Comparison of pharmacokinetic profiles of single and multiple doses of a slow release Oros[®] oxprenolol delivery system in young normotensive and elderly hypertensive subjects

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1 Oxprenolol in an Oros[®] 8/130 sustained release osmotic pump system (equivalent to 120 mg oxprenolol hydrochloride in a conventional formulation and releasing 8 mg h⁻¹) was given to eight normal young subjects (mean age 23 years) and eight elderly hypertensive patients (mean age 77 years).

2 The plasma concentration–time profiles of oxprenolol were determined over 32 h using gas liquid chromatography after the initial dose and following seven doses.

3 The elderly patients had a significantly higher AUC and maximum plasma oxprenolol concentration following both the first and final doses studied.

4 It is unlikely that this difference is due to a prolonged absorption phase in the elderly patients. Reduced drug clearance seems the most probable explanation.

Keywords pharmacokinetics Oros oxprenolol elderly hypertensives

Introduction

Ageing produces many complex changes in physiology and metabolism and geriatric patients are particularly susceptible to undesirable side-effects compared with younger patients (Hurwitz, 1969). While altered drug responsiveness is a potential source of difference, a major factor is likely to be altered drug handling in the elderly. It is difficult to generalise about age-related changes in absorption, distribution, metabolism and elimination for individual drugs and direct investigation in the elderly population appears to be the most appropriate approach. The pharmacokinetics of oxprenolol have been investigated in elderly healthy volunteers following single and multiple twice-daily administration of 80 mg conventional tablets; the results showed

that drug handling was unaffected by age (Kendall & Quarterman, 1982). The individuals tested, however, were not hypertensive and extrapolation of this observation to elderly patients may be inappropriate.

Recently, osmotic drug delivery systems (Oros[®]) have been developed in which the drug is contained within a strong semi-permeable plastic tablet shell. Water from the gut is drawn through the shell by osmosis, dissolves the drug and forces out the resulting solution through a tiny single laser-drilled exit hole. The zero order release rate of drug is dependent on the solubility characteristics of the drug, and the thickness, area and permeability of the semi-permeable membrane. It is essentially independent of extra-

neous factors such as pH, luminal content and intestinal motility (Theeuwes, 1975; Eckenhoff *et al.*, 1981).

The development of an Oros® drug delivery system for oxprenolol has considerably extended the duration of drug release compared with existing slow-release formulations. The present study compares the pharmacokinetics of oxprenolol administered by an Oros® formulation in a group of elderly hypertensive patients with those in young normotensive subjects.

Methods

These studies received approval by the Committees on Ethical Practice of Guy's Hospital and Medical School (for normal subjects) and of Bromley Health Authority (for geriatric patients). All subjects and patients received a detailed explanation of the purposes and nature of the study and freely gave their witnessed consent.

Selection of subjects

The eight young normotensive volunteers were in apparent good health as ascertained by clinical examination, haematological and clinical chemistry tests (Table 1). They were required to have a normal ECG. Although none was taking current drug treatment, three of the females were taking low dose combined oestrogen-progestogen oral contraceptive pills. There were three non-smokers, four smoked less than five and one between five and ten cigarettes per day. They consumed an average of 15 (range 1–35) units of alcohol per week.

The elderly patients, all older than 70 years, had essential hypertension with a diastolic blood pressure >95–115 mm Hg and/or systolic pressure >170 mm Hg. Six were receiving no treatment for hypertension at the beginning of the study although three had previously been so treated. The other two patients were changed from existing, less effective treatment to oxprenolol. Essential treatment for concurrent disease (Parkinson's disease, hypothyroidism or arthritis) was continued during the study. None of the patients smoked more than 5 cigarettes day⁻¹ and only one regularly consumed alcohol (7 units week⁻¹).

Subjects and patients were oxidation phenotyped using debrisoquine according to the procedures used by Evans *et al.* (1980).

Procedures

The young normotensive subjects attended the hospital on the morning of the first and eighth

Table 1 Age, sex, weight and clinical chemistry details of young and old subjects

Group	n	Sex	Age (years)	Weight (kg)	Creatinine clearance (ml min ⁻¹ 1.73 m ⁻²)	ESR (mm h ⁻¹)	Total protein (g l ⁻¹)	Plasma albumin (g l ⁻¹)
Young normotensives	8	4M 4F	23 ± 0.3	68.3 ± 3.0	99 ± 3	3 ± 0.3	78.0 ± 1.4	45.0 ± 0.7
Elderly hypertensives	8	4M 4F	77 ± 1	58.9 ± 4.6	42 ± 7	23 ± 7.9	69.0 ± 1.8	42.0 ± 1.1

day of treatment, having fasted for at least 12 h overnight. The elderly patients were already hospital in-patients prior to enrolment in the study. At between 08.00 and 09.00 h an 8/130 oxprenolol Oros[®] tablet (equivalent to 120 mg oxprenolol hydrochloride in conventional formulations and releasing 8 mg oxprenolol h⁻¹) was administered with 100 ml water. Standardised meals were taken at 4 and 10 h and non-alcoholic drinks were permitted at 2 and 7 h post-dosing. Further doses were administered once-daily between 08.00 h and 09.00 h starting on the third and finishing on the eighth day. On the first and eighth day blood samples (10 ml) for oxprenolol estimation were drawn from a forearm vein via a cannula fitted with a heparin lock immediately before, and at 1, 2, 3, 4, 6, 8, 12, 14, 20, 24 and 32 h after dosing. Samples were placed in heparinised tubes and centrifuged immediately. Plasma fractions were separated and stored at -20°C to await analysis.

