Br. J. clin. Pharmac. (1985), **20**, 327–331

A comparison of the pharmacokinetics of atenolol, metoprolol, oxprenolol and propranolol in elderly hypertensive and young healthy subjects

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1 Six elderly patients with established hypertension and six young healthy subjects were studied after 8 days of treatment with atenolol 50 mg day^{-1}, metoprolol 50 mg day^{-1}, oxprenolol 80 mg day^{-1} and propranolol 80 mg day^{-1}.
2 The area under the blood concentration-time curve was increased in the elderly group for each drug, but the difference was statistically significant only for atenolol.
3 The lower serum albumin concentrations in the elderly group did not result in a decrease in the percentage of propranolol or oxprenolol bound to serum proteins.

Keywords β-adrenoceptor blockers pharmacokinetics elderly

Introduction

Elderly patients have an increased risk of adverse drug reactions. Altered β-adrenoceptor antagonist pharmacokinetics have been reported in the elderly, but many of these studies have been conducted in hospitalised patients and the effect of increased plasma concentrations of β-adrenoceptor antagonists may be counteracted by decreased β-adrenoceptor sensitivity in the elderly (Vestal *et al.*, 1979b; Dillon *et al.*, 1980).

Elimination of β-adrenoceptor antagonists varies with the degree of lipid solubility. Propranolol (lipophilic) is extensively metabolised by the liver while atenolol (hydrophilic) is predominantly excreted by the kidney. In addition propranolol exhibits high affinity binding to α_1 acid glycoprotein (α_1-AGP) whereas atenolol is mainly unbound in plasma (Barber *et al.*, 1978). The aim of this within patient study was to determine the pharmacokinetic parameters of four β-adrenoceptor antagonists, of widely varying lipid solubility, in young volunteers and elderly hypertensive out-patients.

Methods

Subjects and design of investigation

Subjects Six young healthy volunteers (four male; age range 23–33 years; weight 68 ± 3 kg; ESR 3 ± 1 mm h^{-1}; serum creatinine 92 ± 5 μmol l^{-1}) and six elderly patients (four male; age range 66–72 years; weight 70 ± 3 kg; ESR 12 ± 5 mm h^{-1}; serum creatinine 101 ± 13 μmol l^{-1}) with established mild hypertension (mean blood pressure off treatment 161/94 mm Hg) were admitted to the study. Volunteers and patients were confirmed to have normal haematological, renal and hepatic function and none suffered from conditions in which β-adrenoceptor antagonists were contra-indicated. There were two smokers in each group of six subjects.

The study was approved by the Area Ethics Committee and all patients gave informed written consent to participate in the study.

Design Each subject received all four treatments—atenolol (A) 50 mg, metoprolol (M) 50

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mg, oxprenolol (O) 80 mg and propranolol (P) 80 mg—once-daily for 8 consecutive days, except for one elderly male subject (WR) who received only oxprenolol and metoprolol. On the eighth day of each treatment period, following a light breakfast, venous blood samples (10 ml) were taken through a non-heparinised cannula at 0.5, 1, 1.5, 2, 4, 8 and 12 h after the final dose. Urine was collected over the 12 h period for drug concentration measurements and creatinine clearance. A drug-free interval of 6 days intervened between each active treatment period. To facilitate laboratory assay of the drugs the order of administration of treatments was allocated so that one group of subjects (three young, three elderly) received the order OMPA and the other group received these drugs in the reverse order.

Analytical methods

Blood and plasma samples were stored at 4° C until analysis. After plasma protein binding studies, plasma was stored at −20° C until plasma concentrations were measured. Urine was stored undiluted at −20° C. All samples were assayed within 4 weeks of collection by gas liquid chromatography with electron capture detection.

Atenolol was measured as described by Scales & Copsey (1975), propranolol as described by Di Salle *et al.* (1973), and oxprenolol and metoprolol by the method of Degen & Reiss (1976), except that in the latter two methods dichloromethane : toluene (1 : 4 v/v) was used as the extracting solvent instead of ether or dichloromethane : ether (1 : 4 v/v).

