556.
- Levy, R. H., Moreland, T. A., Morselli, P. L., Guyot, M., Brachet-Lierman, A. & Loiseau, P. (1984). Carbamazepine/valproic acid interaction in man and rhesus monkey. *Epilepsia*, **25**, 338–345.
- Macphee, G. J. A. & Brodie, M. J. (1985). Carbamazepine substitution in severe partial epilepsy: implication of auto-induction of metabolism. *Postgrad. med. J.*, **61**, 779–783.
- Macphee, G. J. A., Butler, E. & Brodie, M. J. (1987). Intra dose and circadian variation in circulating carbamazepine and its epoxide in epileptic patients: a consequence of auto-induction of metabolism. *Epilepsia*, **28**, 286–294.
- Macphee, G. J. A., Goldie, C., Roulston, D., Potter, L., Agnew, E., Laidlaw, J. & Brodie, M. J. (1986a). Effect of carbamazepine on psychomotor performance in naive subjects. *Eur. J. clin. Pharmacol.*, **30**, 37–42.
- Macphee, G. J. A., McInnes, G. T., Thompson, G. G. & Brodie, M. J. (1986b). Verapamil potentiates carbamazepine neurotoxicity: a clinically important inhibitory interaction. *Lancet*, **i**, 700–703.
- Macphee, G. J. A., McPhail, E. M., Butler, E. & Brodie, M. J. (1986c). Controlled evaluation of a supplementary dose of carbamazepine on psychomotor function in epileptic patients. *Eur. J. clin. Pharmacol.*, **31**, 195–199.
- Macphee, G. J. A., Thompson, G. G., Scobie, G., Agnew, E., Park, B. K., Murray, T., McColl,

- K. E. L. & Brodie, M. J. (1984). Effects of cimetidine on carbamazepine auto- and hetero-induction in man. *Br. J. clin. Pharmacol.*, **18**, 411–419.
- Marty, J. J., Kilpatrick, C. J., Moulds, R. F. W. (1982). Intra dose variation in plasma protein binding of sodium valproate in epileptic patients. *Br. J. clin. Pharmacol.*, **14**, 399–404.
- Mattson, R. H. & Cramer, J. A. (1980). Valproic acid and ethosuximide interaction. *Ann. Neurol.*, **7**, 583–584.
- Mattson, G. F., Mattson, R. H. & Cramer, J. A. (1982). Interaction between valproic acid and carbamazepine in an *in vitro* study of protein binding. *Ther. Drug Monit.*, **43**, 181–184.
- McKague, L., Tyrer, J. & Eadie, M. J. (1981). Factors influencing simultaneous concentrations of carbamazepine and its epoxide in plasma. *Ther. Drug Monit.*, **3**, 63–70.
- Monks, A., Boobis, S., Wadsworth, J. & Richens, A. (1978). Plasma protein binding interaction between phenytoin and valproic acid *in vitro*. *Br. J. clin. Pharmacol.*, **6**, 487–492.
- Park, B. K. (1978). A direct radioimmunoassay for 6 β -hydroxycortisol in human urine. *J. steroid Biochem.*, **9**, 963–969.
- Patsalos, P. N., Stephenson, J. J., Krishna, S., Elyas, A. A., Lascelles, P. T. & Wiles, C. M. (1985). Side effects induced by carbamazepine 10,11 epoxide. *Lancet*, **ii**, 496.
- Paxton, J. W., Aman, M. G. & Werry, J. S. (1983). Fluctuations in salivary carbamazepine and carbamazepine-10,11 epoxide concentrations during the day in epileptic children. *Epilepsia*, **24**, 716–724.
- Perucca, E., Hebdige, S., Frigo, G. M., Gatti, G., Lecchini, S. & Crema, A. (1980). Interaction between phenytoin and valproic acid: plasma protein binding and metabolic effects. *Clin. Pharmacol. Ther.*, **28**, 779–789.
- Pisani, F., Narbone, M. C., Fazio, A., Crisafulli, P., Primerano, G., D'Agostino, A. A., Oteri, G. & Di Perri, R. (1984b). Effect of viloxazine on serum carbamazepine levels in epileptic patients. *Epilepsia*, **25**, 482–485.
- Pisani, F., Narbone, M. C., Trunfio, C., Fazio, A., La Rosa, G., Oteri, G. & Di Perri, R. (1984a). Valproic acid—ethosuximide interaction: a pharmacokinetic study. *Epilepsia*, **25**, 229–233.
- Pynnonen, S. (1979). Pharmacokinetics of carbamazepine in man: a review. *Ther. Drug Monit.*, **1**, 409–431.
- Rapeport, W. G., McInnes, G. T., Thompson, G. G., Forrest, G., Park, B. K. & Brodie, M. J. (1983). Hepatic enzyme induction and leucocyte delta aminolaevulinic acid synthase activity: studies with carbamazepine. *Br. J. clin. Pharmacol.*, **16**, 133–137.
- Reynolds, E. H., Elwes, R. D. C. & Shorvon, S. D. (1983). Why does epilepsy become intractable? *Lancet*, **ii**, 952–954.
- Richens, A. & Ahmed, S. (1975). Controlled trial of sodium valproate in severe epilepsy. *Br. med. J.*, **4**, 255–256.
- Rumiantsev, D. U., Piotrovski, V. K., Riabokon, O. S., Slastnikova, I. D., Kokurina, E. V. & Metelitsa, V. I. (1986). The effect of oral verapamil therapy on antipyrine clearance. *Br. J. clin. Pharmacol.*, **22**, 606–609.
- Schobben, F. (1983). Valproic acid: pharmacokinetic aspects. *Br. J. clin. Pract.*, (symp suppl) **27**, 48–51.
- Sommerbeck, K. W., Theilgaard, A., Rasmussen, K. E., Lohren, V., Gram, L. & Wulff, K. (1977). Valproate sodium: evaluation of the so-called psychotropic effect: a controlled study. *Epilepsia*, **18**, 159–166.
- Thompson, P. J. & Trimble, M. R. (1981). Sodium valproate and cognitive functioning in normal volunteers. *Br. J. clin. Pharmacol.*, **12**, 819–824.
- Tomson, T. (1984). Interdose fluctuations in plasma carbamazepine concentration determine intermittent side effects. *Arch. Neurol.*, **41**, 830–834.
- Tomson, T. & Bertillon, L. (1984). Potent therapeutic effect of carbamazepine 10,11 epoxide in trigeminal neuralgia. *Arch. Neurol.*, **41**, 598–601.
- Turnbull, D. M., Howell, D., Rawlins, M. D. & Chadwick, D. W. (1985). Which drug for the adult epileptic patient: phenytoin or valproate? *Br. med. J.*, **290**, 815–819.
- Wong, Y. Y., Ludden, T. M., Bell, R. D. (1983). Effect of erythromycin on carbamazepine kinetics. *Clin. Pharmacol. Ther.*, **33**, 460–464.
- Wright, J. M., Stokes, E. F. & Sweeney, V. P. (1982). Isoniazid induced carbamazepine toxicity and vice versa. *New Engl. J. Med.*, **307**, 1325–1327.

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