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Pharmacokinetics of valproic acid in the elderly

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1 The kinetics of a single oral dose of sodium valproate was studied in six healthy elderly patients (age 68–89 years) and six young control subjects (age 24–26 years).
2 The profiles of total plasma valproic acid (VPA) concentrations were very similar in the elderly and in the young. Half-lives (15.3 ± 0.7 s.e. mean in the elderly *vs* 13.0 ± 1.0 h in the young), volumes of distribution (0.16 ± 0.01 l/kg in the elderly *vs* 0.14 ± 0.01 l/kg in the young) and clearance (7.5 ± 0.9 ml h^{-1} kg^{-1} in the elderly *vs* 7.7 ± 0.6 ml h^{-1} kg^{-1} in the young) did not differ significantly between the two groups.
3 Free VPA concentrations were significantly increased in the elderly. The clearance of the free drug (intrinsic clearance) was reduced from 127.0 ± 12 ml h^{-1} kg^{-1} (control value in the young) to 77.7 ± 5.5 ml h^{-1} kg^{-1} ($P < 0.02$). Free VPA fraction was 9.5 ± 0.6% in the elderly and 6.6 ± 0.5% in the young ($P < 0.02$).
4 These findings suggest that the pharmacokinetic alterations of VPA in old age are complex and include at least two separate mechanisms:
(1) a decrease in plasma protein binding and (2) a reduction of drug metabolizing capacity resulting in decreased clearance of free drug by the liver.

Keywords valproic acid pharmacokinetics elderly subjects age

Introduction

Although the kinetics of many therapeutic agents is known to be altered in old age, this phenomenon is not observed for all drugs and is not necessarily a predictable consequence of the physiological changes occurring in old age (Editorial, 1983; Greenblatt *et al.*, 1982; Ramsay & Tucker, 1981). Valproic acid (VPA) is a broad spectrum antiepileptic drug which is widely used in all age groups and for which significant pharmacokinetic changes have recently been described in elderly patients (Bryson *et al.*, 1983). These were found to consist in a marked prolongation of the half-life and in an increase of the volume of distribution, while the total body clearance did not differ from that observed in a control group of young volunteers. In view of the unaltered clearance, it was suggested that the kinetic changes observed were unlikely to be clinically significant.

In the above mentioned study, however, all calculations were based on serum levels of total (free + protein-bound) drug. Since VPA is extensively bound to plasma proteins and only the free drug is pharmacologically active, any impairment in binding (such as suggested by the increased volume of distribution) could have important consequences in the presence of an unaltered clearance of total drug (Perucca & Richens, 1980). The present investigation was undertaken to compare the kinetics of free VPA in young and elderly subjects.

Methods

Subjects and protocol

Six ambulant elderly subjects and six young volunteers gave their informed consent to participate in the study (Table 1). All subjects were in

Table 1 Pharmacokinetic parameters in the young.

Subject	*Sex*	*Age (years)*	*Weight (kg)*	t_{max} *(h)*	C_{max} *(μmol/l)*	$t_{½}$ *(h)*	$AUC_{0-\infty}$ *(μmol l⁻¹ h)*	*CL (ml h⁻¹ kg⁻¹)*	V_d *(l/kg)*	$AUC_{free\ 0-\infty}$ *(μmol l⁻¹ h)*	CL_{free} *(ml kg⁻¹ h⁻¹)*	$V_{d\,free}$ *(l kg⁻¹)*
PP	F	25	50	1	694	11.4	10819	9.0	0.15	84	166	2.3
EV	F	24	59	2.5	507	15.6	12541	6.6	0.15	131	90	1.8
LB	F	25	55	1	555	11.4	9057	9.6	0.16	131	97	2.4
MC	M	26	71	1	527	14.8	9022	7.6	0.16	75	131	2.0
MP	M	25	89	2.5	403	9.7	7016	7.8	0.11	55	143	1.6
RG	M	26	72	1	555	14.9	12096	5.6	0.12	73	133	2.2
Mean	—	25.2	66	1.5	540	13.0	10092	7.7	0.14	92	127	2.0
±s.e. mean		0.3	5.5	0.3	38	1.0	861	0.6	0.01	13	12	0.1

t_{max} = time of peak; C_{max} = peak concentration; $t_{½}$ = half-life; $AUC_{0-\infty}$ and $AUC_{free\ 0-\infty}$ = area under the curve for total and free drug respectively; CL and CL_{free} = body clearance of total and free drug respectively; V_d and $V_{d\,free}$ = apparent volume of distribution of total and free drug respectively.

