Effect of the removal of individual antiepileptic drugs on antipyrine kinetics, in patients taking polytherapy

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1 Antipyrine (AP) clearance, half-life and volume of distribution were determined in 52 patients, taking one or more antiepileptic drug (AED), before and 4 weeks after the complete removal of phenytoin (PHT, $n = 20$), carbamazepine (CBZ, $n = 15$) and sodium valproate (VPA, $n = 17$).

2 PHT removal was associated with a mean 13% fall in AP clearance and a mean 16% increase in AP half-life, in patients who were also taking CBZ with or without barbiturates. There was no significant difference between patients who did, and did not, take barbiturates, in addition to CBZ.

3 CBZ removal was associated with a mean 45% fall in AP clearance and a mean 69% increase in AP half-life, if there was no inducing AED comedication, but had no effect on AP clearance and half-life if PHT and/or barbiturates were also being taken.

4 Removal of VPA had no effect on AP clearance or half-life.

5 The removal of PHT, CBZ and VPA had no significant effect on AP volume of distribution.

6 PHT appears to be a more powerful inducer of hepatic enzyme activity, as measured by the AP test, than is CBZ.

Keywords enzyme induction antipyrine kinetics antiepileptic drugs polytherapy reduction drug interactions

Introduction

Therapeutic doses of the antiepileptic drugs (AEDs) phenytoin (PHT), carbamazepine (CBZ) and phenobarbitone (PB) are potent hepatic enzyme (mixed function oxidase) inducers (Petruch *et al.*, 1974; Roberts *et al.*, 1976; Moreland *et al.*, 1982; Rapeport *et al.*, 1983; Park *et al.*, 1984; Shaw *et al.*, 1985). In contrast, sodium valproate (VPA) does not have any significant enzyme inducing properties (Oxley *et al.*, 1979; Perucca & Richens, 1980; Perucca *et al.*, 1984).

Antipyrine (AP) serum clearance (CL) and half-life ($t_{1/2}$) are useful indices of hepatic enzyme activity (Park, 1982; Boobis *et al.*, 1981). Oral

AP is rapidly and completely absorbed and the CL of oral and intravenously administered AP is very similar in epileptic patients taking enzyme-inducing AEDs (Rimmer *et al.*, 1986).

Enzyme induction by drugs has been shown to be partially additive (Ohnhaus *et al.*, 1983). Cross-sectional studies of patients with epilepsy (Perucca & Richens, 1980; Perucca *et al.*, 1984) found that, at doses used clinically, PHT, CBZ, primidone (PRM) and PB resulted in similar increases in AP CL. Further, there was no evidence that a combination of inducing AEDs had an additive effect, on AP CL, over a single AED. The implication of these studies is that a therapeutic

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dose of one inducing AED may cause maximal induction of AP metabolizing enzymes and that adding, or withdrawing, a second AED may have no further effect. These studies were cross-sectional in design and therefore there are inherent limitations in the methodology. There have been no longitudinal studies addressing this problem. Further, no studies have assessed the effect of the withdrawal of PHT, CBZ or VPA on AP kinetics.

In the present longitudinal study, intra-personal comparisons of AP CL and $t_{1/2}$, before and after the withdrawal of PHT, CBZ or VPA from regimens of polytherapy have been made. Additionally, the effects of concomitant medications on AP CL and $t_{1/2}$ have been assessed.

Methods

We studied 52 patients, aged 17 to 65 years (median 32 years), attending the Chalfont Centre for Epilepsy, who were having PHT, CBZ or VPA discontinued as part of a planned rationalization of AED therapy. Patients taking drugs other than AEDs or vitamins, with a history of alcohol abuse or with other significant illness were excluded. Informed consent was obtained from all patients and the study was approved by the Ethics Committee of the National Hospitals. The AP test was carried out twice in each patient, before and 4 weeks after completion of removal of an AED. No dose changes were made for at least 2 weeks before the AP test, to allow the degree of hepatic enzyme activity to reach steady state (Lai *et al.*, 1978; Døssing *et al.*, 1983; Rapeport *et al.*, 1983) and concomitant medication remained unchanged throughout the study.

