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Original Article

Disposition of Antipyrine and Phenytoin Correlated with Age and Liver Volume in Man

Bodil Bach, J. Mølholm Hansen, J.P. Kampmann, S.N. Rasmussen and Lis Skovsted

Medical Endocrinological Department F and Ultrasonic Laboratory, Herlev University Hospital, Copenhagen

Summary

The half-life and metabolic clearance rate (MCR) of antipyrine and phenytoin were determined in 14 young [mean age: 28.8 ± 8.3 (SD) years] and in 14 elderly [mean age: 83.5 ± 7.1 (SD) years] subjects and correlated with liver volume, which was determined by ultrasonic scanning, to see if an age-dependent difference in drug metabolism could be explained by a reduced liver weight with age.

The size of the liver was smaller in the elderly subjects even when related to decreased body surface. A significant decrease in serum albumin in the elderly compared with the younger group was also noted. The half-life of antipyrine was significantly longer in the elderly than in the younger group, 756 ± 318 and 465 ± 110 minutes, respectively, and the MCR was correspondingly lower in the elderly even when calculated per litre of liver volume, 22.8 ± 7.8 and 36.3 ± 8.9ml/minute/L liver volume, respectively. No significant differences in the 2 age groups were found in half-life and total clearance of phenytoin, but a reduced free phenytoin clearance was demonstrated in the elderly (240 ± 92ml/minute/L liver volume) compared with the younger (325 ± 81ml/minute/L liver volume) group. No significant correlation was found between liver volume and the half-life of antipyrine and phenytoin. However, a significant correlation was demonstrated between liver volume and MCR of antipyrine as well as between total and free clearance of phenytoin. No correlation was found between the half-lives of the 2 drugs, while a significant correlation existed between the clearance values.

It is suggested that the age-dependent reduction in drug clearance is due not only to a smaller liver volume, but is also a result of a reduced capacity of the liver microsomes per unit of liver in the elderly. With regard to age-dependent changes in drug metabolism, the protein binding of the actual drug has to be taken into consideration.

An increased elimination half-life with age has been shown for antipyrine (O'Malley et al., 1971), aminopyrine (Jori et al., 1972), paracetamol (acetaminophen) [Triggs et al., 1974], propranolol (Castleden and George, 1979) and salicylates (Cuny et al., 1979), while the metabolism of phenylbutazone (O'Malley et al., 1971; Triggs et al., 1974), indomethacin (Traeger et al., 1973), propylthiouracil (Kampmann et al., 1979) and warfarin (Hayes et al., 1975) has been found to be unrelated to age. Klotz et al. (1975) demonstrated an increased half-life of diazepam in the elderly, but the total body clearance was unchanged due to a concomitant increase in the total volume of distribution. In a later study, Wilkinson (1979) found unchanged clearance of lorazepam with increasing age, while the clearance of chlordiazepoxide decreased significantly with advancing age.

Kato and co-workers (1964) found an age-dependent decrease in the activity of the hepatic microsomal drug-metabolising enzyme system in biopsies from rats. No such studies have been published in humans, but it is known that the liver shows an age-related reduction in weight (Sato et al., 1970).

In the present study, half-life and metabolic clearance rate of antipyrine and phenytoin have been correlated with liver volume determined by ultrasonic scanning in groups of younger and elderly subjects to establish whether age-dependent difference in drug metabolism could be explained by reduced liver size with age. Parts of this study have been previously presented (Rasmussen et al., 1976).

