PRazosin DISPOSITION IN YOUNG AND ELDERLY SUBJECTS

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- 1 The disposition of prazosin following oral and intravenous administration has been studied in seven young and seven elderly men, all of whom were in good health and living independently in the community.
- 2 The elimination half-life (min) of prazosin was 123 ± 19.4 (s.d.) in the young and 194 ± 36 in the elderly ($P < 0.01$).
- 3 Clearance ($\text{ml min}^{-1} \text{kg}^{-1}$) was 3.94 ± 0.73 in the young and 3.53 ± 1 in the elderly ($P > 0.1$). Volume of distribution at steady state (1 kg^{-1}) was 0.63 ± 0.14 in the young and 0.89 ± 0.26 in the elderly ($P < 0.05$).
- 4 The absolute bioavailability of orally administered prazosin was 0.68 ± 0.17 in the young and 0.48 ± 0.16 in the elderly ($P < 0.05$).
- 5 The significant increase in prazosin half-life in the elderly results from an increased volume of distribution, not from decreased clearance.
- 6 Gastrointestinal absorption of prazosin decreases in old age.

Introduction

The hypotensive drug prazosin is subject to considerable hepatic metabolism. In man prazosin has been shown to undergo first pass metabolism with only 40–60% of orally administered drug reaching the systemic circulation unchanged (Bateman *et al.*, 1979). In the dog a direct study of prazosin hepatic extraction indicated that approximately 50% of the drug is removed at each pass through the liver (Rubin *et al.*, 1979). Following intravenous administration of prazosin to both rats and dogs extensive biotransformation occurs with less than 10% of the drug being excreted unchanged. The major route of metabolism is 6- and 7-*o*-dealkylation (Taylor, Twomey & Schach Von Wittenau, 1977).

It can be predicted that the absorption and elimination of prazosin might be altered when hepatic function is impaired. To date this possibility has only been investigated using oral doses in patients with congestive heart failure when both area under the drug concentration-time curve and half-life are significantly greater than corresponding values found in normal subjects (Jaillon *et al.*, 1979).

Liver function tends to decrease with age (Kampman, Sinding & Moller-Jorgensen, 1975) and several drugs which undergo mainly hepatic clearance have been shown to have altered dispositional characteristics in the elderly (Stevenson, Salem &

Shepherd, 1979). The study reported here was designed to investigate the pharmacokinetics of prazosin in elderly subjects.

Methods

Fourteen subjects participated in the study after giving informed written consent. The study was approved by the Research and Ethical Committee of the Glasgow Northern District. Seven subjects were young and ranged in age from 22 to 32 years and the other seven subjects were elderly with an age range of 66 to 78 years. The elderly subjects were all living independently in the community and were recruited with the help of their family doctors. All subjects were normal on physical examination before entering the study, none had suffered from any serious illness in the past or was receiving any medication and all has normal biochemical, haematological and electrocardiographic indices. The young subjects ranged in weight from 61 to 87.2 kg (mean 77.5 kg) and the elderly from 59.5 to 98 kg (mean 77.8 kg).

Each subject was studied on two occasions at least 1 week apart. On one study day subjects received 1 mg of prazosin orally 3 h after a light breakfast and 5 ml blood samples were drawn through an indwelling venous cannula at 0, 15, 30, 60, 90, 120, 150, 180, 240,

300, 360, 420 and 480 min with the subject supine. On the other study day young subjects received 1 mg and elderly subjects 0.5 mg of prazosin gluconate by rapid intravenous injection and samples were drawn from the other arm at the times given above and in addition at 1, 2, 5, 10, 20 and 40 min. Blood pressure was monitored closely during the injection of prazosin and at regular intervals during both study days using an automated blood pressure recorder. Whole blood was stored at -20°C until analysed by high pressure liquid chromatography using fluorescence detection (Yee, Rubin & Meffin, 1979). This method has a coefficient of variation of 5–10% over the concentration range 2 nmol/l to 100 nmol/l. All samples were analysed within 4 weeks of being collected. It has previously been shown that prazosin is stable in whole blood at -20°C for at least 6 months (Yee *et al.*, 1979).