Tables 1, 2 and 3 show the prescribed doses of the different AEDs in the patients who had PHT ($n = 20$), CBZ ($n = 15$) and VPA ($n = 17$) withdrawn respectively. In the PHT group the following comedication was prescribed: CBZ only ($n = 6$), CBZ + VPA ($n = 5$), CBZ + PB ($n = 4$), CBZ + PRM ($n = 4$) and CBZ + PB + VPA ($n = 1$). In the CBZ group the comedication prescribed was: PHT only ($n = 5$), VPA only ($n = 3$), VPA + ethosuximide (ESM) ($n = 2$), PRM only ($n = 1$), PHT + PRM ($n = 1$) PB + VPA ($n = 1$), PHT + PB ($n = 1$) and PHT + VPA ($n = 1$). The comedication prescribed in the VPA group was: CBZ only ($n = 10$), PHT only ($n = 2$), PRM only ($n = 1$), PHT + CBZ ($n = 2$), PRM + CBZ ($n = 1$) and PHT + CBZ + PRM ($n = 1$).

After an overnight fast subjects drank, at 08.00 h, 18 mg kg⁻¹ of AP (BDH Chemicals Ltd,

Poole) dissolved in water and made up to 100 ml with orange juice (Perucca *et al.*, 1980). Subjects remained fasted for 2.5 h after AP ingestion. Venous blood was drawn into heparinized tubes at 1, 4, 8, 12 and 24 h. Plasma was separated by centrifugation and stored at -18°C until assay.

AP in plasma was measured using a newly developed h.p.l.c. microanalytical technique. Briefly, into a 1.5 ml Eppendorf micro test tube were added 200 μl of plasma, 4 μg of 10-methoxycarbamazepine as internal standard, 150 μl of 4M NaOH and 700 μl of dichloromethane. After shaking for 5 min and centrifuging for a further 5 min in a microcentrifuge, the aqueous layer was vacuum aspirated and the dichloromethane phase evaporated to dryness. Each plasma extract was reconstituted in 17.5 μl of acetonitrile and 10 μl injected into a Spectra Physics SP8000 liquid chromatograph, with data processing capability. The chromatograph was fitted with an automatic 10 μl Valco loop injector and a Spectra Physics 8440 variable wavelength absorption detector set at 270 nm. A Hichrom Lichrosorb RP8 10 μm column and an acetonitrile:water:acetic acid (40:48:12) mobile phase (1.3 ml min⁻¹) were used. The retention times for 10-methoxycarbamazepine and AP were 6.6 and 7.6 min respectively. The lower limit of detection of AP was 2 $\mu\text{mol l}^{-1}$ and the intra-assay coefficient of variation was < 4.5%.

AP half-life ($t_{1/2}$, h) was calculated from the slopes of the terminal log-linear sections of AP concentration/time plots, by least square linear regression. Clearance (CL, ml h⁻¹ kg⁻¹) was calculated from the dose of AP/Area under the plasma concentration/time curve (AUC). AUC was calculated using the trapezoidal rule. Volume of distribution (V , ml kg⁻¹) was by $V = \text{CL} \times t_{1/2} / 0.693$.

Trough serum AED concentrations were assessed on the same days as AP testing was carried out. PHT and CBZ concentrations were measured by homogenous enzyme immunoassay (Emit, Syva UK), VPA and PB by fluorescence polarization immunoassay (TDx, Abbott) and ethosuximide (ESM) by gas liquid chromatography (Latham & McPherson, 1974).

Statistical analysis was by repeated measures analysis of variance (MANOVA), using the Statistical Package for the Social Sciences (SPSS-X). Time was the within-subjects factor and the drugs being taken were between-subjects factors. The analysis generated the univariate statistic F , the degrees of freedom (d.f.) and tests of the significance of F , P . In the three individual drug reduction groups, the time effect determined whether a significant change in a parameter had occurred between the two tests.

Time x between-subject factor interactions analysed whether groups of patients behaved significantly differently from each other, over time, or not.

Results

The dose and serum concentrations of the AEDs withdrawn, and of the concomitant drugs, in the

PHT, CBZ and VPA reduction groups are summarized in Tables 1, 2 and 3. For all three drug reduction groups, the mean trough serum concentrations of the AED withdrawn was approximately 50% of the usually quoted upper limit of the therapeutic range.