Materials and Methods

Subjects

28 subjects were selected for the study (group A). 14 (7 females and 7 males) were more than 70 years of age [mean: 82.5 ± 7.1 (SD) years] and had been admitted to hospital for minor arteriosclerotic or functional disorders. All had stayed in the hospital for at least 2 weeks before the study. 14 (9 females and 5 males) were young healthy persons with a mean age of 28.8 ± 8.3 (SD) years. None of the subjects had any evidence of liver or kidney disease as evaluated by serum creatinine, serum bilirubin and serum concentrations of alkaline phosphatases and transaminases. None was alcoholic or had cardiac insufficiency, nor did any patient receive drugs known to influence hepatic drug-metabolising enzymes. In the elderly group 10 subjects were free of drugs, 1 received 12.5mg bendroflumethiazide daily, another 0.125mg digoxin daily, and 2 received 5mg nitrazepam daily. The younger persons studied did not receive medicaments and none of the females took oral contraceptives. 6 of the young patients smoked 10 to 15 cigarettes daily, while none of the elderly group were smokers. Another 18 subjects (10 healthy young persons and 8 elderly patients) were later included in the study for correlating serum albumin concentration and protein binding of phenytoin (group B).

Informed consent was obtained from all the subjects after careful explanation of the risks and inconveniences that could reasonably be expected.

Trial Design

Liver volume was determined by ultrasonic scanning as described by Rasmussen (1978). The precision of the method tested in an autopsy series of 40 cases showed a correlation of $r = 0.95$ ($p < 0.001$) between volumes determined at autopsy and by ultrasound. The reproducibility of the method was tested in double determinations in 23 females and 26 males, with a mean difference between the two determinations of 12.3 and 9.5ml, respectively, with corresponding standard deviations in absolute liver volumes of 90.2 and 128.3ml, respectively.

The serum half-life and metabolic clearance rate of antipyrine were measured after an intravenous injection of 1g of antipyrine, as described by Johnsen et al. (1976), using the analytical method of Brodie et al. (1949). The half-life and metabolic clearance rate of phenytoin were determined after an intravenous in-

jection of 100mg phenytoin to which 20μCi ^{14}C-phenytoin had been added. The procedure has previously been described in detail (Lumholtz et al., 1975). Serum albumin was determined using the method of Rodkey (1965). The protein binding of phenytoin was determined by ultracentrifugation.

The kinetic studies with antipyrine and phenytoin were separated by a period of 1 to 2 weeks. The values given for antipyrine and phenytoin half-life and clearance rate are the means of 2 determinations analysed on different days. Free phenytoin clearance was calculated by dividing the total phenytoin clearance with the free (unbound) fraction of the drug.

The data were subjected to statistical analyses using the Students t-test and least squares linear regression and correlation.

Results

Figure 1 shows the correlation between serum albumin and the free fraction of phenytoin (group B) [$r = 0.95$; $p < 0.001$]. From this correlation free phenytoin fraction was read for the albumin concentration determined in the patients involved in the liver volume study (group A).

Liver volume varied between 862 and 2708ml. The antipyrine half-life and metabolic clearance rate ranged from 330 to 1578 minutes and from 14.8 to 81.5ml/minute, respectively. Phenytoin half-life and metabolic clearance rate varied from 373 to 1117 minutes and from 13.9 to 164.4ml/minute, respectively. Free phenytoin clearance varied between 90 and 815ml/minute. The coefficients of correlation

