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Single-Dose and Steady-State Pharmacokinetics of Piroxicam in Elderly vs Young Adults

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Summary. Age-dependent changes in pharmacokinetics are considered a possible factor contributing to a higher risk of side-effects from drug treatment in the elderly. However, very little is known about the kinetics and metabolism of most NSAI agents in geriatric subjects. In a prospective age-comparison study, the single dose and steady-state pharmacokinetics of piroxicam 20 mg once daily were determined in 44 subjects ranging in age from 30 to 80 years. Plasma concentrations, elimination half-life, AUC, and volume of distribution were not influenced by age or sex and were in agreement with previously reported results in young adults. Pharmacokinetic parameters in 18 patients with evidence of mild or moderate renal impairment at study entry were not different from those in patients without impairment. Based on this and other studies, elderly patients receiving the recommended dose of piroxicam are not exposed to undue risk related to pharmacokinetic considerations.

Key words: piroxicam; pharmacokinetics, geriatrics, renal insufficiency, drug safety, non-steroidal anti-inflammatory drugs, osteoarthritis

The physiological changes that occur with advancing age have been known for some time [1, 2], but only recently has attention focussed on their influence on drug kinetics and metabolism. Because aging per se is one among many factors contributing to pharmacokinetic heterogeneity [1], it is often difficult to establish specific dosing guidelines for geriatric patients. There appears to be no age-dependent change in absorption for the majority of orally administered drugs studied [3, 4]. However, the well established reduced renal function and associated impaired excretion of drugs and their metabolites in the elderly often require dosage reduction [4, 5]; the age-effect on hepatic metabolism and excretion, in contrast, may be highly variable and unpredictable [6].

Antirheumatic drugs, especially the non-steroidal anti-inflammatory (NSAI) agents, have recently been the subject of increased concern regarding their safety in the elderly, who are considered to be more susceptible to some of the side-effects [7, 8]. For indomethacin and phenylbutazone, increased risk of toxic effects has been attributed to age-related pharmacokinetic changes [9, 10]. In a more recent extreme example, benoxaprofen in female patients over 70 years old was shown to have an elimination half-life and plasma concentrations three- or four-fold greater than in younger subjects [11, 12], a finding unrelated to varying renal function status [11, 13]. Similar, but less dramatic results have been reported for ketoprofen in 7 elderly patients [14].

Piroxicam is a well established NSAI drug, administered once daily, that has a mean plasma half-life in normal subjects or patients of about 50 h [15, 16]. Steady-state following the usual 20 mg daily dosing is reached within one to two weeks. More than 90% of piroxicam is excreted as metabolites, by both renal and hepatic pathways. Plasma concentrations are not influenced by mild or moderate renal impairment [17]. Preliminary data from a retrospective study (Hobbs D.C. and Gordon A.J. 1984, personal communication) and from some small studies ([18] and Jansen W. 1981, personal communication) indicate that the pharmacokinetics of piroxicam in the elderly do not differ from results in younger adults. However, in view of the importance of this subject to the therapeutic usage of piroxicam in older populations, a more comprehensive study has been conducted. Its purpose was to determine prospectively

the pharmacokinetic profile of piroxicam across the broad age range representing the adult treatment population.

Subjects and Methods

Forty-five ambulatory subjects, comprised of 13 males and 32 females from 30 to 80 years of age and within 20% of recommended body weight for age and height, were admitted to the study. Twenty-one were normal volunteers (mean age 48 years, range 30–72 years) and 24 were patients under treatment for osteoarthritis (mean age 63 years, range 30–80 years). None of the subjects had evidence or history of significant renal, hepatic, gastrointestinal or hematological disease. Prior to study entry the patients underwent a drug-free washout period of two weeks and except for paracetamol as a supplemental analgesic to enhance pain relief if necessary, no concomitant analgesic or anti-inflammatory therapy of any type was permitted during the study.

The post-washout baseline examination included the following laboratory tests which were repeated at the end of the treatment period and at a post-study screen about two weeks later: complete blood count including differential count for WBC's and platelets; routine urinalysis; plasma urea, proteins, and creatinine; and serum levels of total bilirubin, fasting glucose, uric acid, SGOT, SGPT, LDH, alkaline phosphatase, sodium, potassium, chloride, and hepatitis B-antigen. Measurements of urinary beta$_2$-microglobulin and N-acetyl-beta-glucosaminidase (NAG), a proximal tubular lysosomal enzyme, were also made; both are highly sensitive indicators of renal tubular damage [19]. NAG is measured in nmoles of substrate hydrolyzed/h/mg creatinine in a urine sample. On each study day of blood sampling or other measurements, subjects were confined to the clinical pharmacology unit or, if appropriate, visited at their homes by medical staff.

