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Antipyrine Disposition and Liver Size in the Elderly

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Summary. This study has examined the contribution of decrease in liver size to the decline in drug metabolising capacity which occurs with ageing. Liver volume and antipyrine kinetics were measured in two groups of healthy individuals aged 20 to 29 years and 75 to 86 years and in a group of hospitalised patients aged 70 to 89 years. Liver volume was reduced in both groups of elderly people compared to the young group. Antipyrine plasma half-life was prolonged and antipyrine clearance was reduced in the group of elderly normal individuals. In this group the index – antipyrine clearance per unit liver volume – was also reduced in comparison to that of the young group. Measurements of antipyrine elimination in the hospitalised elderly group did not differ significantly from those in the young group. It is concluded that both decreased liver mass and decreased hepatic enzyme activity contribute to the impairment of drug oxidation which occurs in the elderly and which may warrant a reduction in dosage of some drugs. However, differences have been demonstrated between groups of elderly people suggesting that under certain circumstances standard doses of such drugs may be normally tolerated.

Key words: Drug metabolism, liver volume, the elderly, antipyrine clearance.

The capacity of the human liver to metabolise certain drugs is reduced in old age (Crooks et al., 1976) and prolongation of plasma half lives of amylobarbitone (Irvine et al., 1974) propranolol (Castleden et al., 1975), paracetamol (Triggs and Nation, 1975) and phenylbutazone (O'Malley et al., 1971) have been reported. Factors influencing drug metabolism have been widely studied by measuring plasma disappearance of antipyrine. This drug provides an ideal model being distributed as body water and being slowly and extensively hydroxylated in the liver (Brodie and Axelrod, 1950). Antipyrine half life is influenced by environmental factors such as drug exposure (Stevenson, 1977), smoking (Vestal et al., 1975) and nutrition (Krishnaswamy and Naidu, 1977), by genetic factors (Vesell and Page, 1968) and by disease processes (Branch et al., 1973). Interindividual differences in antipyrine half life are also caused by variation in body composition particularly liver size which correlates with antipyrine clearance (Roberts et al., 1976; Halliwell et al., 1976) and body water content which determines apparent volume of distribution. Antipyrine half life is prolonged in the elderly (O'Malley et al., 1971) and this has been presumed to be due to decreased hepatic microsomal enzyme activity. However, ageing is a complex process accompanied not only by changes in metabolic function which may be partly explained by environmental influences (Vestal et al., 1975) but also by changes in body composition. Particularly hepatic mass is known to be reduced in the elderly from autopsy studies (Boyd, 1933; Thompson and Williams, 1965). It was postulated that the diminution in hepatic mass could be an important factor in the impairment of antipyrine elimination in the elderly. This study was designed therefore to assess the change in hepatic mass and its contribution to the age-related decrease in drug metabolising capacity by measurement of liver volume and antipyrine kinetics in healthy subjects of differing ages. Possible differences in drug metabolising capacity between groups of elderly people were also explored by studying a group of elderly hospital in patients.

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Subjects and Methods

Three groups were entered into the study which was approved by the hospital ethics committee. Two of these comprised fifteen young healthy volunteers (aged 20–29 years) and eleven elderly healthy volunteers (aged 75–86 years). None had received any medication known to influence hepatic enzymes either at the time of the study or for at least one month previously. All were nonsmokers and had normal routine liver function tests and blood count. The names of the elderly healthy volunteers were obtained from the list of a general practice in South Bristol. All were clinically well, independent and living in their own homes. Informed consent was obtained in every case. The third group was of ten hospital in-patients (aged 70–89 years). They were all undergoing rehabilitation for locomotor disorders such as hemiplegia or osteoarthrosis and did not have other systemic illnesses. In other respects they fulfilled the same criteria as the healthy volunteers.

After control venous blood sampling 1200 mg antipyrine as a freshly prepared solution was administered to the fasting subjects. Further blood samples were obtained at 3, 6, 9, 13 and 24 h. Plasma antipyrine levels were determined by the method of Brodie et al. (1949). Antipyrine half-life ($t_{½}$) was calculated by least squares regression analysis of the log concentration-time plot, apparent volume of distribution (Vd) obtained from the dose divided by the plasma concentration back extrapolated to the time of administration and clearance from the single compartment formula:

$$\text{clearance} = \text{Vd} \times \frac{0.693}{t_{½}}$$

Liver volume was measured by an ultrasonic scanning technique previously described and evaluated (Roberts et al., 1976; Homeida et al., 1976). This method uses a combination of serial transverse and longitudinal ultrasonic B-scans to build up a three dimensional model of the liver. The technique has been shown to correlate closely with allometric methods of liver volume estimation in normal individuals and to be reproducible with a co-efficient of variation of 6%.

Results

The comparative data for age, body weight, liver volume and antipyrine disposition in the three groups are shown in Table 1. Indices derived from these data are shown in Table 2. Ageing was associated with significant reductions in body weight and liver volume. The age-associated reduction in liver volume was statistically significant when normalised for body weight. Ageing was associated with reduction in the volume of distribution of antipyrine and this reduction was statistically significant after normalising for body weight.

In the group of elderly normal subjects antipyrine half-life was prolonged and antipyrine clearance reduced in comparison to the young group. The index – antipyrine clearance per unit volume of liver – was also significantly reduced.