good health, as confirmed by standard laboratory tests (BUN, creatinine, glucose, SGPT, SGOT, electrolytes, serum electrophoresis, FBC) and none was receiving any drug at the time of the study or during the preceding 2 weeks. Each subject received a single 800mg dose of sodium valproate (Depakin®, Sigma-Tau) orally together with 40 ml plain water at 08.00 h after an overnight fast. No food was allowed for 3 h. Blood samples (12 ml) were collected in heparinized tubes (8 i.u. heparin/ml blood) at 0, 1, 2.5, 4, 7, 11, 24 and 32 h after administration. In order to avoid spurious alterations in free drug fraction due to the *in vitro* release of free fatty acids (Albani *et al.*, 1983), the plasma was separated within 1 h and stored frozen at −20 °C until analysis.

Analytical techniques

Total VPA was determined by enzyme-immunoassay (EMIT). Free VPA was determined by ultrafiltration at 25 °C with subsequent immunoenzymatic measurement of the drug in the ultrafiltrate using the Syva Free Level I System (Syva, Palo Alto, California). All measurements were performed in duplicate, with the incorporation of one 7 μmol/l standard into the calibration curve for free VPA.

Kinetic and statistical analysis

Half-lives ($t_{½}$) were calculated by linear regression from the log-concentration-time curve during the elimination phase. Areas under the curve (AUC) were calculated by the trapezoidal rule and extrapolated to infinity. Clearances and volumes of distribution were calculated as $Dose/AUC_{0-\infty}$ and $(Dose \times t_{½})/(AUC_{0-\infty} \times 0.693)$ respectively, assuming that bioavailability was complete (Perucca *et al.*, 1978a, b). Comparisons were made by using the Student's *t*-test for unpaired data.

Results

As illustrated in Figure 1, the profile of total (free + protein bound) VPA in the elderly was similar to that observed in the young. A comparison of kinetic parameters (Tables 1 and 2) confirms the overall similarity. There was only a tendency for the half-life and the volume of distribution to be increased in the elderly, but the difference was small and not statistically significant. Clearance values were virtually identical in the two groups.

When free rather than total drug levels were considered, a completely different pattern

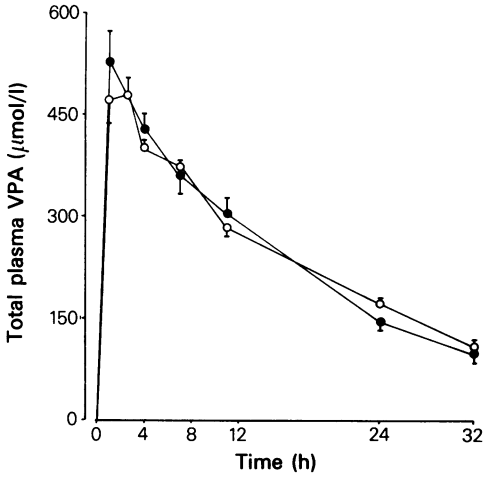

Figure 1 Total plasma VPA concentrations (mean ± s.e. mean) after a single dose of sodium valproate (800 mg) in six young (●) and six elderly (○) subjects.

emerged. At all sampling times, free VPA levels were higher in the elderly than in the young: this allowed measurement of the free drug for up to 32 h in all elderly subjects, while in the young only values up to 24 h could be reliably quantitated (Figure 2). The altered kinetics in the elderly were reflected in significantly larger values of AUC and in a marked reduction of the clearance of the free drug (Tables 1 and 2). The apparent volume of distribution of free VPA, on the contrary, did not differ significantly between the two groups.

