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PHARMACOKINETIC OBSERVATIONS ON PIROXICAM IN YOUNG ADULT, MIDDLE-AGED AND ELDERLY PATIENTS

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Nineteen out of 21 patients with painful conditions of the locomotor system aged between 27 and 94 years completed a study in which they received 20 mg piroxicam daily for 14 days. Plasma piroxicam concentrations were estimated by high performance liquid chromatography. Pharmacokinetic analysis of the data showed the half-life and systemic clearance of piroxicam to be unaffected by age. The apparent volume of distribution in older patients was higher than that of younger subjects. Multiple regression analysis showed that creatinine clearance and plasma albumin concentration had insignificant effects on the systemic piroxicam clearance. Although improvement in joint pain and stiffness occurred during the 2 week study period, this could not be correlated with plasma piroxicam concentration.

Keywords piroxicam pharmacokinetics age

Introduction

Piroxicam is a relatively recently introduced non-steroidal anti-inflammatory agent (NSAIA) which belongs to the novel chemical group of oxicams. Clinical trials in both acute and chronic rheumatic conditions show it to be a useful addition to presently available NSAIAs. It is readily absorbed following oral administration and its long plasma half-life allows once daily dosing which is a possible advantage in improving compliance, particularly in elderly patients. It is extensively metabolised to inactive products in man by ring hydroxylation, glucuronide formation, cyclodehydration and to a lesser extent decarboxylation, ring contraction and *N*-dealkylation (Twomey & Hobbs, 1978). Approximately 10% of the administered dose is excreted unchanged in the urine (Ishizaki *et al.*, 1979). It has been a clinical impression that adverse reactions to NSAIAs may be commoner in patients over the age of 65 years and a predisposition to adverse reaction in the aged was recently demonstrated in the case of benoxaprofen by Halsey & Cardoe (1982). Increased sensitivity to drugs in the elderly patient may result from a complex series of factors affecting both pharmacodynamics and pharmacokinetics. No data are presently available concerning the disposition of piroxicam in elderly patients.

Methods

An open multiple dose study was carried out in patients with rheumatoid or osteoarthritis or other painful conditions of the locomotor system which included elderly patients in the Department of Geriatric Medicine. Suitable patients consented to take part in this study after an explanation of the protocol which was approved by the Guy's Hospital Ethics Committee. Piroxicam 20 mg was administered daily as their initial NSAIA or, following a washout period of 1 week, instead of their regular NSAIA. Dosing was continued daily for a period of 14 days following which the drug was discontinued for 48 h before being recommenced or replaced by an alternative treatment. Other necessary drug therapy for concurrent medical conditions was employed but no other NSAIA was administered concurrently with piroxicam. Paracetamol or DF118 were used as supplementary analgesics when required. Highly protein-bound drugs were avoided and enzyme inducing drugs or drugs altering gastro-intestinal function were not commenced during the study but patients necessarily on such agents continued at a constant dose throughout. Twenty-one patients with ages ranging between 27 and 94 years were admitted to the study. The majority of the geriatric patients had concurrent illness which included cardiac failure, diabetes, Parkinson's disease, myxoedema and urinary tract infection.

On the first day of the study patients received 20 mg piroxicam plus 100 ml water and 5 ml blood samples were taken for piroxicam estimation into lithium heparin tubes at 2, 4, 6, 8, 10, 12 h and at 24 h, just before the second dose. Piroxicam was continued for 14 days at a dose of 20 mg daily. On the 14th day

blood samples for piroxicam estimation were taken before the last dose and at 2, 4, 6, 8, 10, 12, 24, 36, 48 h. Serum was separated by centrifugation and stored at −20°C.

Before starting piroxicam therapy, one of the investigators (AW) assessed the patient's joint pain and stiffness on a four point scale (marked, moderate, slight, none). The presence or absence of oedema was also recorded, and if present graded as mild, moderate or severe. These assessments were repeated at the end of the first week of piroxicam treatment and on the last day of treatment (day 14), together with a global assessment of improvement in the patient's condition on a similar four point scale.