The binding of all four drugs in plasma was measured by equilibrium dialysis using a Dianorm apparatus. A sample of 1 ml of plasma was dialysed against phosphate buffer (pH 7.4, 0.1 M) at 37° C for 3 h in Teflon half cells separated by a membrane (Visking 36/32). The percentage drug bound in plasma was measured either by the addition of trace amounts of radio-labelled drug (propranolol and metoprolol) or by g.l.c. analysis of drug concentrations on both sides of the membrane. [^{3}H]-propranolol (sp. activity 22 Ci mmol^{-1}) was obtained from Amersham International, U.K. [^{3}H]-metoprolol (sp. activity 145 mCi mmol^{-1}) was a gift from Hassle, Sweden.

Serum and urinary creatinine concentrations were measured by the routine service laboratory. All subjects had a basal level measurement as well as measurement on the eighth study day of each treatment period.

Pharmacokinetic analysis

The elimination rate constant, λ_z, and the terminal half-life, $t_{½}$, were calculated by linear regression analysis of data obtained between 4 and 12 h. The area under the blood concentration time curve (AUC) was calculated using the trapezoidal rule, the area beyond the last data point, extrapolated to infinity, being determined by dividing the concentration at the last data point by λ_z. The apparent oral clearance was calculated by dividing the administered dose by AUC. Renal clearance was calculated by dividing the amount of drug excreted in time, t, by the area under the blood concentration-time curve from $0 \rightarrow t$ (Harries *et al.*, 1972).

Statistical analysis

Pharmacokinetic parameters were compared between the two groups using Wilcoxon's rank sum test. Published values of the variance in the pharmacokinetics for the four drugs indicated that inclusion of six subjects in each group was adequate to give an 80% chance of seeing a two-fold difference between the young and elderly (Armitage, 1971).

Results

The mean values for peak blood concentration (C_{max}), time to reach peak concentration (t_{max}), area under blood concentration-time curve to ∞ (AUC), apparent oral clearance and terminal half-life for the four drugs in the two groups of subjects are shown in Table 1.

The mean values for C_{max} and t_{max} for each of the four drugs were not significantly different between the elderly and young groups although higher values were noted in the elderly group. AUC was higher for all four drugs in the elderly patients but significantly different only for atenolol. Consequently the apparent oral clearance was lower in elderly patients, the difference being most marked for atenolol. There was a trend towards longer half-life values in the elderly group, but sampling was not continued over a sufficiently long period for half-life values to be determined with precision.

In all four treatments, and off treatment, creatinine clearance was lower in the elderly group, but the decrease was not significant at the 5% level. However, there was no marked effect of either non-selective or selective β-adrenoceptor antagonists on renal function as measured by creatinine clearance, in either the young or the elderly group.

The correlation between atenolol renal clearance and creatinine clearance ($r = 0.92$; $P < 0.001$) is shown in Figure 1. There was also a weaker correlation ($r = 0.63$, $P < 0.05$) between

Table 1 Pharmacokinetic parameters of atenolol, metoprolol, oxprenolol and propranolol in young volunteers (Y) and elderly hypertensive patients (E) after oral dosing for 8 days.

		C_{max} (ng ml^{-1})	t_{max} (min)	AUC (ng ml^{-1} h)	CL (ml min^{-1})	$t_{1/2}$ (h)
Atenolol	Y	290 ± 39	148 ± 30	2556 ± 369	366 ± 52	4.8 ± 0.4
	E	380 ± 39	156 ± 35	5202 ± 960*	179 ± 27*	8.0 ± 1.4
Metoprolol	Y	83 ± 23	93 ± 11	557 ± 195	3380 ± 1302	3.7 ± 3.7
	E	105 ± 19	115 ± 27	898 ± 224	1179 ± 222	8.2 ± 3.7
Oxprenolol	Y	428 ± 47	80 ± 16	1493 ± 227	968 ± 101	2.0 ± 0.6
	E	546 ± 55	100 ± 30	2202 ± 322	672 ± 94	1.9 ± 0.3
Propranolol	Y	77 ± 14	130 ± 23	376 ± 85	4518 ± 932	3.0 ± 0.4
	E	99 ± 16	180 ± 37	787 ± 145	1982 ± 431	4.7 ± 0.8