The elevation of free VPA levels in the presence of unchanged total levels implies that the free fraction was increased in the elderly. An estimate of the degree of this increase was obtained by calculating the ratio between AUC of free drug and AUC of total drug in all subjects (in order to avoid unnecessary extrapolations, AUC values from 0 to 24 h were used). This calculation yielded free fraction values of 9.5 ± 0.6% in the elderly, as compared to 6.6 ± 0.5% in the young ($P < 0.02$).

Plasma albumin levels were 35 ± 2 g/l in the elderly and 44 ± 2 g/l in the young ($P < 0.02$). When all data were considered, there was a significant negative relationship between drug free fraction and plasma albumin concentration ($r = -0.82$, $P < 0.01$). Within groups, this relationship reached statistical significance only in the young ($r = -0.85$, $P < 0.05$).

Discussion

In a recent study, Bryson *et al.* (1983) reported a two-fold prolongation of the serum half-life and

Table 2 Pharmacokinetic parameters in the elderly (For explanation of abbreviations see Table 1).

Subject	*Sex*	*Age (years)*	*Weight (kg)*	t_{max} *(h)*	C_{max} *(μmol/l)*	$t_{½}$ *(h)*	$AUC_{0-\infty}$ *(μmol l⁻¹ h)*	*CL (ml h⁻¹ kg⁻¹)*	V_d *(l/kg)*	$AUC_{free\ 0-\infty}$ *(μmol l⁻¹ h)*	CL_{free} *(ml kg⁻¹ h⁻¹)*	$V_{d\,free}$ *(l kg⁻¹)*
AS	F	84	72	2.5	458	16.9	11409	5.8	0.14	156	62	1.7
CO	F	89	67	1	500	16.6	12020	6.0	0.14	129	81	1.4
FA	F	76	69	2.5	479	14.1	9640	7.2	0.15	115	88	2.2
RL	M	68	65	1	527	15.1	9945	7.5	0.16	150	72	1.7
PC	M	76	63	2.5	472	16.1	11486	6.7	0.15	167	66	1.9
CM	M	80	45	1	590	12.9	9383	11.6	0.22	160	97	1.7
Mean	—	78.8	63.5	1.8	504	15.3	10647	7.5	0.16	146	78	1.8
±s.e. mean		3.0	3.9	0.3	20	0.7	457	0.9	0.01	8	6	0.1

$P < 0.05$ (*vs* value in the young)

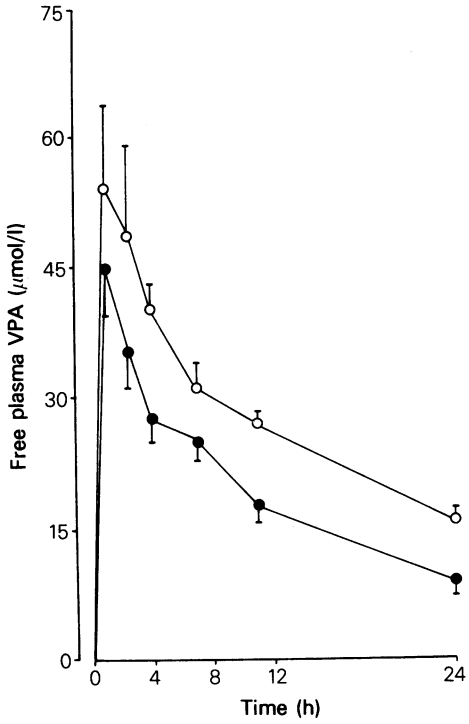

Figure 2 Free plasma VPA concentrations (mean ± s.e. mean) after a single dose of sodium valproate (800 mg) in six young (●) and six elderly (○) subjects.