All 20 patients who had PHT withdrawn were also prescribed CBZ, and 9 of these also took a barbiturate (Table 1). Five of the 15 patients who discontinued CBZ did not take any other

Table 1 Antiepileptic drug (AED) dose and serum concentrations in phenytoin withdrawal group

AED	Number of patients	Daily dose (mg) Median (range)	Baseline concentration ($\mu\text{mol l}^{-1}$) (mean $\pm$ s.d.)	Concentration after PHT removal ($\mu\text{mol l}^{-1}$) (mean $\pm$ s.d.)
PHT	20	300 (200–400)	38.6 $\pm$ 17.0	0
CBZ	20	1200 (400–2000)	22.4 $\pm$ 6.9	33.1 $\pm$ 10.0
VPA	6	1650 (1200–2000)	301 $\pm$ 92	351 $\pm$ 125
PB	5	90 (30–180)	115 $\pm$ 42	78 $\pm$ 26
PRM	4	750 (750)		

PHT = phenytoin; CBZ = carbamazepine; VPA = valproic acid; PB = phenobarbitone; PRM = primidone.

PB concentrations are shown for patients taking PRM.

Table 2 Antiepileptic drug (AED) dose and serum concentrations in carbamazepine withdrawal group

AED	Number of patients	Daily dose (mg) Median (range)	Baseline concentration ($\mu\text{mol l}^{-1}$) (mean $\pm$ s.d.)	Concentration after CBZ removal ($\mu\text{mol l}^{-1}$) (mean $\pm$ s.d.)
PHT	8	325 (200–450)	37.5 $\pm$ 8.8	27.9 $\pm$ 5.2
CBZ	15	1000 (600–1600)	26.4 $\pm$ 8.6	0
VPA	7	2000 (1400–2400)	324 $\pm$ 75	459 $\pm$ 110
PB	2	150 (120–180)	110 $\pm$ 15	109 $\pm$ 21
PRM	2	562 (375–750)		
ESM	2	1000 (1000)	388 $\pm$ 128	575 $\pm$ 95

PHT = phenytoin; CBZ = carbamazepine; VPA = valproic acid; PB = phenobarbitone; PRM = primidone; ESM = ethosuximide.

PB concentrations are shown for patients taking PRM.

Table 3 Antiepileptic drug (AED) dose and serum concentrations in valproic acid withdrawal group

AED	Number of patients	Daily dose (mg) Median (range)	Baseline concentration ($\mu\text{mol l}^{-1}$) (mean $\pm$ s.d.)	Concentration after VPA removal ($\mu\text{mol l}^{-1}$) (mean $\pm$ s.d.)
PHT	5	300 (300–400)	33.0 $\pm$ 12.5	33.0 $\pm$ 12.6
CBZ	14	1000 (800–1800)	29.2 $\pm$ 9.1	30.7 $\pm$ 8.6
VPA	17	2000 (600–2400)	343 $\pm$ 89	0
PRM	3	750 (750–1000)	117 $\pm$ 39	102 $\pm$ 15

PHT = phenytoin; CBZ = carbamazepine; VPA = valproic acid; PRM = primidone.

PB concentrations are shown for patients taking PRM.

Figure 1 Changes in mean antipyrine clearance ($\text{ml min}^{-1} \text{kg}^{-1}$) before (B) and after (A) removal of phenytoin (PHT), carbamazepine (CBZ) and valproic acid (VPA), illustrating the effect of comedication. For further details regarding comedication see Tables 1, 2 and 3. — PHT removal (comedication CBZ + barbiturate) ($n = 9$); ---- PHT removal (comedication CBZ) ($n = 11$); — CBZ removal (comedication PHT +/– barbiturate) ($n = 10$); ---- CBZ removal (no inducing comedication) ($n = 5$); — VPA removal (all with inducing comedication) ($n = 17$).

enzyme inducing drug (three reducing to monotherapy with VPA, and two to VPA + ESM). The remaining 10 patients took PHT (8 cases) and/or barbiturates (4 cases) (Table 2). All patients who discontinued VPA were taking inducing AEDs (Table 3).

The effects of PHT, CBZ and VPA removal on AP CL and $t_{1/2}$ are summarized in Tables 4, 5 and 6 and Figure 1. AP V was unaffected by PHT, CBZ or VPA removal. Results for the

PHT group are divided into patients with (9) and without (11) barbiturate comedication, and the CBZ group is divided into patients with (10) and without (5) enzyme-inducing comedication.

Removal of PHT (Table 4) led to a mean 13% fall in AP CL ($P = 0.001$) and a mean 16% increase in AP $t_{1/2}$ ($P = 0.015$). There was no significant difference between the groups of patients with and without barbiturate comedication.