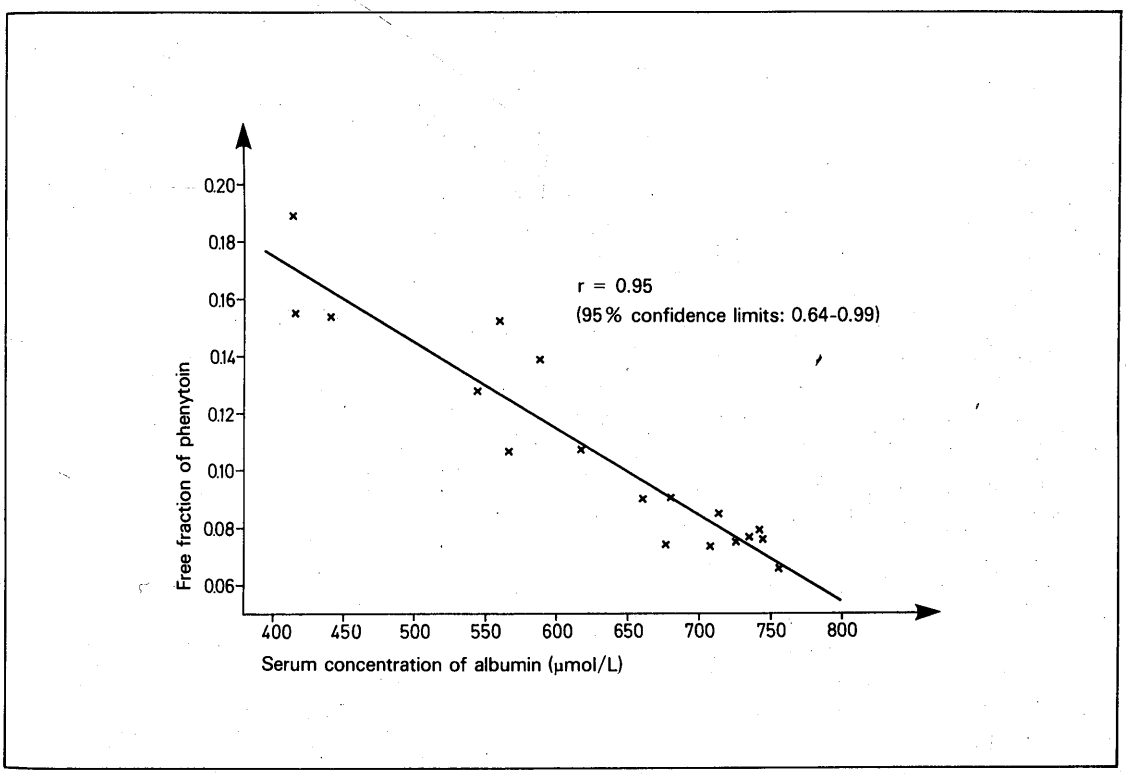

Fig. 1. Correlation between the serum concentration of albumin and the free fraction of phenytoin in 18 patients ($r = 0.95$; $p < 0.001$).

Table I. Correlation between liver volume and kinetic parameters of phenytoin and antipyrine[1]

Correlation	r	Significance
Liver volume and phenytoin $t_{1/2}$	− 0.34	NS
Liver volume and phenytoin clearance	0.71	$p < 0.001$
Liver volume and free phenytoin clearance	0.76	$p < 0.001$
Liver volume and phenytoin Vd	0.70	$p < 0.001$
Liver volume and antipyrine $t_{1/2}$	− 0.08	NS
Liver volume and antipyrine clearance	0.59	$p < 0.01$
Liver volume and antipyrine Vd	0.86	$p < 0.001$
Phenytoin $t_{1/2}$ and antipyrine $t_{1/2}$	0.31	NS
Phenytoin clearance and antipyrine clearance	0.43	$p < 0.05$
Free phenytoin and antipyrine clearance	0.73	$p < 0.001$

1 Abbreviations: $t_{1/2}$ = half-life; Vd = volume of distribution; NS = not significant.

between the above mentioned parameters are shown in table I. No significant correlation was found between liver volume and the half-lives of antipyrine and phenytoin. A significant correlation was, however, demonstrated between liver volume and metabolic clearance rate of antipyrine as well as between total and free clearance of phenytoin. No correlation was found between the half-lives of the 2 drugs, while a significant correlation existed between the clearance values.

Table II demonstrates (mean ± SD) body surface, liver volume and serum albumin in the younger patients (group I) compared with the elderly patients (group II). Body surface was significantly smaller in the elderly group. The size of the liver was also smaller in this group, and the difference was significant when related to the decrease in body surface. A significant decrease in serum albumin in group II compared with group I was also noted.

The pharmacokinetic parameters of antipyrine and phenytoin in the 2 groups of patients are given in table III. The half-life of antipyrine was significantly longer in the elderly and the metabolic clearance rate correspondingly lower, even when calculated per litre of liver volume. No significant differences in the 2 age groups were found in half-life and total clearance of phenytoin, while the free phenytoin clearance was significantly greater in the younger compared with the elderly subjects. The volume of distribution in younger subjects was significantly greater than in the elderly with antipyrine and free phenytoin, but no difference was found in total phenytoin.