Values are given as mean ± s.e. mean.
*$P = 0.02$, using Wilcoxon's rank sum test. P values refer to differences between the young and elderly subjects.

atenolol apparent oral clearance and creatinine clearance. There was no correlation of creatinine clearance with apparent oral clearance for any of the other β-adrenoceptor antagonists which are cleared mainly by hepatic metabolism. The mean values for plasma protein binding over a ten-fold concentration range for each of the four drugs are given in Table 2.

Propranolol and oxprenolol were extensively bound to plasma proteins (> 80%), whereas metoprolol and atenolol were 15 and < 10% bound to plasma proteins respectively. Albumin concentrations were significantly lower in the elderly group (Table 2), but there was no significant change in the drug plasma protein binding between the two groups, for any of the four drugs studied. α_1-AGP concentrations were not measured in this study but one elderly subject who had an ESR value of over 30 mm h^{-1} on each study day had the highest value in the group for the plasma protein binding of propranolol and as a result had the highest value in the group for the AUC of propranolol.

Table 2 Plasma protein binding of metoprolol, oxprenolol and propranolol at therapeutic concentrations

	Young	*Elderly*
Total protein (g l^{-1})	70 ± 1	66 ± 1
Albumin (g l^{-1})	46 ± 1	42 ± 1*
% drug bound		
Metoprolol	15 ± 1	15 ± 2
Oxprenolol	81 ± 3	84 ± 2
Propranolol	88 ± 1	90 ± 2

Values are given as the mean ± s.e. mean
*$P = 0.02$, using Wilcoxon's rank sum test.

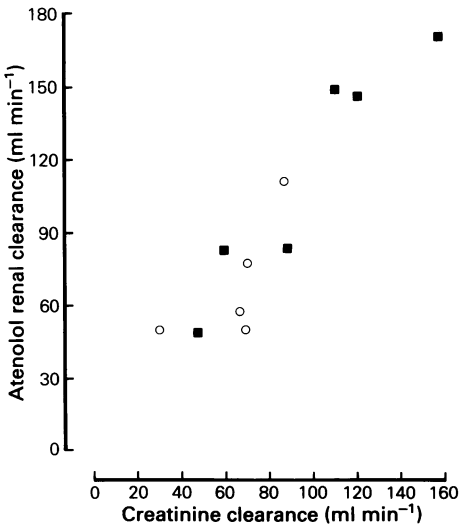

Figure 1 The relationship between atenolol renal clearance and creatinine clearance in young (■) and elderly (○) subjects.

Discussion

The overall trend in the present study was for the mean blood concentrations of all four β-adrenoceptor antagonists to be higher in the elderly, particularly in the post-absorption phase. The calculated areas under the blood concentration-time curves, extrapolated to infinity, for all four drugs were also greater in the elderly. The interindividual variation was least in the atenolol studies, which partly accounted

for the fact that the only statistically significant pharmacokinetic difference was seen in the atenolol comparison.

The increase in AUC could be due to either an increase in the amount of drug absorbed or a reduced rate of drug elimination. An increased absorption for propranolol, oxprenolol and metoprolol seems unlikely since all three drugs have been reported to be almost completely absorbed after oral administration (Paterson *et al.*, 1970; Reiss *et al.*, 1970; Regardh *et al.*, 1974). Atenolol is incompletely absorbed but a comparison of atenolol apparent oral clearance with atenolol renal clearance indicated that 31 ± 3% and 41 ± 6% of the dose was absorbed in the young and elderly groups respectively. These values are not statistically significantly different.

This suggests that for all four β-adrenoceptor antagonists the increased areas under the blood concentration-time curves in the elderly group are the result of decreased drug elimination, which in turn may be due to decreased hepatic metabolism, increased plasma protein binding and/or decreased renal excretion. The apparent oral clearance in the elderly group was statistically significantly different from the young group only for atenolol. This reflects the smaller inter-individual variation in atenolol kinetics compared with the lipid soluble β-adrenoceptor antagonists which undergo extensive first pass metabolism. In this study using a small group of fit elderly volunteers, renal clearance appears to be a more predictable determinant than hepatic clearance of altered pharmacokinetics due to age.