In the group of hospitalised elderly patients antipyrine half-life and clearance were similar to those of the young group and differed significantly from those of the elderly normal subjects. Antipyrine clearance expressed per unit liver volume was also significantly higher than in the elderly normal group and was higher than that of the young group although the latter difference was not statistically significant.

There was a significant correlation between antipyrine clearance and liver volume ($r + 0.54$, $p<0.01$) in the healthy individuals but no such correlation in the hospitalised elderly patients.

Discussion

This study has confirmed the previous observations that there is a decline in drug metabolising capacity with ageing. This decline can be attributed to a fall both in liver mass and in hepatic microsomal activity. However, it has demonstrated differences between groups of elderly subjects.

Antipyrine was used because it is rapidly and completely absorbed, minimally protein bound, distributed as total body water, and slowly and extensively hydroxylated in the liver (Brodie and Axelrod, 1950). Consequently its rate of clearance from the blood provides an index of hepatic drug oxidising capacity and it has been used widely to assess factors influencing drug metabolism (Stevenson, 1977). It does not serve as an indicator of non-oxidative pathways of drug metabolism, such as acetylation, which may show no impairment with ageing (Farah et al., 1977).

The prolonged antipyrine half-life and diminished antipyrine clearance observed in the elderly normal subjects in this study are consistent with previous findings (O'Malley et al., 1971; Vestal et al., 1975), and confirm the suggestion that drug oxidising ability declines with age. The reduced volume of distribution of antipyrine is consistent with the suggestion that total body water decreases with age (Edelman et al., 1952).

Table 1. Comparison of physical characteristics and antipyrine disposition in young and elderly normal subjects and elderly hospitalised patients

Subjects	Age range (years)	Body weight (kg)	Liver volume (ml)	Antipyrine disposition		
				Plasma half life (h)	Volume of distribution (l)	Clearance (ml/min)
Young normal n = 15	20–29	67±12	1303±289	11.8±2.9	41.6±8.7	41.8± 9.7
Elderly normal n = 11	75–86	58± 9*	990±166*	16.7±4.9**	32.8±5.8**	24.1± 7.2***
Elderly hospitalised n = 10	70–89	56±11*	838±242***	10.4±3.1[II]	28.0±4.1**[I]	33.7±11.0[I]

Mean±Standard deviation

(Student's t test)

* $p<0.05$
** $p<0.01$
*** $p<0.001$
in comparison to young subjects

I $p<0.05$ in comparison to elderly normal subjects
II $p<0.01$ in comparison to elderly normal subjects

Table 2. Derived data in young and elderly normal subjects and elderly hospitalised patients

Subjects	Liver volume/ Body weight (ml/kg)	Antipyrine volume of distribution/ Body weight (ml/kg)	Antipyrine clearance/ Liver volume (ml/min. vol -1)
Young normal	19.4±1.9	624±87	33.3±10.1
Elderly normal	15.3±3.8**	566±51*	24.5± 6.4**
Elderly hospitalised	15.6±3.9*	500±92**	42.7±17.1[I]

Mean±standard deviation
* $p<0.05$ compared to young subjects
** $p<0.01$ compared to young subjects
(Student's t test)
I $p< 0.01$ compared to elderly normal

The differences in liver volume and body weight demonstrated between the groups were anticipated from autopsy evidence that liver size decreases with age in association with a fall in body weight (Boyd, 1933; Thompson and Williams, 1965). In this population the decrease in liver volume was greater than the decrease in body weight. The postulate that the age-related fall in drug metabolising capacity could be explained by a fall in hepatic parenchymal mass has therefore been partly supported. However, the finding in the healthy volunteers that the index antipyrine clearance per unit liver volume was also lower in the elderly suggests that there is a reduction in the microsomal enzyme activity within the liver tissue. In studies on ageing in rats it has been found that liver size becomes smaller and microsomal preparations incubated with various substrates show reduced metabolic activity (Kato et al., 1964). The acquisition of comparable direct data in human subjects is not feasible on ethical grounds. This study, however, provides indirect evidence for the occurrence of similar changes with age in man.

The results obtained in the elderly hospital inpatients provide an interesting contrast which is not readily explained. Whilst liver volume and body weight were similar to those of the elderly healthy subjects the clearance of antipyrine was considerably greater being similar to that of the young subjects. The elevated value for the index antipyrine clearance per unit liver volume suggested a degree of hepatic microsomal enzyme induction in these patients. Factors to account for this difference could not be identified nor has such an effect been shown in previous studies using hospital patients (O'Malley et al., 1971). Nine of these ten patients were receiving drugs but none known to cause enzyme induction. There has so far been little investigation in man into the effect of ageing on the capacity of liver enzymes to respond to inducing agents. The results of one study in man (Salem et al., in press) and of animal

work (Kato and Takanaka, 1968) suggest that it may be reduced. The findings of this study suggest that the capacity for enzyme induction is at least partly retained in elderly people.

In conclusion hepatic drug oxidation as measured by antipyrine clearance declines in man with ageing and this is partly due to a decrease in liver size and partly to reduction in microsomal enzyme activity. There are also changes in body composition resulting in decreased body weight and decreased body water. Differences between groups of elderly people in their drug metabolising capacity exist so that under certain circumstances drug elimination rates may be normal. Research aimed at identifying factors which account for these differences should be undertaken. In particular direct evidence on the influence of ageing on enzyme induction is needed.

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