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The disposition of primidone in elderly patients

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1 The pharmacokinetics and metabolism of primidone at steady-state were studied in 10 elderly patients aged 70–81 years and eight control subjects aged 18–26 years.
2 Primidone half-lives and clearance values (means ± s.d.) were similar in the elderly and in the young (12.1 ± 4.6 *vs* 14.7 ± 3.5 h and 34.8 ± 9.0 *vs* 33.2 ± 7.2 ml h^{-1} kg^{-1} respectively.
3 The serum concentrations of the metabolites phenylethylmalonamide (PEMA) and phenobarbitone relative to those of parent drug were higher in the elderly than in the young, the difference being significant ($P < 0.01$) in the case of PEMA.
4 The renal clearances of primidone, phenobarbitone and PEMA were moderately decreased in the elderly but this reduction was statistically significant only for PEMA. Elderly patients excreted a reduced proportion of unchanged primidone and an increased proportion of PEMA in urine.
5 Ageing is associated with a greater accumulation of PEMA, which is unlikely to have a major clinical significance.

Keywords primidone kinetics metabolism elderly

Introduction

The antiepileptic drug primidone has been used increasingly for the treatment of essential tremor, in which condition it has been shown to be as effective as propranolol (Dietrichson & Espen, 1987; Gorman *et al.*, 1986) and more effective than phenobarbitone (Sasso *et al.*, 1988). Since essential tremor affects predominantly the elderly, it would be important for a rational use of the drug to assess whether its pharmacokinetics are altered in old age. Despite extensive studies on the influence of pregnancy (Battino *et al.*, 1984), neonatal age (Nau *et al.*, 1980), childhood (Kaufman *et al.*, 1977), disease (Heipertz *et al.*, 1979; Pisani *et al.*, 1984) and drug interactions (Perucca, 1982) on primidone kinetics, the potential changes in the disposition of this drug in elderly patients have not been investigated. These changes could be important because primidone is eliminated partly by renal excretion and partly by biotransformation, both of which may be altered in old age.

The present study was designed to characterize the pharmacokinetics and metabolism of primidone in elderly patients with essential tremor receiving chronic drug therapy. A group of young patients with epilepsy also treated with primidone was included for comparison.

Methods

Patients

Ten elderly patients with essential tremor (age 70 to 81 years) and eight young patients with epilepsy (age 18 to 26 years) receiving chronic

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Table 1 Details of the patients included in the study

	Young (n = 8)	*Elderly* (n = 10)	P *value*
Sex distribution	5M/3F	7M/3F	
Age (years)	21.4 ± 3.5	73.5 ± 3.4	< 0.001
Body weight (kg)	71.8 ± 11.8	70.2 ± 7.6	NS
Creatinine clearance (ml min^{-1})	110 ± 25	68 ± 17	< 0.001
Primidone dosage (mg day^{-1})	422 ± 115	575 ± 206	NS

treatment with primidone (without associated anticonvulsants) at a constant dosage for at least 2 months gave their consent to participate in the study. Details of the subjects are given in Table 1. The two groups were comparable in sex distribution and body weight. The mean daily dosage of primidone was moderately higher in the elderly patients, but the difference was not statistically significant. All patients were ambulant and in good physical condition as assessed by medical examination and laboratory tests (including serum creatinine and, in the elderly patients, thyroid function tests). Creatinine clearance was significantly lower in the elderly (Table 1). Six of the elderly patients were receiving concurrent therapy with other drugs (digoxin and nifedipine in two cases, canrenoate, amiloride, cinnarizine, imecromone, pentoxyphilline, and acenocoumarol in one case each).

Sampling protocol

In order to allow a dosage interval compatible with estimation of kinetic parameters without compromising therapeutic needs, the dosing regimen was modified in all patients by dividing the total daily dosage of primidone into two equal amounts given every 12 h for 7 consecutive days. Blood samples were collected on the 7th day at 0, 1.5, 3, 5, 8 and 12 h after the morning dose. Total urine collections were obtained over the same period. Serum and urine samples were stored at −20° C until analysis.

Analytical procedures and data analysis

Primidone and its metabolites phenobarbitone and phenylethylmalonamide (PEMA) were measured in serum and urine by the h.p.l.c. method of Kunze *et al.* (1981) with minor modifications. In urine, the concentration of the second-step metabolite *p*-hydroxyphenobarbitone (*p*-OH-phenobarbitone) was also measured by the same method. In order to determine both unconjugated and conjugated metabolites, all urine samples were assayed before and after hydrolysis with β-glucuronidase/arylsulphatase (Sigma, 3000 u ml^{-1}) at pH 5.0 and at 37°C for 3 h (Kunze *et al.*, 1981). Preliminary experiments established that this time interval was sufficient to obtain complete hydrolysis.