Pharmacokinetic analysis

Blood concentration *v* time data following intravenous administration were fitted to a biexponential function of the form:

$$\text{Cp}(t) = \text{Ae}^{-\alpha t} + \text{Be}^{-\beta t} \quad (1)$$

using a nonlinear least squares regression programme based on the Marquardt algorithm (Bevington, 1969) with reciprocal weighting on a Varian V70 series computer. The slope of the disappearance phase after oral prazosin was estimated by fitting the terminal log-linear phase of the prazosin concentration-time curve to a monoexponential decay function using the nonlinear least squares computer programme. The area under the concentration versus time curve during the blood sampling period was calculated using the trapezoidal rule. The extrapolated area beyond the last data point was calculated by dividing the concentration at the time of the last sample by the terminal slope obtained from the computer fit of the data following intravenous injection. The total area under the curve ($\text{AUC}_{\text{oral}}]_{0}^{\infty}$ or $\text{AUC}_{\text{i.v.}}]_{0}^{\infty}$) is the sum of these two areas.

The absolute bioavailability (F), defined as the fraction of an oral dose which reaches the systemic

circulation in unchanged form, and clearance (Cl) were determined by the following model-independent expressions:

$$F = \frac{\text{AUC}_{\text{oral}}/\text{dose}_{\text{oral}}}{\text{AUC}_{\text{i.v.}}/\text{dose}_{\text{i.v.}}} \quad (2)$$

$$\text{Cl} = \frac{\text{Dose}_{\text{i.v.}}}{\text{AUC}_{\text{i.v.}}} \quad (3)$$

The first pass metabolism of prazosin is not saturable over a wide dose range: the AUC/mg following 5 mg to young subjects (Jaillon *et al.*, 1979) is not greater than the AUC seen in the present study. The coefficients of the biexponential equation were used to calculate the volume of distribution at steady state (V_{dss}) according to standard techniques assuming a two compartment open model with elimination from the central compartment.

Statistical analysis

Data are expressed as mean $\pm$ s.d. However, in order to minimise assumptions about the distribution of data, comparisons between young and elderly groups were performed using the Wilcoxon rank sum test.

Results

Supine blood pressure did not fall substantially following prazosin administration and none of the subjects experienced any adverse effects.

Table 1 shows the coefficients of the biexponential equation to which the intravenous data were fitted. The elimination half-life of prazosin was the same following intravenous and oral administration both for the young group who received the same dose by each route (123 min i.v.; 126 min oral) and for the elderly subjects who received a lower intravenous compared to oral dose (194 min i.v.; 188 min oral).

The half-life, clearance, V_{dss} and bioavailability of prazosin in young and elderly subjects are shown in Table 2. Half-life was significantly longer in the elderly subjects but clearance did not differ between

Table 1 Coefficients of the equation: $\text{Cp}(t) = \text{Ae}^{-\alpha t} + \text{Be}^{-\beta t}$. Young subjects received 1 mg and elderly subjects 0.5 mg of prazosin intravenously. Data are expressed as means $\pm$ s.d. The mean coefficients of determination for the fitted curves were 0.97 (young) and 0.933 (old). A and B have the units of nmol l^{-1} ; α and β have the units of min^{-1} .

	A	α	B	β
Young	202 $\pm$ 187	0.232 $\pm$ 0.187	45.8 $\pm$ 13.7	0.00573 $\pm$ 0.0009
Old	84.5 $\pm$ 42.4	0.172 $\pm$ 0.13	18.0 $\pm$ 3.1	0.00368 $\pm$ 0.0006

Table 2 Pharmacokinetic indices of prazosin in young and old subjects: mean $\pm$ s.d.

	$T_{1/2}$ (min)	Cl (ml min ⁻¹ kg ⁻¹)	V_{dss} (l kg ⁻¹)	F
Young	123 $\pm$ 19.4	3.94 $\pm$ 0.73	0.63 $\pm$ 0.14	0.68 $\pm$ 0.17
Old	194 $\pm$ 36.0**	3.53 $\pm$ 1.0	0.89 $\pm$ 0.26*	0.48 $\pm$ 0.16*

** $P < 0.01$, * $P < 0.05$ compared to young subjects (Wilcoxon Rank Sum Test)

the two groups either when expressed in terms of unit weight (see Table 2) or in absolute terms (308 $\pm$ 80 ml min⁻¹ in the young, 274 $\pm$ 84 ml min⁻¹ in the elderly; $P > 0.1$). Volume of distribution at steady state was significantly greater in the elderly both when expressed in absolute terms (49.4 $\pm$ 14.8 l in the young, 69.2 $\pm$ 20.0 l in the elderly; $P < 0.05$) and when analysed in terms of unit weight (Table 2).