Each subject was instructed to take two 10 mg piroxicam capsules once daily with the morning meal; compliance was verified throughout the study by medication count and by supervised dosing in the clinic or at home. Paracetamol (500 mg tablets) was also provided to be used by patients only if necessary and up to a maximum of 8 tablets daily (2 tablets q.i.d.). In order to determine single dose pharmacokinetics, piroxicam was taken on Day 1, and no drug on Days 2–4. Drug was continued on Days 5 to 36 inclusive. Venous blood (3 ml) was drawn according to the following schedule: Day 1: 0 (predose), 3, 6, 12, 24, 48, and 72 h; Days 5, 25, 30, and 33: 0 (predose), 3, 6, 12, and 24 h; Day 36: 0 (predose), 3, 6, 12, 24, 48, 72, 96, and 120 h. After addition of heparin, plasma was separated from cells and the samples were frozen immediately at $-20\,^{\circ}C$. All assays were carried out by the Huntingdon Research Centre (UK) using the published HPLC method [20] modified by substitution of an Apex C8 chromatography column. Repeat analyses were performed on 135 (9%) of the samples, randomly selected. The coefficient of variation was better than 0.1 below 2 μg/ml and better than 0.05 above that concentration. Areas under the concentration curves were computed by the trapezoidal method. Half-lives were determined from the slope of the least squares fit of the logarithms of the concentrations at 12 h and thereafter, following the single dose on Day 1 and the final dose. Mean steady-state peaks were computed for each subject from the highest values observed on Days 30, 33, and 36; these were then averaged for groups of subjects of different ages. Mean 24 h steady-state AUCs were similarly determined. The volumes of distribution, in ml/kg, were calculated from the terminal drug elimination curves and the ratios of steady-state to single dose areas under the concentration curves. Comparisons between groups of subjects were carried out by between-group *t*-testing.

Results

Clinical and Chemical Findings

Piroxicam was well tolerated by all subjects; 4 experienced mild nausea which resolved within 1 day. The use of paracetamol as adjunct analgesic therapy was used only once by 5 subjects and twice by 2 subjects, taken randomly between Days 5 and 39. One patient, a 70 year old male, dropped out of the study on Day 19 for personal reasons unrelated to therapy; while not included in the pharmacokinetic calculations, he is included in this discussion of clinical observations. No clinically significant changes in hematology and liver function tests were observed at the end of the treatment period or at the post-study screen. The same was true for other biochemical tests except for a higher mean plasma urea on Day 36 of the study (6.9 ± 0.4 mmol/l) compared to pre-study values (5.6 ± 0.4 mmol/l). This upward shift, common with NSAI drugs [21], was partially reversed at the post-study screen (6.3 ± 0.4 mmol/l). The change was evident in all age groups but was of slightly greater magnitude in the older groups. However, this was not reflected by an elevation in plasma creatinine or in urinary beta$_2$-microglobulin.

Evidence of mild to moderate renal tubular damage, as reflected by NAG levels ranging from

Table 1. Pharmacokinetic parameters of piroxicam in subjects of differing age and renal status. Mean ± (SEM)

Age Group [years]	*n*	Half-Life [h]		Steady-State		Volume of Distribution [ml/kg]
		Single Dose	Terminal	Peak [μg/ml]	AUC [h·μg/ml]	
30–59	21	48.6 (4.2)	55.2 (4.0)	9.6 (0.7)	196 (15)	150 (12)
60–69	12	40.0 (4.1)	51.6 (3.9)	8.8 (0.6)	179 (13)	142 (8)
70–80	11	40.3 (3.2)	45.4 (4.0)	7.8 (0.5)	153 (12)	171 (18)
Elevated NAG	14	41.7 (3.6)	47.9 (4.2)	8.8 (0.6)	176 (13)	173 (14)
Elevated Plasma Creatinine	3	45.5 (6.8)	53.4 (9.0)	7.1 (0.2)	139 (2)	118 (11)
Elevated Plasma Urea	8	41.8 (4.1)	49.9 (1.9)	8.7 (0.5)	175 (10)	152 (11)

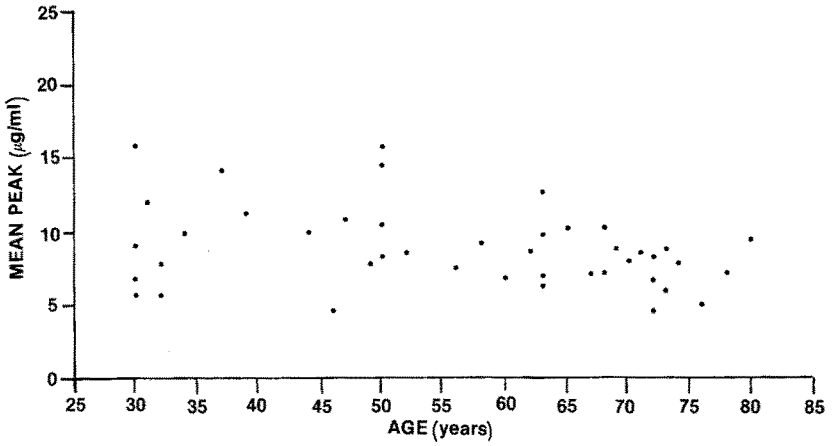

Fig. 1. Mean steady-state peak plasma concentrations of piroxicam 20 mg daily as a function of age ($n = 44$; peak normalized for body weight)

300–1447 nmol/h/mg creatinine [19], was present in 15 subjects at study entry; 6 were in the 30–69 year age group and for all 6 urinary NAG was reduced on day 36 of the treatment period. There were 12 subjects from 70 to 80 years old, 9 of whom demonstrated elevated NAG levels at entry. At Day 36, NAG levels had increased for 6 of the 9 and decreased for the other 3. One subject (72 years) with a normal NAG level (280) at entry demonstrated a very marked increase in this parameter (3,352) on Day 36. However, at the post-study screen, the value had fallen to 310 nmol/h/mg creatinine. No other abnormal chemical or clinical findings were observed for this subject.