CBZ removal (Table 5) was followed, overall, by a mean 17% fall ($P = 0.073$) in AP CL. AP CL did not alter in patients who also took PHT and/or barbiturates, but fell by a mean 45% ($P = 0.007$) in those patients who were not taking other inducing AEDs. The difference in changes in AP CL in these two subgroups was significant ($P = 0.001$). AP $t_{1/2}$ increased by a mean 23% overall ($P = 0.036$) on removal of CBZ, with no change in those who took inducing comedication, but there was a mean 68% increase ($P = 0.016$) in those who were on no other inducing drugs. The difference between the changes in AP $t_{1/2}$ in these two sub-groups was significant ($P = 0.005$). There were no significant changes in AP CL or $t_{1/2}$ on discontinuation of VPA (Table 6).

The mean trough serum concentrations of concomitant AEDs, in the three drug reduction groups, at the times of AP testing are summarized in Tables 1, 2 and 3. PHT removal led to a mean 48% increase in the serum CBZ concentration, a mean 17% rise in serum VPA concentration and a mean 32% fall in serum PB concentration. Discontinuation of CBZ was associated with a mean 26% fall in serum PHT concentration, a mean 42% increase in serum VPA concentration and no change in mean serum PB concentration.

Table 4 Effect of phenytoin removal on antipyrine kinetics

	Before (mean $\pm$ s.d.)	After (mean $\pm$ s.d.)	F	d.f. (Before vs After)	P
CL ($\text{ml min}^{-1} \text{kg}^{-1}$)					
All patients ($n = 20$)	1.38 ± 0.36	1.19 ± 0.30	17.0	1,19	0.001
+ Barbiturates ($n = 9$)	1.37 ± 0.34	1.18 ± 0.33			
– Barbiturates ($n = 11$)	1.38 ± 0.40	1.20 ± 0.29			
Time $\times$ barbiturate interaction:			0.01	1,18	0.93
$t_{1/2}$ (h)					
All patients ($n = 20$)	5.1 ± 1.3	5.9 ± 1.9	7.1	1,19	0.015
+ Barbiturates ($n = 9$)	5.3 ± 1.3	6.1 ± 2.4			
– Barbiturates ($n = 11$)	5.0 ± 1.4	5.7 ± 1.6			
Time $\times$ barbiturate interaction:			0.03	1,18	0.86

+ Barbiturate comedication = phenobarbitone in five patients, primidone in four.

– Barbiturate comedication = non barbiturate comedication.

For further details see Methods.

CL = clearance; $t_{1/2}$ = half life.

Table 5 Effect of carbamazepine removal on antipyrine kinetics

	Before (mean $\pm$ s.d.)	After (mean $\pm$ s.d.)	F (Before vs After)	d.f.	P
CL (ml min ⁻¹ kg ⁻¹)					
All patients (n = 15)	1.27 $\pm$ 0.33	1.05 $\pm$ 0.40	3.8	1,14	0.073
+ Coinducing AED (n = 10)	1.15 $\pm$ 0.27	1.16 $\pm$ 0.44	0.001	1,9	0.95
- Coinducing AED (n = 5)	1.50 $\pm$ 0.34	0.33 $\pm$ 0.17	26.0	1,4	0.007
Time $\times$ coinducing AED interaction:			17.3	1,13	0.001
t _{1/2} (h)					
All patients (n = 15)	6.1 $\pm$ 1.6	7.5 $\pm$ 2.8	5.4	1,14	0.036
+ Coinducing AED (n = 10)	6.4 $\pm$ 1.8	6.7 $\pm$ 2.6	0.35	1,9	0.57
- Coinducing AED (n = 5)	5.5 $\pm$ 1.1	9.3 $\pm$ 2.5	15.9	1,4	0.016
Time $\times$ coinducing AED interaction:			11.5	1,13	0.005

+ Coinducing AED = phenytoin in eight patients, phenobarbitone in four.

- Coinducing AED = valproic acid in five patients, ethosuximide in two.

For further details see Methods.

CL = clearance; t_{1/2} = half-life; AED = antiepileptic drug.

