PHARMACOKINETICS OF AZAPROPAZONE IN THE ELDERLY

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Plasma concentrations of azapropazone have been measured in young and elderly subjects after a single dose of 600 mg azapropazone. Maximum concentrations were higher in the elderly. Renal function was impaired in the older subjects. Mean azapropazone clearance was significantly reduced ($P < 0.001$) in the old, compared to the young. Elimination half-life was prolonged but the difference did not reach statistical significance due to the wide variation of the values in the elderly. The volume of distribution of azapropazone and degree of adipose tissue did not differ between the two groups. Azapropazone clearance correlated well with creatinine clearance ($P < 0.001$) when all the subjects were included and for the younger subjects only but not for the elderly patients alone. The addition of fat mass into the regression equation improved the relationship in all groups but in the older group levels of statistical significance were not achieved. Reasons for the difference between young and old are discussed. The effect of age on the pharmacokinetics of azapropazone suggest that therapeutic plasma levels may be achieved with a dose of 600 mg daily.

Introduction

Non steroidal anti-inflammatory drugs are frequently used in the management of elderly patients suffering from all forms of arthritis. However, they are all capable of causing damage to the gastric mucosa by a complex mode of action (Duggan, 1981). The risk of such damage may be greater in the elderly because the frequency of adverse drug reactions in general increases with advancing age (Hurwitz, 1969). Altered pharmacokinetic parameters in the aged resulting in raised plasma drug concentrations may be partly responsible for this increase. This is of particular importance for drugs eliminated by the kidney (Triggs *et al.*, 1975).

Azapropazone (5-dimethylamino-9-methyl-2-propyl-1H-pyrazolo [1,2- α] [1,2,4] benzotriazine-1-3 (2H)-dione dihydrate, Rheumox®) is a non steroidal antirheumatic agent introduced into clinical practice in the UK in 1976. Preliminary pharmacokinetic studies (Schatz *et al.*, 1970) suggested that the half-life of azapropazone in healthy volunteers was between 4 and 16.5 h. Klatt & Koss (1973) using [14 C]-azapropazone broadly confirmed these findings; showing a mean half-life of 12 h. Metabolic studies (Schatz *et al.*, 1970) demonstrated that azapropazone is not extensively metabolised. Approximately 60–70% of the administered dose appears in the urine as unchanged azapropazone, with approximately 15–20% appearing as the 6-hydroxylated metabolite. Thus, clearance of azapropazone appears to be primarily renal. In view of this, and because of the deterioration in renal

function with age (Davies & Shock, 1950), the present study was undertaken to compare the pharmacokinetic profile of azapropazone in elderly patients and young volunteers.

Methods

Twelve elderly patients aged from 76 to 96 years and six volunteers aged from 19 to 37 years took part in the study. Eleven of the patients presented with osteoarthritis, the remaining patient had rheumatoid arthritis; they were all symptom free and none were receiving analgesics chronically. All gave their informed consent. An attempt was made to select patients not receiving concurrent drug therapy. If this was not possible, all drugs were withheld for 24 h before the start of the study, and a record was made of all drugs taken within the 2 weeks prior to the study. Five patients had received one drug each in this period. The drugs involved were co-trimoxazole, flavoxate, benorylate, danthron with poloxamer and dextropropoxyphene with paracetamol. Serum creatinine and urea, weight and skinfold thickness were measured immediately before the start of the study. Skinfold thickness was measured by Harpenden calipers from the biceps, triceps, subscapular and suprailiac regions.

All subjects were fasted for 10 h prior to and for 2 h subsequent to the administration of azapropazone.

During the latter period they were not allowed to assume the recumbent position. Azapropazone 600 mg was administered (in the form of two Rheumox capsules) with 200 ml of water. Venous blood samples were taken at the following times relative to the administration of azapropazone: 0, 0.5, 1, 2, 4, 8, 12, 24, 48, and 72 h. The blood was collected in EDTA tubes containing 10 mg ascorbic acid, centrifuged immediately, and the plasma stored at -20°C . Azapropazone in the plasma was assayed using a colorimetric method based on the method of Farrier (1974). The limit of sensitivity of the method was 2 $\mu\text{g/ml}$ and the precision varied from 1.8 per cent to 2.3 per cent at concentrations of 100 $\mu\text{g/ml}$ and 40 $\mu\text{g/ml}$ within batch and from 2.4% to 6.7% between batches.