Before starting piroxicam treatment and after 14 days, blood was also taken for clinical chemistry (Na^+, K^+, HCO_3^-, urea, creatinine, uric acid, Ca^{++}, PO_4^{3-}, albumin, bilirubin, total protein, glucose, aspartate aminotransferase, alkaline phosphatase) and haematology (haemoglobin, white cell count and differential, MCV, MCH, MCHC, ESR). Plasma piroxicam concentration was estimated in our laboratory by reverse-phase high pressure liquid chromatography. In outline 0.2 ml plasma was extracted with 0.1 ml N hydrochloric acid and 3 ml l-chlorobutane following addition of the internal standard isoxicam. The upper organic phase was separated and back extracted with 0.2 ml 0.05 N sodium hydroxide and 50 μl of the resulting aqueous phase was injected into the injection loop of the chromatograph. The column was 25 cm × 4 mm, packed with Li Chrosorb RP_8, 10 μm particle size and separations were affected at ambient temperature. The mobile phase was a mixture of methanol, 0.05 M ammonium phosphate and 0.05 M phosphoric acid in the proportions 3 : 1 : 1. Detection was by ultraviolet absorption at 340 nm. At a flow rate of 1.4 ml/min the retention times of piroxicam and isoxicam were 5.0 and 8.2 min respectively. The assay was linear over the concentration range investigated (0.1–20 μg/ml) and had a minimum level of detection of 0.1 μg/ml. In an accuracy study of plasma samples spiked with 2, 5 and 20 mg l^{-1} piroxicam (six assays in each case) the mean amounts found were 1.9, 5.2 and 21.3 mg l^{-1} with coefficients of variation of 8.7, 3.4 and 5.1% respectively. The method had a between assay coefficient of variation of 4% at 1 μg ml^{-1} and 3% at 10 μg ml^{-1}. Creatinine clearance was estimated from serum creatinine (Cockroft & Gault, 1972) on samples taken at days 1 and 14. The mean of these estimates was utilised for correlation with piroxicam concentration and other variates.

Pharmacokinetic parameters were estimated using the accumulation factor R, and the equations of Bjornsson & Shand (1979):

$$R = \frac{1}{1 - e^{-k\tau}} = \frac{\overline{C^{ss}}_{min}}{C^{1}_{min}}$$

where k is the first order elimination rate constant; τ is the dose interval and C^{1}_{min} and $\overline{C^{ss}}_{min}$ are the predose plasma drug concentrations 24 h after the first dose and at steady state respectively. The estimates of apparent volume of distribution and systemic clearance derived by this method are dependent upon the bioavailability fraction which has been assumed to be unity. The absolute bioavailability of piroxicam is unknown since no intravenous dosage data is available in man. In subsequent discussions these relative clearances and apparent volume of distribution will be considered as if they were absolute values. Areas under plasma concentration-time curves were estimated by trapezoidal approximation. The mean observed plasma concentration during the last dosage interval $\overline{C^{ss}}_{p}$ was found from the integrated plasma concentration, time profile during the last interval (14–15 days)

$$\int_{\tau 14}^{\tau 15} C\mathrm{pdt}/\tau = \text{Observed } \overline{C^{ss}}$$

A predictive estimate of this $\overline{C^{ss}}$ was made from the integral of first dosage interval

$$\int_{0}^{\tau 1} C\mathrm{pdt}$$

since

$$\overline{C^{ss}} = \frac{\int_{0}^{\tau 1} C\mathrm{pdt}}{\tau (1 - e^{-k\tau})}$$

Relationships between variates were explored using multiple linear regression and analysis of variance. The significance of changes in clinical measures was determined by either the sign test, or where appropriate the Wilcoxon signed rank test.

Results

Nineteen patients completed the study. Of those failing to complete, one (aged 82 years) had haematemesis and melaena on the eleventh day of piroxicam treatment and the drug was discontinued; another (aged 81 years) suffered a fatal cerebrovascular accident on the fourteenth day of the study. Although quite possibly the former event was related to piroxicam administration, there was no objective evidence to link the latter with drug administration.

