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Piroxicam and 5'-Hydroxypiroxicam Kinetics Following Multiple Dose Administration of Piroxicam

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Summary. Piroxicam (20 mg once daily) was administered orally to six healthy young volunteers for 15 days. Trough steady-state levels of piroxicam and 5'-hydroxypiroxicam were 5.5 and 1.2 μg/ml, respectively. Piroxicam's plasma half-life (54.9 h) was significantly shorter than that of 5'-hydroxypiroxicam (70.5 h). Percent unbound piroxicam and 5'-hydroxypiroxicam in plasma at steady-state averaged 1.10 and 8.07 respectively. An average of 25.2% of the dose was recovered in urine as 5'-hydroxypiroxicam; approximately two-thirds (17.2%) in the form of the glucuronide conjugate. Average steady-state plasma levels ($\overline{C}_{ss}$) of piroxicam (7.0 μg/ml) were significantly higher than predicted from a previously reported single dose study (5.3 μg/ml).

Key words: piroxicam, 5'-hydroxypiroxicam; multiple dosing, steady-state pharmacokinetics, urinary excretion, plasma protein binding

Piroxicam is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic activity (Brogden et al. 1984). It has pharmacokinetic properties similar to most other NSAIDs except for its long plasma half-life of approximately 2 days (Verbeeck et al. 1983). Piroxicam is extensively metabolized in man with hydroxylation of the pyridyl ring to 5'-hydroxypiroxicam the most important pathway (Twomey and Hobbs 1978; Wiseman and Hobbs 1982). The 5'-hydroxy metabolite has little or no anti-inflammatory activity in animal models (Lombardino 1981). The present report describes a detailed multiple dose study of piroxicam in six healthy subjects.

Methods

Six healthy young (23-33 years) volunteers (3 males, 3 females) who had previously participated in a single dose study (Richardson et al. 1985) agreed to take 20 mg of piroxicam every morning for 15 consecutive days. Venous blood samples were taken before each drug dose on Days 0, 2, 4, 7, 9, 11, 14 (last piroxicam dose) and on Days 15, 16, 18, 21, 23 and 25. All samples were taken in the morning before breakfast. Additional blood samples were withdrawn on Day 14 at 1, 2, 4, 8 and 12 h after ingestion of the last piroxicam dose. On that day urine was collected during one dosing interval (24 h) and an aliquot was stored at −20 °C.

Plasma and urine concentrations of piroxicam and its major metabolite, 5'-hydroxypiroxicam, were measured by a high pressure liquid chromatographic (HPLC) method (Richardson et al. 1986). Analysis of urine was also carried out following overnight incubation with β-glucuronidase (500 IU, 37 °C, pH 5).

To determine the protein binding of piroxicam and 5'-hydroxypiroxicam, a 1 ml aliquot of the plasma sample obtained on Day 14 (before ingestion of the last dose) was dialyzed using exactly the same conditons as for the single dose study (Richardson et al. 1985). Piroxicam and 5'-hydroxypiroxicam concentrations in aliquots of the dialyzed plasma were measured by HPLC (Richardson et al. 1986). Concentrations of the two compounds in the buffer samples were measured by direct injection onto the HPLC column using a method described elsewhere (Richardson et al. 1985).

Plasma half-life ($t_{½}$), volume of distribution (V/f), oral clearance of total and unbound piroxicam (CL/f, CL'/f) and average steady-state concentration of piroxicam ($\bar{C}_{ss}$) were calculated by standard methods. Differences between single dose (Richardson et al. 1985) and multiple dose pharmacokinetic parameters were evaluated by paired or unpaired *t*-tests. A *p*-value of 0.05 or less was considered significant.

Results

The mean plasma concentration-time profiles for piroxicam and 5'-hydroxypiroxicam are shown in Fig. 1. Steady-state for parent drug and metabolite

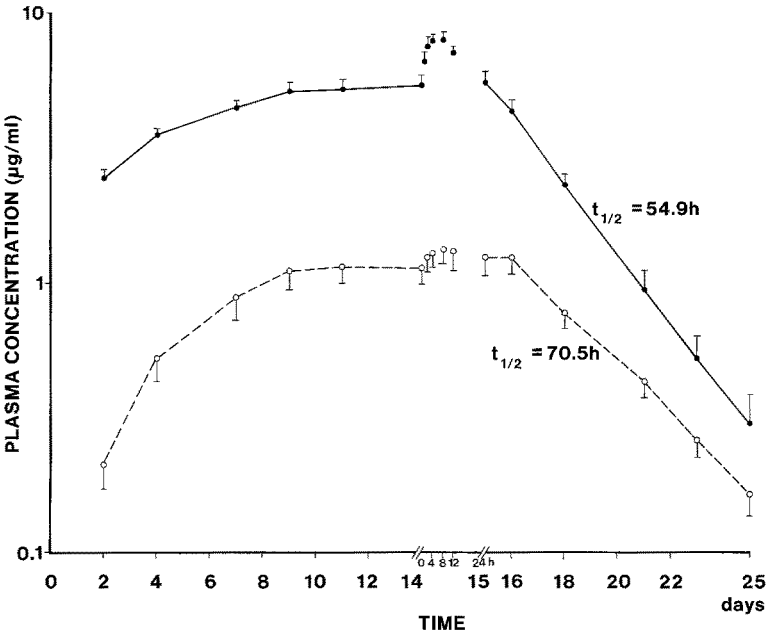

Fig. 1. Semi-logarithmic plasma concentration-time profiles for piroxicam (●—●) and 5'-hydroxypiroxicam (○—○) during and after multiple dose piroxicam administration to six volunteers (mean ± SD)

