Pharmacokinetics of Pirazolac – a New Anti-Inflammatory Drug – in Human Volunteers II. Dose Linearity of Plasma Levels and Excretion

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Abstract: The concentration-time course of pirazolac in plasma and its urinary excretion were investigated in 6 young volunteers (3 males, 3 females) after oral administration of 50, 150, 300, 450, and 600 mg pirazolac as a crystalline suspension at weekly intervals. Only unchanged pirazolac was detected in the plasma. Maximum plasma levels and areas under the plasma level curve increased linearly with the dose. All other pharmacokinetic parameters such as t_{max} (3 h), oral clearance CL (0.3 ml/min/kg) and terminal plasma half life $t_{1/2}$ (16–18 h) were independent of the dose. A total of 65 % of the dose was renally excreted within 72 hours mainly as pirazolac glucuronide.

Pirazolac [4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazole acetic acid] is a new nonsteroidal anti-inflammatory drug (NSAID) which is being clinically tested in phase III trials (1). Pirazolac shows good anti-inflammatory efficiency combined with excellent gastrointestinal tolerance in rheumatic diseases (2). To minimize the risk of side effects in long-term treatment of rheumatic diseases with NSAIDs a therapeutic regimen consistent with the pharmacokinetic properties of the drug is an absolute necessity. Previous investigations of the basic pharmacokinetic properties of pirazolac in volunteers showed complete systemic availability when the drug was given orally as a solution and simple biotransformation – only free pirazolac and its glucuronide were found in the urine (3). Since patients with different rheumatic diseases require treatment with different doses of pirazolac, the question of a possible dose dependency of pharmacokinetic parameters is of importance. The aim of the present study was to investigate the time course of pirazolac plasma levels and its renal excretion after oral administration of pirazolac as a crystalline suspension in a dose range from 50 to 600 mg.

Material and Methods

Subjects

Six healthy young adults participated in the study after they had given their written, informed consent. Sex (3 males, 3 females), age (18–35 years), height (168–184 cm) and weight (45–75 kg) of the subjects are summarized in Table I.

They were considered healthy on the basis of a detailed medical history, physical examination and laboratory tests. No medication except the intended one was allowed up to at least 14 days before and during the study.

Design

The trial corresponded to an open five-fold, change-over design. The study consisted of 5 administrations of increasing doses of pirazolac (50, 150, 300, 450, 600 mg) at weekly intervals. The drug was administered as an aqueous crystalline suspension in a beaker of 100 ml water at 8.00 a. m. during a standard breakfast consisting of a bread with butter and jam.

Blood and Urine Sampling

Venous blood (5 ml) was sampled immediately before and at 16 specified time points after drug administration up to 72 hours. Urine was collected daily up to 72 hours. Plasma from heparinized (7.5 I.U. ammonium heparinate/ml) blood samples and urine were stored at −24 °C until analysis.

Measurement of Pirazolac in Plasma and Urine

Unchanged and conjugated pirazolac in plasma and urine were determined after diethyl ether extraction at pH 2.0 by reversed phase HPLC chromatography and fluorimetric detection (3).

For the measurement of total pirazolac (unchanged and conjugated) urine samples were hydrolyzed with 1 N HCl at 60 °C for 24 hours prior to extraction (3).

Data Processing and Pharmacokinetic Analysis

Areas under the plasma level-time curves (AUC_{0-72h}) were calculated by means of the trapezoidal rule. The half-life was determined by regression analysis of plasma levels later than 10 hours after dosing. Total plasma clearance was obtained from $CL = D_{p.o}/AUC$.

Results

Pirazolac Plasma Levels

The mean pirazolac plasma levels obtained after oral administration of 50, 150, 300, 450 and 600 mg pirazolac as a crystalline suspension are shown in Figures 1 A and B. Pirazolac was rapidly absorbed, reaching its peak values of 4.1 ± 0.8, 11.7 ± 1.7, 23.1 ± 4.2, 33.7 ± 5.7 and 42.2 ± 2.6 µg/ml between 2 and 3 hours after administration.