The first order rate constant describing drug elimination (λ_z) was calculated by linear regression analysis of the log-linear decay of drug concentration, which occurred between 1.5–3 h to 12 h after the dose. Half-lives were calculated as $0.693/\lambda_z$. Areas under the curve (AUC (0,12 h)) were calculated by the linear trapezoidal rule and dose-normalized, if necessary. Clearance (CL) and volume of distribution (*V*) were calculated as (Daily dose × 0.5/AUC (0, 12 h) and CL/λ_z respectively, assuming complete bioavailability (Perucca & Richens, 1985). Renal clearance was calculated as (amount excreted in urine between 0 and 12 h)/AUC (0, 12 h).

Results are reported as means ± s.d. Statistical comparisons were made using Student's unpaired *t*-test.

Results

The time courses of serum primidone concentration in two representative patients are shown in Figure 1. In all subjects, the concentration of the

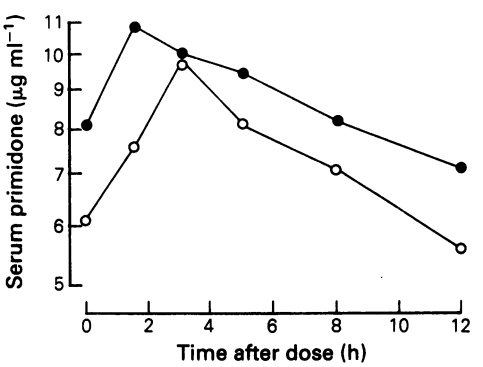

Figure 1 Serum primidone concentrations during the dosing interval in a 70 year old patient (○) and in an 18 year old subject (●) receiving chronic drug treatment (250 mg twice daily)

Table 2 Parameters describing the disposition of primidone and its metabolites in the two study groups

	Young (n = *8*)	*Elderly* (n = *10*)	P *value*
Primidone terminal elimination rate constant (h^{-1})	0.0510 ± 0.0184	0.0655 ± 0.0244	NS
Primidone half-life (h)	14.7 ± 3.5	12.1 ± 4.6	NS
Primidone volume of distribution (l kg^{-1})*	0.69 ± 0.18	0.56 ± 0.14	NS
Primidone AUC (0, 12 h) (mg l^{-1} h)**	112 ± 33	110 ± 28	NS
Primidone total clearance (ml h^{-1} kg^{-1})*	33.2 ± 7.2	34.8 ± 9.0	NS
Phenobarbitone AUC (0, 12 h) (mg l^{-1} h)**	78.7 ± 44.5	111.6 ± 51.0	NS
PEMA AUC (0, 12 h) (mg l^{-1} h)**	33.7 ± 22.0	57.1 ± 20.7	< 0.05
Phenobarbitone AUC/Primidone AUC	0.71 ± 0.33	1.10 ± 0.63	NS
PEMA AUC/Primidone AUC	0.29 ± 0.15	0.54 ± 0.21	< 0.01
Renal clearance of unchanged primidone (ml h^{-1} kg^{-1})	15.3 ± 6.7	11.3 ± 4.8	NS
Renal clearance of unchanged phenobarbitone (ml h^{-1} kg^{-1})	1.0 ± 0.2	0.8 ± 0.3	NS
Renal clearance of PEMA (ml h^{-1} kg^{-1})	26.4 ± 8.0	18.3 ± 6.6	< 0.05
Proportion of dose recovered in urine as unchanged primidone (%)+	45.9 ± 16.5	36.1 ± 22.7	NS
Proportion of dose recovered in urine as phenobarbitone (%)+	2.0 ± 0.8	2.1 ± 0.9	NS
Proportion of dose recovered in urine as unconjugated *p*-OH-phenobarbitone (%)	2.3 ± 2.1	1.5 ± 0.6	NS
Proportion of dose recovered in urine as total (unconjugated + conjugated) *p*-OH-phenobarbitone (%)	4.3 ± 4.1	3.5 ± 1.8	NS
Proportion of dose recovered in urine as PEMA (%)+	21.2 ± 8.6	27.1 ± 8.8	NS

* Assuming complete oral availability.
** Normalized for a dose of 500 mg day^{-1}.
+ No conjugates of these compounds were detected.

drug reached a peak within 1.5 to 3 h after the morning dose and in most cases declined mono-exponentially thereafter (a biphasic decline was observed only in three cases). Pharmacokinetic parameters derived from serum primidone concentration data in the elderly and in the young are shown in Table 2. No statistically significant differences were observed.