Pharmacokinetic parameters were calculated using standard techniques (Gibaldi & Perrier, 1975) on the assumption that the drug was completely absorbed in all subjects. Rate constants were calculated using the computer program ESTRIP (Brown & Manno, 1978). Area under the curve (AUC) from 0 to 72 h was calculated using the trapezoidal rule. AUC from 0 to ∞ was calculated by dividing the concentration at 72 h by the elimination rate constant (k_{el}) and adding this to AUC 0–72 h.

Creatinine clearance was calculated from serum creatinine using a modification by Kerr (1980) of the formula of Cockcroft & Gault (1976) as follows:

$$\text{Creatinine clearance} = \frac{K \times (140 - \text{Age}) \times \text{Weight (kg)}}{\text{Serum creatinine}}$$

In males $K = 1.23$, and
in females $K = 1.04$

Fat mass was calculated from the sum of the four skinfold thicknesses using the nomogram of Durnin & Rahaman (1967). In the statistical analysis no paired *t*-tests were used to compare the two groups and the linear regression was calculated using the MINITAB program.

Results

The physical characteristics of the subjects are shown in Table 1. In addition to age, there were significant differences in creatinine clearance and serum urea between the two groups ($P < 0.001$ and $P < 0.002$

respectively) reflecting impaired renal function in the elderly.

Mean plasma concentrations are shown in Figure 1. The differences between the two groups are clearly shown in terms of increased AUC, maximum plasma concentration and increased elimination half-life in the elderly patients. The relevant pharmacokinetic parameters are shown in Table 2. There was a statistically significant difference between the two groups in terms of AUC and azapropazone clearance ($P < 0.02$ and $P < 0.001$ respectively). Although marked differences were found in the half-life and maximum plasma concentration, statistical significance was not achieved due to the large variation in these parameters, particularly in the elderly patients. For example, one patient aged 93 years had a half-life of 73.4 h whereas another aged 96 had a half-life of only 20.6 h. There was no difference in volume of distribution, either in absolute terms, or related to body weight.

There was a significant correlation between creatinine clearance (CL_{cr}) and azapropazone clearance (CL_{az}) for all the subjects studied ($r = 0.75$, $P < 0.001$) and for the younger volunteers alone ($r = 0.80$, $P < 0.05$). However, the relationship between these two variables was poor in the elderly group ($r = 0.03$, $P > 0.05$). Using multiple regression analysis, azapropazone clearance could be predicted by the following equation:

$$\text{CL}_{az} = 0.206 + 0.0065 \text{CL}_{cr} - 0.0129 \times \text{Fat mass}$$

Again, there was a significant correlation between 'observed' clearance and 'calculated' clearance of azapropazone when data from all the subjects were used ($r = 0.83$, $P < 0.001$) and for the younger group ($r = 0.97$, $P < 0.001$) but not for the elderly group ($r = 0.31$, $P > 0.05$).

Discussion

The main kinetic differences between the groups were azapropazone clearance and terminal half-life. Delayed plasma clearance due to the decline in renal function with old age is in keeping with the findings of studies using digoxin (Cusack *et al.*, 1979) and sulphamethiazole (Triggs *et al.*, 1975). It is surprising that there was a poor correlation with creatinine

Table 1 Physical characteristics of the subjects studied. Mean $\pm$ s.d. values are given

	n	Age (years)	Weight (kg)	Fat mass (kg)	Creatinine clearance (ml/min)	Serum urea (mmol/l)
Patients	12	85 ± 7	56 ± 13	16 ± 6	36 ± 11	6.7 ± 1.7
Volunteers	6	26 ± 7	65 ± 9	17 ± 3	63 ± 29	4.6 ± 0.5