Table I Biological Data of the Volunteer Subjects.

No. of volunteers initials	1 U. K.	2 J. R.	3 B. S.	4 E. S.	5 M. S.	6 M. W.
Sex	M	M	F	F	F	M
Weight (kg)	70	75	58.5	45	62	61
Height (cm)	168	184	174	163	178	178
Age (years)	27	18	35	25	24	18

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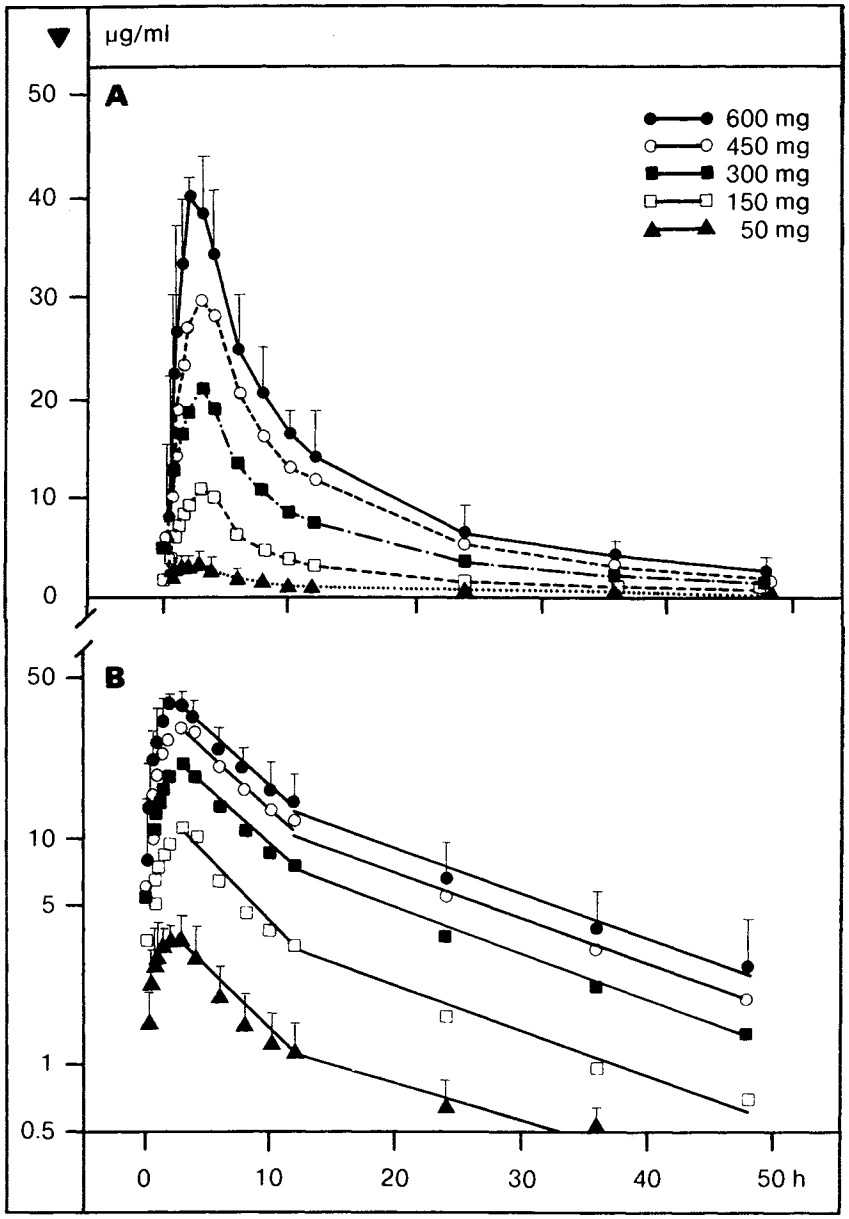

Fig. 1 Pirazolac plasma level (µg/ml) following oral administration of 50, 150, 300, 450 and 600 mg pirazolac to 6 volunteers (mean values ± S.D. are shown only for the 50 and 600 mg doses). A. Linear plot. B. Semilogarithmic plot.