Bioavailability was significantly lower in the elderly than in the young, less than half the orally administered drug reaching the circulation in unchanged form (Table 2). The AUC_{0- ∞} values per mg (μ mol min l⁻¹) were as follows: Intravenous: 9.0 $\pm$ 2.5 young; 10.2 $\pm$ 2.9 old; oral: 6.1 $\pm$ 1.7 young; 4.6 $\pm$ 0.4 old.

Discussion

The disposition of several drugs which undergo liver metabolism has been studied in the elderly and in most cases the half-life has been prolonged. However, a knowledge of half-life alone provides only limited information about the changes in disposition which might occur in the elderly. This is because half-life is itself determined both by clearance and by volume of distribution:

$$T_{1/2} = \frac{V_d}{Cl} \times 0.693 \quad (4)$$

Volume of distribution and clearance can properly be determined only from data produced by intravenous administration of a drug as described above. Pharmacokinetic studies in the elderly have been performed using intravenous administration with only a few drugs including antipyrine (O'Malley *et al.*, 1971) phenytoin (Hayes, Langman & Short, 1975) diazepam (Klotz *et al.*, 1975), chlordiazepoxide (Roberts *et al.*, 1978), propranolol (Castleden & George, 1979), chlormethiazole and lignocaine (Triggs, 1979).

Increasing age had no consistent effect on the disposition of these drugs. Antipyrine, propranolol, chlordiazepoxide and chlormethiazole showed a decreased clearance in the elderly. While phenytoin was reported to have an increased clearance in old

subjects the data cannot be considered persuasive for two reasons: the number of data points is small and the clearance values do not differ significantly on testing by non-parametric analysis. Both diazepam and lignocaine showed a significant prolongation of half-life in the elderly but in neither case did this result from a reduction in clearance. For both these drugs a significant increase in volume of distribution at steady state was found in the elderly and was responsible for the longer half-lives.

It is this last pharmacokinetic pattern—prolonged half-life associated with greater V_{dss} —which characterises the influence of age on the disposition of prazosin. The V_{dss} is determined largely by the physicochemical interaction between drug and body. In general terms a lipophilic drug will distribute widely across membranes and will accumulate particularly in adipose tissue. Since the ratio of adipose to lean tissue increases with age (Bender, 1964) it would not be unexpected to find lipophilic drugs demonstrating a greater V_{dss} in the elderly. Prazosin has, in fact, only modest lipophilic properties (Taylor *et al.*, 1977) and its 40% greater V_{dss} in the elderly is presumably a reflection of this fact when viewed against the 200–300% changes seen with the far more lipophilic drug diazepam.

Prazosin, diazepam and lignocaine have in common not only the V_{dss} changes with age and the similarity of clearance between young and old, but also their route of elimination: demethylation. Four drugs which undergo demethylation have so far been studied adequately in the elderly and only one, chlordiazepoxide, demonstrates a reduction in clearance. Among the other drugs with a proven decrease in clearance with age antipyrine and chlormethiazole are hydroxylated while propranolol undergoes complex degradation which includes hydroxylation. It would seem possible that different metabolic pathways are influenced to a different extent by the ageing process.

The bioavailability of prazosin was significantly reduced in the elderly, about 40% less unchanged drug reaching the systemic circulation compared with the young. This is in contrast to the findings with propranolol (Castleden & George, 1979) which is the only other drug whose bioavailability has been comprehensively studied in the elderly. Both the

decreased clearance and increased bioavailability of propranolol in the elderly have been attributed to decreased activity of the metabolic pathways responsible for clearance and pre-systemic extraction. Although the enzymes which mediate these two processes are not necessarily the same, we have demonstrated that prazosin clearance is not reduced in the elderly and it is, therefore, not altogether surprising that first pass metabolism is apparently not reduced either. Instead, the absorption of prazosin is actually lower in older subjects. Again, physiological changes of old age can explain this observation since intestinal blood flow decreases, the number of absorbing cells probably decreases and malabsorption (secondary to colonisation of increased numbers of duodenal diverticula) tends to increase in the elderly (Bender, 1968).

The pharmacokinetic changes described here for prazosin in the elderly are unlikely to have major clinical importance. A prolonged half-life caused by

increased V_{dss} will result in a longer time to steady state but the concentration at steady state will not differ from the young. However, even the time to steady state is of little clinical interest for a hypotensive drug with such a short half-life. It would appear that elderly patients are likely to absorb significantly less drug than their younger counterparts, though the clinical significance of this fact cannot be determined until concentration-effect relationships in the elderly have been defined.

The results presented here illustrate well the importance of using intravenous administration of drug when performing pharmacokinetic studies. Half-life alone provides only limited information concerning distribution and elimination.

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