Editorial

Age and the Metabolism of Drugs

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Many factors contribute to the altered responsiveness of the elderly to drug therapy [1]. Of these, particular attention has been given to investigating the effect of age upon the rate of drug elimination since, unless appropriate reductions in dosage are made, significant age-related reductions in clearance will tend to lead to higher blood levels, and hence a greater risk of toxicity [2]. The effects of age on renal drug clearance are now well-documented [3-5], and parallel the decline in renal function which occurs in the elderly. Physicians are thus accustomed to matching the dosages of drugs which undergo renal excretion to elderly patients' renal function. In many instances, serum creatinine levels alone provide sufficient guide to appropriate doses although, for drugs with low therapeutic ratio, it may be necessary to measure plasma drug levels to avoid toxicity.

Age-related changes in the rates of drug metabolism have also been reported for many common therapeutic agents. Unfortunately, no clear pattern has emerged, and those changes that do occur are superimposed on the wide range of genetic and environmental factors known to influence rates of drug metabolism. Two general trends have emerged: first, and with some notable exceptions, drugs undergoing hepatic microsomal oxidation are likely to be metabolised more slowly in the elderly, whilst those that are conjugated are usually uninfluenced by age; second, drugs with high hepatic clearances and extraction ratios (such as chlormethiazole and labetalol), and which undergo extensive 'first-pass' metabolism during oral absorption, may show substantially increased bioavailability in the elderly [2].

It has been implied that age-related changes in drug metabolism occur as a consequence of diminished enzyme activities within the elderly human liver [6]. In the rat, particularly in the male, the specific activities of a variety of hepatic microsomal monooxygenases fall with age [6, 7] both in relation to the content of microsomal protein and to liver weight [8]. Moreover, these changes do not appear to be accompanied by an alteration in the affinity of microsomal monooxygenases for their substrates [8]. Studies in primates, however, have so far failed to replicate these findings. In macaque monkeys no age-related decline in the specific activities of enzymes involved in microsomal drug oxidation has been detected [9, 10]. Similar findings have emerged from studies of human hepatic microsomal monooxygenase activity. Thus, in liver obtained at cholecystectomy from patients aged 20 to 74 years, neither the specific activities [11], nor affinities [12], of three 'model' substrates for microsomal oxidation showed any correspondence with chronological age. Elderly individuals who are fit enough to undergo elective cholecystectomy are, of course, a selected population and these findings may not be
applicable to frail elderly patients either in hospital or in the community. Indeed, while we have recently shown that the activity of plasma aspirin esterase, a non-microsomal enzyme system responsible for the hydrolysis of aspirin [13], and whose activity in plasma correlates with that in liver, is similar in fit elderly volunteers and in healthy young adults, its activity is significantly reduced in ‘frail’ elderly patients in hospital.

‘Frailty’, even though of imprecise definition may thus be associated with altered hepatic drug metabolism. Such a possibility does not, however, explain why the rates of metabolism of some drugs decline with age while metabolising enzyme specific activity and affinity are unchanged even in fit individuals. Some years ago Swift and colleagues [8] suggested that a reduction in liver mass might account, at least in part, for decreased drug clearance in the ‘fit’ elderly [14]. Studies relating liver mass to age have relied on the obvious limitations of post-mortem data [15, 16]. We have therefore undertaken an investigation of the effect of age on both liver size (using ultrasound to measure liver volume), and liver blood flow (derived from the measurement of indocyanine green clearance), in 65 healthy volunteers aged between 24 and 91 years [17]. This has confirmed that both liver volume and apparent liver blood flow diminish with age irrespective as to whether these are expressed in absolute terms or in proportion to body weight. Relative liver volume was thus reduced by 42 per cent, and apparent liver blood flow by 47 per cent, over the age range studied although there was substantial variation between individuals. Liver perfusion, expressed as apparent blood flow per unit volume of liver, declined by 20 per cent.

These changes in apparent liver size and blood flow may explain, at least in part, the altered rates of drug metabolism which may accompany ageing. In particular, they may account for the reduced ‘first pass’ metabolism that has frequently been observed in the elderly. ‘Frailty’ may impose an additional decrease in metabolic drug clearance if there is an association with reduced specific activities of the enzymes involved. Unhappily, and unlike renal drug clearance, there is no simple method (such as measuring the serum creatinine levels) by which the metabolic drug clearance of an elderly individual can be assessed before initiating treatment with drugs which undergo metabolism mainly in the liver.

REFERENCES