Table 1 summarises the derived pharmacokinetic parameters and contrasts them with published data. The half-life of piroxicam varied from 25.9 to 136.8 h in our patients. Figure 1 shows the relationship between age and the observed steady-state plasma piroxicam concentrations and the estimated apparent

Table 1 Summary of means (s.d.) of pharmacokinetic parameters determined in present study with those for younger subjects from published data

	Present study	*Rogers* et al. *(1981)*	*Tilstone* et al. *(1981)*	*Ishizaki* et al. *(1979)*
Piroxicam dose	20 mg daily × 14	20 mg daily × 8	20 mg daily to steady state	30 or 60 mg single dose
Subjects—*n*	Patients—19	Normals—8	Normals—8	Normals—27
Age range (years)	27–94	26–38	24–36	18–24
Half-life (h)	73.4 (24.6)	52.9 (20.1)	46.2	34.3 (3.5)
Clearance ($ml\ h^{-1}\ kg^{-1}$)	3.2 (1.8)	2.08 (0.46)	1.8	2.94 (0.14)
Apparent volume of distribution (l/kg)	0.31 (0.16)	0.15 (0.05)	0.12	0.14 (0.01)
R	4.9 (1.5)	3.7 (1.1)	3.3	2.6*
$\overline{C^{ss}}$ (mg/l)	6.1 (3.1)	5.3 (1.3)	approx 8*	4.3*

* = Estimated from authors' data

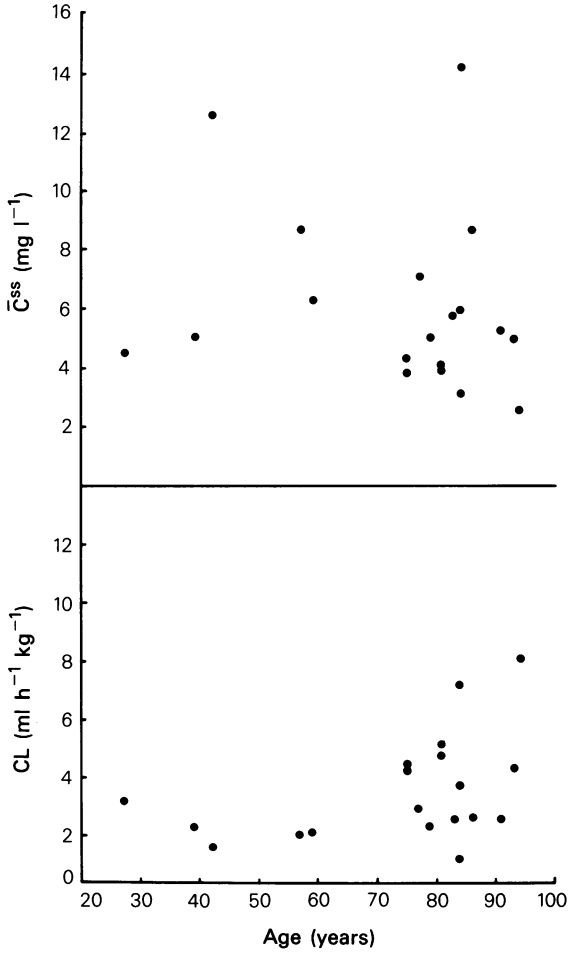

Figure 1 Average plasma concentration of piroxicam ($\overline{C^{ss}}$) after 14 days once daily dosing and systemic clearance (CL) as a function of age.

systemic clearance (CL). Multiple regression analysis showed that the following predictor variables for systemic piroxicam clearance: age, creatinine clearance and plasma albumin, could be deleted from the regression without significant effect. The apparent volume of distribution and observed mean steady state plasma concentration, however, were, as would be anticipated from pharmacokinetic theory, significant predictors. Thus age makes only a small contribution to the variability of piroxicam clearance. The simple linear relationship between age and piroxicam clearance had a coefficient of determination of 0.186. Therefore, less than 20% of the total variation about the regression was accounted for by age.

$$\text{Since } \overline{C^{ss}} = \frac{\text{Dose}}{\tau.\text{CL}},$$

if dose and systemic clearance were normalised for body weight, both panels of the figure would be expected to show a similar distribution of variates with age. The observed differences in the figure suggest that there is a weight-related change in clearance and there was a trend ($r = 0.501$) for decreasing clearance to be associated with increased body weight. There was, however, a correlation ($r = 0.672$) between age and weight with, as might be expected, the older patients having the lower body weights.

The predicted and observed mean steady state plasma piroxicam concentrations were compared by repeated measures analysis of variance and the intra-class correlation coefficient (Fleiss, 1975), R_1 was 0.85 ($P < 0.001$). The excellent correlation between these variates suggests that there is little deviation from linear pharmacokinetic behaviour with multiple dosing of piroxicam since steady state levels are predictable from the assumption of such behaviour. This is in agreement with studies demonstrating linearity after multiple doses of 10–30 mg piroxicam/day (Hobbs & Twomey, 1979).