The supine resting pulse rate was recorded before drug administration and at 2, 4, 8, 12 and 24 h after dosing on days 1 and 8.

Drug and metabolite assay

Oxprenolol was determined in plasma by gas chromatography following derivatisation with trifluoroacetic anhydride (TFA). The plasma was extracted with diethyl ether/dichloroethane (4/1: v/v) under alkaline conditions (pH > 13) and then back extracted into acid which was then extracted again using the same solvent in the presence of a strong alkaline buffer (pH > 13). This organic phase was evaporated to dryness and derivatised with TFA. The derivative was chromatographed on 3% OV 1 on Gas Chrom Q using electron capture gas chromatography. Propranolol was used as an internal standard. This assay is linear over the range investigated (10–1500 ng ml⁻¹) with a lower limit of sensitivity of 10 ng ml⁻¹. Recovery of oxprenolol from spiked blank plasma is complete and the coefficient of variation for reproducibility is about 5% over the whole range 10–1500 ng ml⁻¹. Further details of this method in a slightly modified form have been published by Sioufi *et al.* (1983).

Debrisoquine and its 4-hydroxy metabolite were estimated in 8 h urine collections by gas chromatography with nitrogen-selective detection (Lennard *et al.*, 1977).

Pharmacokinetic data analysis

The maximum plasma concentration observed and time to this peak plasma concentration were taken directly from the data. The area under the

plasma concentration, time curve for the 32 h sampling interval was calculated using the linear trapezoidal approximation. Statistical comparisons were made using the non-parametric Wilcoxon signed rank tests for matched and unmatched pairs.

Results

Figure 1 shows the mean plasma oxprenolol concentration–time profiles on the first and eighth day of treatment for the two groups. Although unsuitable for formal pharmacokinetic modelling the least squares linear regression of ln (plasma concentration on time) yielded mean slopes of -0.0571 (normal subjects) and -0.0508 (elderly hypertensives). These give mean half lives of 12.2 h and 13.6 h, respectively. The plasma half-life of oxprenolol after intravenous injection is 2.31 ± 0.64 h in healthy subjects (Mason & Winer, 1976). This suggests that in the present study the rate of elimination is being controlled by the absorption rate.

Table 2 summarises the AUC and maximum plasma oxprenolol concentrations attained and the time of this peak. There were significant ($P < 0.002$) differences between the young normotensives and the elderly hypertensives for both AUC and peak plasma concentrations on both occasions. There were no significant

Figure 1 Plasma oxprenolol concentrations on days 1 and 8 of repeated administration of an 8/130 Oros system to young volunteers (●) and elderly hypertensives (□). Mean $\pm$ s.e. mean of eight individuals in each group.

differences in the times to reach peak concentrations.

The resting heart rates (mean $\pm$ s.e. mean) on day 1 for the young subjects and elderly patients were 65.3 ± 3.8 and 76.0 ± 2.6 beats min^{-1} , respectively ($P < 0.025$). At day 8 these became 59.5 ± 3.9 and 62.0 ± 1.7 beats min^{-1} (NS). The maximum reductions from baseline values in resting heart rate observed at day 1 were 10.1 ± 2.0 beats min^{-1} for the young normotensives and 18.0 ± 2.8 beats min^{-1} for the elderly hypertensives ($P < 0.025$). These were 5.0 ± 2.5 and 5.75 ± 1.2 beats min^{-1} respectively (NS) by day 8.

Mild adverse effects were noted by five of the young subjects (lethargy and tiredness on exertion, 3; sweating and flushing, 1; orthostatic giddiness, 1). Two of the elderly hypertensives complained of a single episode of vertigo (one of these 'blacked out' briefly).