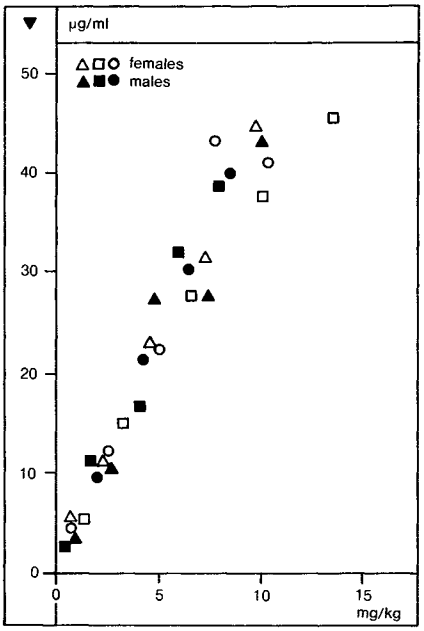

Fig. 2 Maximum plasma concentration of pirazolac (µg/ml) as a function of oral dose (mg/kg body weight).

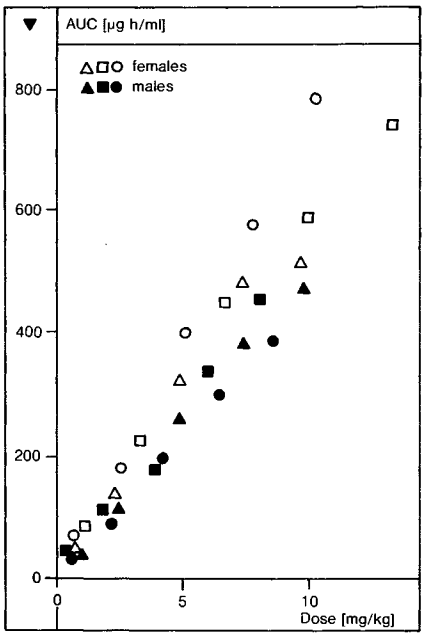

Fig. 3 Area under the pirazolac plasma level-time curve as a function of oral dose (mg/kg body weight).

The shape of the different curves was independent of the dose. Maximum pirazolac levels (C_{max}) and areas under the plasma level-time curves (AUC) increased linearly with the dose as shown in Figures 2 and 3.

There was a tendency for C_{max} and AUC values in females to be higher compared to males. The terminal half-lives were determined as 16.7 ± 2.9 h (males) and 18.2 ± 2.4 h (females) independently of the dose (Table II).

The total clearance calculated from the ratio dose/AUC was higher in males (22.0 ± 3.2 ml/min) than in females (13.8 ± 2.6 ml/min), but it was independent of the dose (Table II). After correction for different body weights, the plasma pirazolac clearance amounted to 0.32 ± 0.04 ml/min/kg for males and 0.25 ± 0.03 ml/min/kg for females.

Urinary Excretion of Pirazolac and Metabolites

Previous studies with ^{14}C-pirazolac in human volunteers revealed that it is renally excreted mainly as the pirazolac ester-glucuronide. Approximately 10 % of the dose administered has been identified as unchanged pirazolac (3). Table III summarizes the cumulative renal excretion of total (free and conjugated) pirazolac following administration of the different doses.

60–70 % of the dose administered was renally excreted within 72 hours, which was independent of the dose. HPLC analysis of urine samples showed small amounts (8–10 % of the dose adminis-

Table II. Compilation of Pharmacokinetic Parameters after Oral Administration of 5 Individual Dose Levels of Pirazolac to 6 Volunteers.