A trend for systemic piroxicam clearance to increase with age and thus to be associated with lower steady state drug concentrations at advanced age was noted (see above). The study period of 14 days was relatively short in relation to the long half-life of piroxicam in some patients: 94% of the theoretical infinite steady state would be reached in four times the half-life but even when those patients in whom 14 days $< 4 \times t_{1/2}$ were omitted from consideration this trend was not significant.

A significant improvement ($P < 0.001$) in joint pain occurred after 1 and 2 weeks treatment with piroxicam and only six patients showed no change in pain severity during the trial. Joint stiffness was significantly improved after 1 week's treatment ($P < 0.05$) and further improved after 2 weeks ($P < 0.01$). Eleven patients showed no improvement in stiffness during the trial: these included the six patients who showed no change in pain. Although the rating of the patients' overall condition (or global assessment) did not significantly improve after the first week of therapy, 11 patients (58%) were recorded as having marked or moderate improvement at the end of the second week, and this change was statistically significant ($P < 0.001$).

Oedema was initially noted in seven patients and its severity was unchanged throughout the trial. No significant changes in patients' body weights were observed.

During the study there were significant ($P < 0.01$) increases in urea (1.81 mmol/l), uric acid (0.05 mmol/l) and potassium (0.47 mmol/l) with less significant ($P \leq 0.05$) increases in phosphate (0.13 mmol/l) and fall in estimated creatinine clearance (3 ml/min). The ESR was not significantly changed by the treatment.

Discussion

The half-life of piroxicam has been found to range between 14.1 and 158.3 h in normal young men (Hobbs & Twomey, 1979). The mean half-life for our group of mainly elderly patients is longer than those described for younger subjects in the Table 1. The relative standard deviation is 0.34, however, and the degree of variability is therefore such that there is an overlap with previously published estimates of half-life. Examination of Table 1 shows that there is a wide dispersion of piroxicam half-lives between individuals. This is also observed for other drugs, e.g. phenylbutazone (10–140 h) and probably reflects differences in the rate of biotransformation between individuals. On the other hand, piroxicam kinetics within a given individual show much less variation (Hobbs, 1983). The systemic clearance for the present group of patients is also comparable to data from younger subjects. The apparent volume of distribution is larger than that found in younger persons. Piroxicam, like many NSAIAs is highly protein-bound, mainly to albumin, and is mainly limited to the approximate extracellular fluid space. The elderly sick have lower plasma albumin concentrations than young, fit subjects (Woodford-Williams *et al.*, 1968). In the present study the mean plasma albumin concentration for patients over the age of 65 was 35.2 (s.d. 3.8) g/l and for those under 65 was 41.4 (s.d. 2.6) g/l. This difference was significant ($P = 0.003$) and the slope of the regression for plasma albumin with age was -0.13 ($r = 0.54$). For a drug with low clearance like piroxicam, a decrease in blood binding will, other things being equal, increase the apparent volume of distribution (Gibaldi & Koup, 1981). Plasma albumin concentration, however, contributed little to the variability of systemic drug clearance. The renal clearance of piroxicam is 0.28 ml h^{-1} kg^{-1} and represents only 10.5% of the systemic clearance (Ishizaki *et al.*, 1979). Clearly renal function plays little part in piroxicam elimination and the effect of diminished creatinine clearance associated with aging would be expected to be small.

Increased blood urea nitrogen is a known effect of piroxicam administration and is attributed to the inhibition of renal prostaglandin synthesis produced by non-steroidal anti-inflammatory agents which results in diminished renal blood flow (Pitts & Proctor, 1979). The changes in uric acid could have similar aetiology or may represent a competitive interaction between uric acid and piroxicam in the renal tubule.

Although this study was not primarily intended to examine therapeutic outcome, analysis of the global assessment at the end of the 14th day of treatment showed that 11 patients were recorded as having marked or moderate improvement and eight patients were scored as having little or no improvement. The point biserial correlation coefficient for the relationship of this dichotomy with steady state plasma piroxicam concentration was 0.264 and is not significant.

No evidence was therefore found in this study to suggest that the pharmacokinetics of piroxicam are grossly different in the elderly arthritic patient. Any predisposition of this group of patients to adverse drug effects is not apparently associated with higher total plasma concentrations of piroxicam.

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