These results are in contrast to those of several other workers. Castleden and co-workers (1975, 1979) showed that propranolol blood concentrations were statistically significantly higher in the elderly after oral drug administration and suggested that this was due to a reduced hepatic extraction and 'first-pass' effect. However in their study the subjects were selected from older patients in long stay geriatric wards who may have had concurrent disease. In the present within patient study the subjects were fit, healthy and active. Such patients are not easy to select and studies are necessarily often based on small numbers. Our findings are supported by separate studies where the pharmacokinetics of propranolol, metoprolol and oxprenolol have been shown to be not significantly different between young and elderly subjects (Schneider *et al.*, 1980; Quaterman *et al.*, 1981; Regardh *et al.*, 1983; Kendall & Quarterman, 1982). However, Vestal and co-workers (1979a) found an age related reduction in intrinsic total clearance of propranolol in smokers. They suggest a decreased induction of drug-metabolising enzymes with ageing.

The reduced atenolol renal clearance with age is in contrast to a recent study by Rubin and co-workers (1982). In their study they found no correlation between creatinine clearance and atenolol clearance after intravenous administration. This was due partly to the greater variability in atenolol clearance, particularly in the young group, compared with creatinine clearance. They also suggested that after a low intravenous dose active tubular secretion may be important in the elimination of atenolol.

The reduction in atenolol renal clearance is in agreement with the results obtained with two other β-adrenoceptor antagonists, practolol and sotalol, that are also mainly eliminated by renal excretion (Castleden *et al.*, 1975; Ishikazi *et al.*, 1980). The reduction in atenolol renal clearance follows the general trend that the elimination of renally excreted drugs is decreased with increasing age.

Other factors were considered which may have contributed to the greater variability in the pharmacokinetics of the drugs eliminated entirely by metabolism. Firstly two subjects in each group were classified as smokers, but these subjects did not have the highest apparent oral clearance for propranolol, oxprenolol or metoprolol. Constituents of tobacco smoke are well known to induce hepatic drug metabolism (Pantuck *et al.*, 1974; Jusko, 1979). Secondly, after oral administration, changes in plasma protein binding may have a marked effect on the pharmacokinetics of highly bound drugs, such as propranolol and oxprenolol. That the plasma protein binding of propranolol and oxprenolol is unrelated to changes in serum albumin concentrations is not unexpected, as total blood concentrations of these drugs correlate better with serum α_1-AGP concentrations (Piafsky & Borga, 1977; Belpaire *et al.*, 1982). α_1-AGP concentrations were not measured in this study, but the ESR, which reflects serum concentrations of α_1-AGP was markedly raised in one subject. This subject showed the highest propranolol plasma protein binding and the highest total blood concentrations of propranolol. This confirms observations that variations in binding, unrelated to the ageing process, contribute to the altered pharmacokinetics of basic highly bound drugs.

In summary, from the results in our small group of selected subjects and other reports in the literature it is difficult to explain or attribute differences in the pharmacokinetics of drugs that are eliminated by hepatic metabolism to the increase in age. In contrast the pharmacokinetics

of drugs eliminated by renal excretion are more easily predicted from a knowledge of the creatinine clearance in individual subjects. However, a decreased creatinine clearance does not necessarily indicate the need for a reduced dosage, since cardiac β-adrenoceptor responsiveness is decreased in the elderly (Vestal *et al.*, 1979b; Dillon *et al.*, 1980) and β-adrenoceptor antagonists do not have a narrow therapeutic index. Only if renal excretion is markedly impaired would it appear prudent to decrease the dosage of non-metabolised β-adrenoceptor antagonists.

JWR was partly supported on a grant from I.C.I. Pharmaceuticals Ltd.

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(*Received 2 January 1985, accepted 31 May 1985*)