In the younger age group no difference was found in the clearance rates of antipyrine and phenytoin between smokers and non-smokers.

Discussion

The method of determining liver volume by ultrasonic scanning used in this study has previously been shown to correlate with liver weights measured

at autopsy (Rasmussen, 1978). We found a decreased liver volume in a group of elderly subjects compared with a group of younger persons, and this decrease was significant when liver volume was related to the concomitant decrease in body surface. These results have been presented previously (Rasmussen et al., 1976) and confirmed by the later study of Swift et al. (1978).

No significant correlation was found between the half-lives of antipyrine and phenytoin and liver volume, while the metabolic clearance rate of antipyrine and total and free clearance rate of phenytoin correlated significantly with liver volume. The correlation coefficients, however, were so small that determination of liver volume seems of limited use in predicting the kinetics of drugs in clinical practice. Our results are in accordance with the studies of Roberts et al. (1976), Halliwell et al. (1977), Swift et al. (1978) and Pirttiaho et al. (1978), who also found a significant correlation between liver volume and antipyrine clearance in younger subjects and in patients with chronic liver diseases. Contrary to the present study, the latter work showed a significant correlation between liver size measured by technetium scans and antipyrine half-life. The findings are also in agreement with the results of Brien and co-workers (1975), who demonstrated a significant correlation between the half-lives of phenytoin and amylobarbitone (amobarbital), while no correlation was shown to exist between the half-lives of antipyrine and phenytoin.

Both antipyrine and phenytoin are metabolised in the microsomal enzyme system of the liver, and antipyrine has been proposed as a test drug of this system. Several correlations between the metabolism of antipyrine and other drugs metabolised in the liver have been carried out. Davies and co-workers (1973) found a significant correlation between the half-life of antipyrine and the half-lives of phenylbutazone and oxyphenbutazone after multiple dosing with the latter drugs, and also showed a significant correlation between the clearances of antipyrine and phenytoin, but no correlation was found between the half-lives of antipyrine and phenytoin. Cunningham and associates (1974) demonstrated a significant correlation between plasma acetanilide clearance and phenytoin clearance. Vesell and Page (1968, 1975) found a significant correlation between the half-lives of dicoumarol and phenylbutazone, but no correlation between the half-lives of these 2 drugs and that of antipyrine. Furthermore, Kadar and co-workers (1973) were also unable to show a significant correlation between the half-lives of antipyrine and amylobarbitone, sulphinpyrazone and glutethimide, while a

Table II. Clinical data and liver volume in the 2 age groups in group A (see text)[1]

Patient data	Group I (younger subjects)	Group II (elderly)	Significance
Number of patients	14	14	
Age (years)	28.8 ± 8.3	82.5 ± 7.1	
Body surface (m^2)	1.82 ± 0.23	1.60 ± 0.28	$0.03 < p < 0.05$
Liver volume (ml)	1732 ± 372	1435 ± 488	$0.05 < p < 0.10$
Liver volume per body surface (ml/m^2)	948 ± 109	795 ± 153	$0.01 < p < 0.02$
Serum albumin (μmol/L)	695 ± 45	549 ± 63	$p < 0.001$

1 Data are expressed as mean ± SD.

positive correlation among the half-lives of the latter 3 drugs was found. In accordance with the findings of Davies et al. (1973), we found no correlation between the half-lives of antipyrine and phenytoin, but showed a correlation between the clearance values of the 2 drugs. Comparing antipyrine clearance with free phenytoin, clearance increased the correlation coefficient from 0.43 to 0.73, and it thus seems likely that the lack of correlation in some of the above-mentioned studies could be caused by the use of inappropriate indices of drug disposition, such as half-life or the total clearance, instead of the appropriate index, free clearance of protein-bound drugs. The use of antipyrine as a test drug for dosage regimens of other drugs metabolised by the liver should be re-evaluated in the light of differences in protein binding.