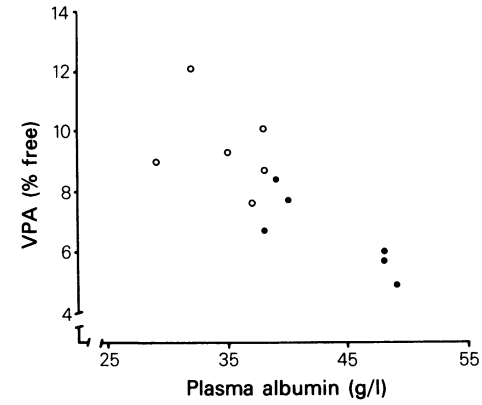

Figure 3 Relationship between free VPA fraction ($AUC^{free}_{0-24}/AUC^{total}_{0-24}$) and serum albumin concentration in six young (●) and six elderly (○) subjects. $r = -0.85$, $P < 0.05$ (young); -0.39, NS (elderly); -0.82 $P < 0.01$ (all data).

an increase of the volume of distribution of intravenously administered VPA in a group of six elderly patients compared with 7 young volunteers. These findings contrast with those obtained in our elderly subjects, whose kinetic parameters calculated from total drug levels did not differ significantly from those observed in young control subjects. Although half-life and volume of distribution values tended to be higher in the elderly, the difference was very minor. The discrepancies between our findings and those reported in the previous study cannot be explained by differences in route of administration: in fact, VPA is known to be completely absorbed from the gastro-intestinal tract in young subjects (Perucca *et al.*, 1978a, b) and a possible reduction of bioavailability in the elderly would have resulted in overestimation rather than underestimation of its volume of distribution. On inspection of the data presented by Bryson *et al.* (1983) it is also unlikely that differences in type of kinetic analysis (calculation of $V_{d\,ss}$, or volume of distribution at steady-state, rather than Vd) could account for the observed discrepancies. It can be concluded that the latter were probably related to the characteristics of the populations investigated: it is unclear, for example, whether the elderly patients included in the earlier study were ambulant or bedridden and whether they were receiving associated drug therapy (although it was stated that none was taking drugs 'likely to interact' with VPA). Differences between the control groups (e.g. in alcohol intake) should be considered, especially in view of the fact that the young volunteers included in the Bryson *et al.* (1983) study showed unusually short VPA half-lives.

The results of the free VPA determinations clearly illustrate the limitations and possible misinterpretations arising from the measurement of total drug levels when a change in protein binding has occurred (Perucca, 1984; Perucca & Richens, 1980). While the kinetics of total VPA were virtually identical in the elderly and in the young, old age was associated with an appreciable and consistent elevation of the concentration of free drug. These findings are especially important in view of the evidence that free plasma VPA reflects the drug concentration in the CSF (Gugler & Von Unruh, 1980; Rapeport *et al.*, 1983) and is putatively responsible for the production of pharmacological effects (Levy, 1980).

The elevation of the free VPA *fraction* in the elderly is probably due to the reduced plasma albumin levels, as suggested by the relationship shown in Figure 3. For a drug like VPA which is subject to restrictive clearance (Gugler & Von Unruh, 1980), however, a decrease in binding capacity would be expected to result in enhanced elimination, leading to a decrease in total drug levels but leaving unchanged the levels and the clearance of the free drug (Wilkinson & Shand, 1975; Perucca & Richens, 1980). This did not

occur in the elderly patients in whom the clearance of the free drug, also termed 'intrinsic clearance' since it reflects the intrinsic capacity of the eliminating organ (Wilkinson & Shand, 1975), was found to be markedly reduced. These findings can be taken as evidence that the pharmacokinetic alterations of VPA in old age include at least two independent mechanisms: (1) a decrease in plasma protein binding and (2) a reduced metabolizing capacity in the liver. Since VPA is metabolized to a large extent by oxidation (Gugler & Von Uhruh, 1980), the latter finding is consistent with the decreased oxidative metabolism of many other drugs in elderly patients (Greenblatt *et al.*, 1982).

As far as the therapeutic consequences of these data is concerned, the reduction in free drug clearance suggests that the dosage requirements of VPA may be moderately decreased in the elderly. Moreover the interpretation of serum drug levels as a guide for dosage adjustments should be made cautiously in these patients, since the total VPA concentration may provide a misleading estimate of the amount of drug which is in the free, pharmacologically active form.

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