Table 6 Effect of valproic acid removal on antipyrine kinetics

	Before (mean $\pm$ s.d.)	After (mean $\pm$ s.d.)	F (Before vs After)	d.f.	P
17 patients					
CL (ml min ⁻¹ kg ⁻¹)	1.30 $\pm$ 0.47	1.47 $\pm$ 0.61	1.9	1,16	0.19
t _{1/2} (h)	5.7 $\pm$ 1.4	5.8 $\pm$ 1.9	0.02	1,16	0.88

CL = clearance; t_{1/2} = half-life

VPA removal was associated with a mean 5% increase in serum CBZ concentration, no change in mean serum PHT concentration and a mean 13% fall in PB concentration.

Discussion

This is the first longitudinal study of the effect of AED withdrawal on AP kinetics. We have analysed alterations in hepatic enzyme activity (as measured by AP CL and t_{1/2}) on the withdrawal of PHT, CBZ and VPA, and have determined the influence of comedication on these changes.

The advantage of a longitudinal, over a cross-sectional, study design is that the former approach is more sensitive, as each patient acts as his or her own control. A previous cross-sectional study suggested that two or more inducing AEDs, at doses used clinically, may not have a greater effect on hepatic enzyme activity, than does a single AED (Perucca *et al.*, 1984). At the doses used in the present study, PHT appeared to have a slight enzyme inducing effect (as measured by AP CL and t_{1/2}) over and above that of CBZ or CBZ and a barbiturate in combination. There

were no patients in which PHT was the only enzyme inducing drug taken, so it is not possible to compare the effect of PHT alone with that of PHT in combination with CBZ, or CBZ and a barbiturate. In contrast to the present findings, Shaw *et al.* (1985) found that PHT given alone resulted in a 91% increase in AP CL. The implication of these results is that PHT has enzyme inducing activity over and above that of CBZ with or without barbiturate, but that the effect of PHT is, to some extent, masked by comedication with these other drugs.

When CBZ was the only enzyme inducing drug being taken, its removal resulted in a marked, *circa* 50%, decrease in AP CL. However, if PHT and/or barbiturates were also taken, the removal of CBZ had no effect on AP CL. These observations suggest that, at the doses studied, CBZ has no additional effect on AP CL, over and above that of PHT and/or barbiturates. The absence of any change in AP kinetics on removal of VPA suggests that this drug has no additional enzyme inducing effect over that of PHT, CBZ or PB. This is in keeping with previous studies that have indicated that VPA lacks any significant enzyme inducing properties (Oxley *et al.*, 1979; Perucca *et al.*, 1984).

The mean 48% rise in serum CBZ concentration and 17% rise in VPA concentration on removal of PHT are consistent with the demonstrated decrease in AP CL, on discontinuation of this drug. The fall in PB concentration on removal of PHT indicates that PHT was inhibiting PB metabolism in these patients. This finding is consistent with the study of Kutt (1984).

The mean 26% fall in serum PHT concentration on removal of CBZ suggests that CBZ was inhibiting, and not inducing, PHT metabolism. This finding is consistent with the lack of change in AP kinetics when CBZ was discontinued, in patients who were also taking PHT and/or barbiturates (Table 5). In contrast, the mean 48% rise in serum CBZ concentration upon the removal of PHT suggests that PHT is a potent inducer of CBZ metabolism, and this is reflected in the AP kinetic analysis of these patients (Table 4). This clinically important dual interaction between CBZ and PHT has been previously reported (Zielinski & Haidukewych, 1987). The mean 42% rise in serum VPA concentration, when CBZ was stopped, correlates well with the decrease in AP CL and increases in AP $t_{1/2}$, and confirms the action of CBZ as an enzyme inducer.

The small reduction in the mean serum PB concentration, on removal of VPA, is consistent

with the lack of significant enzyme inducing activity of VPA, and the drug's action as an inhibitor of PB metabolism (Bruni *et al.*, 1980; Kapetanovic *et al.*, 1981).

In conclusion, it appears that PHT has hepatic enzyme inducing activity (as measured by AP CL and $t_{1/2}$) over and above that of CBZ, or CBZ and PB, and that the withdrawal of PHT from such combination therapy results in significant deinduction. CBZ in contrast, is also an inducing agent but its effect is swamped by that of PHT and PB, so that withdrawal of CBZ results in deinduction only in patients remaining on VPA monotherapy, or VPA and ESM. These findings have clinical relevance as withdrawal of CBZ and PHT were associated with significant changes in the serum concentrations of concomitant AEDs and reinforces the need to be alert to pharmacokinetic interactions when making drug changes in patients with epilepsy.

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