The serum concentrations of the major primidone metabolites phenobarbitone and PEMA showed negligible fluctuation during the sampling interval, in accordance with their long half-lives. The concentrations of these metabolites tended to be higher in the elderly patients, significantly so in the case of PEMA. The PEMA/primidone ratio was also significantly higher in the elderly (Table 2).

Approximately 74% of the dose was recovered as unchanged drug and metabolites in the urine of the young subjects (Table 2). The overall recovery in the elderly patients was 63%. Compared with the young, the elderly excreted a larger proportion of PEMA and a lower proportion of unchanged primidone, although the difference failed to reach statistical significance. The renal clearances of primidone, phenobarbitone and PEMA were also lower in the elderly, but the difference was statistically significant only in the case of the latter compound ($P < 0.05$) (Table 2).

The renal clearance of PEMA, unlike that of primidone and phenobarbitone, was found to be correlated significantly with creatinine clearance ($r = 0.51$, $P < 0.05$).

Discussion

The pharmacokinetic parameters of unchanged primidone found in the present study are comparable with those reported previously for untreated subjects (Pisani *et al.*, 1984; Zavadil & Gallagher, 1977) and patients receiving chronic monotherapy (Cloyd *et al.*, 1981). Although terminal elimination half-lives could be calculated with limited accuracy owing to the relatively short sampling interval, the similarity of these values and of clearance values in young and elderly patients suggests that ageing is not associated with major changes in the elimination of this compound. Age-related differences in free drug concentration can also be excluded, since

primidone is negligibly bound to plasma proteins (Perucca & Richens, 1985).

Despite the unchanged serum clearance, the disposition of primidone does appear to be altered in old age. Thus, the concentrations of phenobarbitone and PEMA relative to those of parent drug tended to be higher in the elderly. The renal clearances of all compounds examined (primidone, PEMA and phenobarbitone) were also lower in the elderly than in the young, probably as a result of the decline in kidney function in old age, even though the difference reached statistical significance only in the case of PEMA. Altogether, these findings are consistent with the hypothesis that in elderly patients a moderately reduced capacity to eliminate unchanged primidone in urine is accompanied by an increase in the proportion which is converted to PEMA and, possibly, phenobarbitone. In agreement with this interpretation, elderly patients were found to excrete proportionally lower amounts of unchanged primidone and larger amounts of PEMA as compared with young control subjects.

Although PEMA is pharmacologically active in animal models of epilepsy, studies in patients with essential tremor have demonstrated that this compound is therapeutically ineffective in this condition (Calzetti *et al.*, 1981). Therefore, it is unlikely that the relative accumulation of this metabolite observed in the elderly would produce any clinical benefit in patients with tremor. There is also little evidence that PEMA can induce toxic symptoms, unless very high concentrations are achieved (Stern *et al.*, 1977). It is noteworthy, in any case, that PEMA was the only compound for which pharmacokinetic differences could be clearly demonstrated between the elderly and the young: the accumulation of this metabolite in serum was probably a consequence of both increased formation and decreased renal elimination. Unlike primidone and phenobarbitone, PEMA is eliminated only by renal excretion (Cottrell *et al.*, 1982).

In the case of phenobarbitone, the pattern of serum and urinary kinetics within both groups was too variable to allow any definite conclusion to be made. Although only limited information is available on the urinary profile of parent drug and metabolites in patients treated with primidone, our data are in agreement with those reported by Kaufman *et al.* (1977) in children indicating that only about 5% of a primidone dose can be recovered as phenobarbitone and *p*-OH-phenobarbitone in the urine. The overall urinary recovery of parent drug and metabolites (73% in young subjects, 64% in elderly patients) was lower than that (72–123%) reported by Kaufman *et al.* (1977) in children, but comparable with that (75%) found by Zavadil & Gallagher (1976) in urine samples collected for 5 days after a radiolabelled dose.

In conclusion, the present findings indicate that total primidone clearance is unaltered in fit elderly patients, although evidence is provided that the renal clearances of parent drug and metabolites may differ from those observed in young subjects. Since elderly subjects are known to represent a very heterogeneous group with respect to physiological and pathological features, our findings may not be extrapolated to particular subgroups, especially those with associated disease or more severe impairment in renal function.

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