We have confirmed the findings of O'Malley et al. (1971) and Vestal et al. (1975) concerning the longer half-life of antipyrine in the elderly. Our findings of decreased metabolic clearance rate of antipyrine in the elderly, even when related to liver volume (Rasmussen et al., 1976), indicate that the age-dependent reduction in antipyrine clearance is not only due to a smaller liver volume, but is also a result of reduced capacity of liver microsomes per unit of liver.

Conflicting results concerning age and phenytoin metabolism have been presented previously. Hayes et al. (1975b) found an increased clearance of phenytoin in the elderly, and suggested this to be caused by a documented decreased binding to serum albumin with increasing age. Houghton et al. (1975), however, demonstrated a weak positive correlation between age

Table III. Pharmacokinetic parameters of antipyrine and phenytoin in the 2 age groups in group A (see text)[1]

Pharmacokinetic parameter	Group I (younger subjects)	Group II (elderly)	Significance
Antipyrine $t_{1/2}$ (min)	465 ± 110	756 ± 318	$0.001 < p < 0.005$
Antipyrine Vd	40.4 ± 9.1	29.5 ± 8.6	$0.005 < p < 0.01$
Antipyrine clearance (ml/min)	61.9 ± 13.9	29.6 ± 9.5	$p < 0.001$
Antipyrine clearance (ml/min/L liver volume)	36.3 ± 8.9	22.8 ± 7.8	$p < 0.001$
Phenytoin $t_{1/2}$ (min)	636 ± 212	708 ± 218	NS
Phenytoin Vd (L)	40.9 ± 8.5	44.4 ± 18.1	NS
Free phenytoin Vd (L)	486.8 ± 89.1	296.3 ± 101.3	$p < 0.001$
Phenytoin clearance (ml/min)	48.4 ± 16.6	50.5 ± 36.9	NS
Phenytoin clearance (ml/min/L liver volume)	27.8 ± 7.7	32.8 ± 13.0	NS
Free phenytoin in serum (%)	8.6 ± 1.6	12.9 ± 2.1	$p < 0.001$
Free phenytoin clearance (ml/min)	569 ± 164	309 ± 134	$p < 0.001$
Free phenytoin clearance (ml/min/L liver volume)	325 ± 80	240 ± 92	$p < 0.05$

1 Data are expressed as mean ± SD.
Abbreviations: $t_{1/2}$ = half-life; Vd = volume of distribution; NS = not significant.

and serum phenytoin concentration. As regards phenytoin clearance rates and age, we found no correlation when total phenytoin clearance was used, while a significant difference in the 2 age groups was demonstrated when free phenytoin clearance was calculated. This is in accordance with the finding of decreased serum albumin concentrations in the elderly. The metabolism of phenytoin seems to be restricted to the circulating free drug concentration; consequently, the higher free (non-protein-bound) fraction in the elderly might compensate for the lower intrinsic metabolic capacity in the liver, resulting in unchanged total phenytoin clearance with increasing age (Wilkinson and Shand, 1975). The problems concerning dose-dependent kinetics of phenytoin do not seem to influence the results of this study, since first-order kinetics have been demonstrated after a single dose of 100mg phenytoin (Hansen et al., 1966).

In conclusion, we found decreased activity of the liver microsomes per unit liver in the elderly, demonstrated by reduced antipyrine and free phenytoin clearance. Protein binding of the drugs has to be taken into consideration when discussing age-dependent changes in drug metabolism.

Therapeutic Implications

The decreased ability of the hepatic microsomes to metabolise drugs in the elderly suggests the need for caution, when administering drugs which are biotransformed in the liver to this age group. However, general rules concerning dosage reduction with age cannot be given, since the protein binding of the drugs also has to be taken into consideration.

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Author's address: Dr *J. Mølholm Hansen*, Medical Endocrinological Department F, Herlev Hospital, *DK-2730 Herlev* (Denmark).