Pharmacokinetic Findings

For purpose of analysis, the 44 evaluable subjects are divided arbitrarily into 3 subgroups by age: 30–59 years ($n = 21$, mean age 42 years), 60–69 years ($n = 12$, mean age 64 years), and 70–80 years ($n = 11$, mean age 73 years). Of the scheduled 1,584 samples for these subjects, only 7 were missed, a remarkably low incidence for a study of this magnitude; interpolation was used to calculate parameters in these cases. Three patients under treatment with piroxicam before the study had low blood levels of the drug immediately prior to the first study dose; this did not materially influence calculated parameters for that day.

An examination of differences between the sexes in each age group with regard to mean peaks and AUCs at steady state (adjusted for body weight) and half lives after the first and final doses revealed no statistically significant differences. Therefore, for purposes of further analysis data from both sexes were combined in all age groups.

Steady-state was clearly achieved, based on the similarity of peaks and AUCs on Days 30, 33, and 36 for each subject. Mean half-lives after the single-dose and following steady-state were similar in the three age groups and ranged from 40 to 55 h (Table 1). The values at steady state are in good agreement with those previously reported for healthy young volunteers [16]; slightly lower values were seen after the first dose, for reasons which are not fully understood. Steady state peaks and AUCs were also similar in the three age groups, as were volumes of distribution. None of the pairwise comparisons of the above parameters revealed any significant differences. Variability within each age group, as reflected by the standard errors, was also similar. Normaliza-

tion of the mean peaks and mean AUCs for body weight did not alter any of the conclusions.

In addition to the group-wise comparisons, a regression analysis of age vs single-dose half-life, terminal half-life, mean peak, mean AUC and volume of distribution yielded slopes not significantly different from zero. Figure 1 illustrates the absence of a correlation between age and steady-state peaks (normalized for bodyweight).

At entry into the study 18 of the 44 evaluated subjects had one or more above-normal renal function parameters. Three patients had elevated plasma creatinine (mean ± SEM, 119 ± 5 μmol/l; upper limit of normal 110 μmol/l for this lab) and 8 had elevated plasma urea (7.9 ± 0.3 nmol/l), reflecting mild to moderate renal impairment; 14 demonstrated elevated NAG levels (584 ± 76 nmol/h/mg creatinine), indicative of tubular injury. Kinetic parameters for these subjects (Table 1) differed little and non-significantly, and with no particular pattern, relative to values for subjects without impairment.

Discussion

Pharmacokinetic changes represent one of several explanations for alterations in drug sensitivity with old age [3, 6] and it has been suggested that for some drugs a normal adult dose may represent an "overdose" in the elderly [4, 6]. Although there are many NSAI drugs available, information regarding the influence of age on their pharmacokinetics is very sparse [22]. However, except for acetylsalicylic acid [23], there has been no reported demonstration of a relationship between plasma concentrations and adverse reactions, even though the incidence of side-effects appears to be dose-related. The present study has examined prospectively the effect of age on the pharmacokinetics of piroxicam, 20 mg once daily for 1 month, in 44 carefully monitored subjects. Whether examined in selected age groups or in the population as a whole, plasma concentrations and derived parameters show no meaningful changes with age across a 50 year span from 30 to 80. The single dose and steady state elimination half-lives and the volume of distribution for all age groups in this population are in good agreement with previously reported findings in young adults, both normal volunteers and arthritic patients.

Piroxicam is cleared primarily by conversion to inactive metabolites [15, 16] and in view of its low mg dosage, only small amounts of material need be handled in the biotransformation and excretory processes. Thus, it is not surprising to find that the pharmacokinetics in patients with mild or moderate renal impairment did not change.

An increased incidence and possibly severity of side-effects in the elderly have been associated with some NSAI agents [9, 10]. However, analysis of data from several studies with piroxicam [25 and Pitts et al. 1981, personal communication) involving more than 20,000 patients with osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and acute musculoskeletal conditions has revealed that the incidence and severity of side-effects, including severe gastrointestinal reactions, is similar in elderly and young patients.

Certainly special attention should be given when prescribing drugs for the elderly and recommendations governing individualized treatment of geriatric patients are available [4, 26, 27]. However, based on the results of this and previous studies, elderly patients receiving the usual recommended doses of piroxicam are not exposed to any special risk associated with pharmacokinetics.

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