Figure 1 Mean plasma azapropazone concentrations following the administration of azapropazone 600 mg. (O) volunteers, (●) elderly patients.

clearance in the older group, particularly as Ewy *et al.* (1969) have demonstrated a direct relationship between the renal clearance of digoxin and endogenous creatinine clearance. One reason for the discrepancy may have been that creatinine clearance in our study was not measured directly. However, the formula used had been derived from subjects aged between 18 and 92 years. Another possibility is an increase in hepatic metabolism in the presence of reduced renal elimination. This is unlikely to have exerted a profound effect on plasma clearance of azapropazone as the extent of hepatic metabolism of this drug is usually small and there was no consistent increase in drug clearance in patients with low creatinine clearance. The influence of previous drug therapy on

hepatic or renal function is also unlikely since only two patients had been receiving drugs which could have had such an effect. It is possible that the drug was eliminated by the kidney by means of tubular secretion. However, if this were the main method of excretion, it is unlikely that drug clearance would have shown a highly significant correlation with creatinine clearance in the young subjects. Tubular function could have played a more important role in the elderly group. However, it also declines with advancing age (Davies & Shock, 1950) and would not explain why some elderly individuals had values for drug clearance in the same range as the younger subjects. The lack of correlation between drug and renal clearance may have been due to the fact that

Table 2 Pharmacokinetic parameters (mean $\pm$ s.d.). The range of values is shown in parentheses.

	n	$AUC_{0-\infty}$ ($\mu\text{g ml}^{-1} \text{ h}$)	$t_{1/2}$ (h)	V (l/kg)	C_{max} ($\mu\text{g/ml}$)	CL_{az} (l/h)
Patients	12	2368 ± 1010 (1258–4017)	31 ± 15 (11.8–73.4)	0.21 ± 0.08 (0.10–0.38)	51.5 ± 19 (27.5–86.1)	0.292 ± 0.11 (0.145–0.481)
Volunteers	6	1144 ± 291 (833–1508)	18 ± 5 (12.9–24.3)	0.22 ± 0.09 (0.12–0.38)	43.4 ± 9 (34.4–54.0)	0.551 ± 0.15 (0.386–0.734)

$t_{1/2}$ = Terminal half-life

V = Apparent volume of distribution

C_{max} = Maximum plasma concentration achieved

CL_{az} = Azapropazone clearance

AUC = Area under the curve.

the method for estimating renal function based on creatinine becomes less accurate at greatly reduced glomerular filtration rates when tubular secretion of creatinine occurs (Kerr, 1980). Thus, it may not be possible to predict drug clearance in elderly individuals by simple methods of renal function.

Although the difference in elimination half-life did not reach statistical significance, due to wide variability, its prolongation in the older group almost certainly was a real effect, particularly in view of the data obtained with other renally cleared drugs in the studies quoted above. The much greater variation in half-life with age has also been noted by Cusack *et al.* (1979) although their mean values for digoxin were significantly different ($P < 0.05$). However, the range for azapropazone was greater than that for digoxin, possibly because one quarter of our elderly group were nonagenarians.

Crooks *et al.* (1976) suggested that the changes in body composition due to ageing may affect drug distribution so that lipid soluble drugs may distribute

more widely in old age. However, fat mass is not usually measured in pharmacokinetic studies and a difference in body composition between old and young has been assumed. We have shown that such generalisations cannot be applied to small groups of individuals since mean body fat content was the same in both our groups.

Our findings have important implications in terms of dosage of azapropazone in the elderly. The patients used in the study were typical of those treated with non steroidal anti-inflammatory agents. The reduced azapropazone clearance suggests that multiple dosing in older subjects with the same daily dose used for younger individuals would result in higher steady state plasma concentrations which would increase the risk of adverse reactions. Further, therapeutic concentrations could be achieved with a reduced daily dose. We would, therefore, advise that therapy be commenced in elderly patients with a daily dose of 600 mg rather than the currently recommended dose of 1200 mg.

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