Discussion

The plasma concentrations of oxprenolol following an 8/130 Oros formulation given singly or in multiple dose were higher in elderly hypertensives than in the young normal subjects. This is at variance with previously reported observations of no-difference between fit young and elderly subjects receiving oxprenolol in conventional formulation (Kendall & Quarterman, 1982). Another study (Rigby *et al.*, 1985) showed a mean increase of 48% in the area under the plasma concentration-time curve although this did not reach statistical significance. Similar observations of increased plasma concentrations of β -adrenoceptor blockers in elderly patients as compared to younger subjects have been made for propranolol (Castleden & George, 1979; Hitzengerger *et al.*, 1982), pindolol (Hitzengerger *et al.*, 1982) atenolol (Rigby *et al.*, 1985) and acebutolol (Roux *et al.*, 1983). However, other comparisons of the kinetics in young and old healthy subjects have failed to reveal differences for propranolol (Schneider *et al.*, 1980; Rigby *et al.*, 1985), or metoprolol (Quarterman *et al.*, 1981; Rigby *et al.*, 1985). The reason for the differences found in the present study may therefore lie in the fact that the elderly subjects studied were patients often on drug therapy for other disease processes rather than healthy old persons in the community, i.e. ageing *per se* need not necessarily affect the pharmacokinetics of oxprenolol. From the present study it is not possible to ascertain the mechanism for this observed difference. A number of possibilities may be considered.

Table 2 Parameters of plasma oxprenolol concentration-time curve following single and once daily dosing with 8/130 Oros® formulation to young healthy volunteers and elderly hypertensives (as mean $\pm$ s.e. mean apart from time to peak plasma concentration where median and range are given).

Subject group	AUC ($\text{ng ml}^{-1} \text{ h}$)		Peak plasma concentration (ng ml^{-1})		Time to peak plasma concentration (h)	
	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8
Young normotensives	1720 $\pm$ 411	2685 $\pm$ 612	105 $\pm$ 18	154 $\pm$ 28	9 (range 4-12)	6 (range 4-8)
Elderly hypertensives	6685 $\pm$ 1161	8127 $\pm$ 1339	375 $\pm$ 59	434 $\pm$ 63	10 (range 4-12)	8 (range 4-12)

(a) Increased absorption. In the case of conventional oxprenolol formulation, absorption is virtually complete (Reiss *et al.*, 1970). Although elderly hospitalised patients could possibly have a longer gastro-intestinal transit time than young free-living subjects, this is unlikely to have a significant effect on the total drug absorbed since nearly all of the drug contained in the Oros® system is released within 20 h (data on file, Ciba-Geigy). Also such factors are unlikely to affect the first few hours of drug absorption when the difference between our two groups of subjects was already apparent.

(b) Decreased hepatic first-pass metabolism and/or decreased hepatic oxprenolol metabolism in the older patients. There is a pre-systemic elimination of 60–75% of the absorbed fraction of drug (Mason & Winer, 1976; Kendall *et al.*, 1976). Differences in alcohol consumption or cigarette smoking between the two groups could contribute to the difference, for smoking reduces the steady state plasma concentrations of propranolol in both young and old individuals (Vestal *et al.*, 1979). There were no poor metabolisers of debrisoquine in either group, the metabolic ratios ranged from 0.13 to 7.83 for the young subjects and 0.30 to 7.18 in the elderly hypertensive patients.

(c) Changed oxprenolol distribution in the patients: basic β -adrenoceptor blockers exhibit high affinity binding to α_1 -acid glycoprotein which is a component of the acute phase proteins (Barber *et al.*, 1978; Belpaire *et al.*, 1982). Oxprenolol is about 78% bound in plasma and it has been found that patients with a raised erythrocyte sedimentation rate (ESR) $> 20 \text{ mm h}^{-1}$ had significantly higher peak plasma oxprenolol concentrations and larger AUCs than healthy subjects (Kendall *et al.*, 1979). Table 1 gives data for our subjects relating to ESR and protein and albumin concentrations in the plasma. There

was a significant difference ($P < 0.001$) between the two groups with respect to ESR. In addition, whilst the young subjects have a significantly ($P < 0.001$) higher total protein concentration, there was no significant difference between the albumin concentrations in the two groups. The binding of oxprenolol is unaffected by albumin concentration (Rigby *et al.*, 1985) being better correlated with α_1 -acid glycoprotein concentration and ESR (Belpaire *et al.*, 1982). Since the volume of distribution would increase in the presence of lower plasma protein concentrations, if a raised ESR were associated with higher plasma levels in our elderly patients, this implies increased binding in the presence of a raised ESR. This might also protect bound oxprenolol from hepatic clearance. The absence of data on the binding of oxprenolol in this investigation precludes further analysis.

(e) Miscellaneous effects to be considered include reduced renal function and creatinine clearance in the elderly (renal elimination is a minor pathway of oxprenolol elimination), lower body weight of patients, nutritional effects (the elderly were hospital patients) and the effects of hypertension itself.

Thus the present study, although unable to elucidate the mechanisms involved, indicates the magnitude of the difference in plasma concentration and kinetics encountered in practice in a population of elderly hypertensives. These results may be compared to those from groups of healthy young or elderly volunteers on which so much of our present knowledge of pharmacokinetics is based. They confirm the trend for higher plasma oxprenolol concentrations to occur in elderly hypertensive patients recently observed by Rigby *et al.* (1985). Further studies will be required to elucidate the mechanisms involved when an Oros® sustained release formulation is administered to elderly patients.

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