Table 1. Pharmacokinetic parameters of piroxicam following multiple dose administration

Subject	$t_{½}$ (h)	V/f (l)	CL/f (ml/min)	CL'/f (ml/min)	$\bar{C}_{ss}$ (µg/ml)	f_u[a] (%)
1	47.1	9.6	2.35	188.0	5.9	1.25
2	71.2	10.5	1.70	157.4	8.2	1.08
3	63.6	12.9	2.35	293.8	5.9	0.80
4	43.6	7.0	1.86	136.8	7.5	1.36
5	56.3	10.8	2.22	201.8	6.3	1.10
6	47.8	6.8	1.65	165.0	8.4	1.00
mean	54.9	9.6	2.02	190.5	7.0	1.10
± SD	10.8	2.4	0.32	55.6	1.1	0.20

[a] f_u: fraction of drug unbound in plasma (expressed as percent)

was reached by approximately Day 9. Table 1 lists the pharmacokinetic parameters of piroxicam following multiple dose administration. Minimum steady-state concentrations of piroxicam averaged 5.5 ± 0.9 µg/ml, a value approximately five times greater than that of the 5'-hydroxy metabolite (1.2 ± 0.4 µg/ml). Piroxicam's elimination half-life (54.9 ± 10.8 h) was significantly ($p = 0.036$) shorter than the plasma $t_{½}$ of 5'-hydroxypiroxicam (70.5 ± 11.3 h). Percent unbound piroxicam and 5'-hydroxypiroxicam in plasma at steady-state averaged 1.10 ± 0.20 and 8.07 ± 1.17 respectively.

Piroxicam could not be detected in measurable concentrations in untreated or β-glucuronidase treated urine. An average of 25.2 ± 3.4% of the dose was recovered in urine as 5'-hydroxypiroxicam. Approximately ⅔ of this total recovery was in the form of the glucuronide conjugate (17.2 ± 5.0%).

Discussion

Kinetic parameters of piroxicam obtained in the present study show general agreement with values reported previously (Rogers et al. 1981; Fourtillan and Dubourg 1984).

Plasma concentrations of 5'-hydroxypiroxicam have not been reported before. Wiseman and Hobbs (1982) state that only traces of the metabolite can be found in plasma and, therefore, that its elimination must be rapid. Although results of the present study show steady-state levels of 5'-hydroxypiroxicam to be approximately 20% of piroxicam levels, its plasma half-life which is a function of its formation, elimination and distribution is long (70.5 ± 11.3 h).

Excretion of unchanged and conjugated 5'-hydroxypiroxicam in urine and feces accounts for up to 60% (Wiseman and Boyle 1980) or 75% (Hobbs, personal communication) of a daily piroxicam dose. In the present study, approximately 25% of the piroxicam dose was recovered in urine as the 5'-hydroxy metabolite, and two-thirds of this recovery was in the form of the glucuronide conjugate. Urinary excretion of unchanged piroxicam was negligible and below the detection limit of the assay.

Experimental evidence to date suggests that the pharmacokinetics of piroxicam are linear (Nuotio and Makisara 1978; Hobbs and Twomey 1979). However, steady-state clearances for both total (2.02 ± 0.32 ml/min) and unbound piroxicam (190.5 ± 55.6 ml/min) were significantly lower, and average steady-state levels (7.0 ± 1.1 µg/ml) significantly higher than values calculated from data de-

rived from a single dose study in the same volunteers (single dose values: 2.72 ± 0.61 ml/min, 414.3 ± 80.2 ml/min and 5.3 ± 1.1 μg/ml respectively). The single dose study was carried out 0.5 to 1.5 years before the multiple dose study, and, therefore, these comparisons should be interpreted with caution. However, although clearance may change with time or be affected by numerous factors, it is unlikely that six healthy young volunteers would all develop a decreased ability to eliminate piroxicam during the time interval between the two studies. It should be pointed out that the HPLC procedures to measure piroxicam concentrations in both studies yielded identical results and that the same dosage form (20 mg capsules) was used on each occasion. In addition, in both studies the capsules were taken in the morning after an overnight fast. Other investigators have also noted a prolonged half-life for piroxicam with repeated dosing, but were unable to explain it (Fourtillan and Dubourg 1984; Darragh et al. 1985).

Plasma protein binding of piroxicam measured at steady-state in the present multiple dose study (1.10 ± 0.20% unbound) was significantly different from binding measured in the single dose study (0.66 ± 0.12% unbound). The discrepancy, however, may be the result of a methodological difference between the two studies. For the single dose study binding was measured by adding piroxicam to blank plasma from each volunteer before dialysis (concentration 6 μg/ml). For the multiple dose study, however, plasma was obtained from the volunteers at steady-state and subsequently dialyzed. The same dialysis conditions and analytical procedures were used for both studies. The multiple dose samples contained both piroxicam and 5'-hydroxypiroxicam. Since piroxicam binding does not change over a concentration range of 5 to 50 μg/ml (Hobbs and Twomey 1979) and concentrations of the hydroxy metabolite in plasma were relatively low, it is unlikely that 5'-hydroxypiroxicam would have significantly displaced piroxicam from its plasma binding sites.

The present study has provided new information on the pharmacokinetics of piroxicam in man. However, the elimination of piroxicam in man is still poorly understood (e.g. only 25% of the dose is accounted for as the 5'-hydroxy metabolite in urine). The possible role of biliary secretion and enterohepatic recycling in the overall elimination of piroxicam should be evaluated (Verbeeck et al. 1986). Alterations in enterohepatic recycling following multiple dose administration could possibly result in a higher bioavailability (f) and, therefore, lower CL/f values.

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