A. MALES Test subjects	1				2				6			
Dose adm. (mg)	C_{max} (μg/ml)	$t_{1/2}$ (h)	AUC (μg · h/ml)	CL (ml/min)	C_{max} (μg/ml)	$t_{1/2}$ (h)	AUC (μg · h/ml)	CL (ml/min)	C_{max} (μg/ml)	$t_{1/2}$ (h)	AUC (μg · h/ml)	CL (ml/min)
50	3.3	19.3	40.0	20.8	3.3	19.3	45.3	18.4	3.8	15.1	52.1	16.0
150	10.2	19.6	95.7	26.1	11.3	23.3	114.6	21.8	10.8	16.3	114.8	21.8
300	21.6	17.1	192.3	26.0	16.8	18.9	188.2	26.6	27.5	16.3	268.5	18.6
450	30.2	14.9	307.2	24.4	31.8	15.5	342.1	21.9	27.7	13.6	385.9	19.4
600	40.0	13.5	386.2	25.9	38.9	16.1	461.4	21.6	43.1	11.9	479.5	20.9
B. FEMALES Test subjects	3				4				5			
Dose adm. (mg)	C_{max} (μg/ml)	$t_{1/2}$ (h)	AUC (μ · h/ml)	CL (ml/min)	C_{max} (μg/ml)	$t_{1/2}$ (h)	AUC (μg · h/ml)	CL (ml/min)	C_{max} (μg/ml)	$t_{1/2}$ (h)	AUC (μg · h/ml)	CL (ml/min)
50	4.1	15.0	67.0	12.4	5.1	14.4	84.7	9.8	5.0	21.9	51.5	16.2
150	12.0	17.9	181.8	13.8	15.0	20.3	224.8	11.1	11.0	21.0	140.7	17.8
300	22.4	16.1	399.1	12.5	28.0	20.8	451.3	11.1	22.5	15.9	327.3	15.3
450	43.2	18.1	580.6	12.9	37.7	19.5	591.9	12.7	31.7	16.7	484.2	15.5
600	41.0	20.1	794.1	12.6	45.3	19.3	752.3	13.3	44.8	16.2	515.4	19.4

Table III. Urinary Excretion Rate and Cumulative Excretion of Total Pirazolac Following Different Oral Doses to 3 Young Male (M) and Female (F) Volunteers (% of dose).

Dose (mg)	50		150		300		450		600	
Sex	M	F	M	F	M	F	M	F	M	F
Day 1	64.9 ± 12.4	50.1 ± 4.5	50.5 ± 1.8	49.3 ± 10.2	49.7 ± 7.2	43.3 ± 9.9	46.3 ± 3.9	44.1 ± 9.1	46.2 ± 3.7	42.9 ± 9.4
Day 2	8.4 ± 8.4	8.3 ± 4.3	1.8 ± 1.0	11.5 ± 1.9	9.7 ± 2.3	14.7 ± 1.9	12.8 ± 3.2	15.1 ± 0.2	11.7 ± 2.3	13.8 ± 2.8
Day 3	0.2 ± 0.3	0.3 ± 0.9	0.0	3.1 ± 0.4	1.1 ± 1.1	6.0 ± 2.0	3.6 ± 2.7	5.6 ± 1.7	2.2 ± 1.7	8.4 ± 2.8
Total	73.5 ± 20.6	59.1 ± 3.2	52.2 ± 1.7	64.0 ± 8.5	60.5 ± 9.6	64.0 ± 6.6	62.6 ± 1.8	64.8 ± 7.9	60.1 ± 7.4	65.0 ± 6.7

Table IV. Concentration of Unchanged Pirazolac and its Glucuronide in Urine after oral Administration of 300 mg to one Volunteer. Analysis was immediately performed after sampling. (PAA = pirazolac).

Time p. adm. (hours)	PAA (μg/ml)	PAA-glucuronide (μg PAA-equiv./ml)	PAA/PAA-gluc.
0–1	0.2	–	–
1–2	0.2	–	–
2–3	0.5	63	0.008
3–4	0.8	129	0.006
4–9	3.6	105	0.03
9–22	8.9	170	0.05
22–27	27.9	654	0.04

tered) of unchanged drug besides the glucuronide. In the case of ketoprofen and naproxen the amounts excreted unchanged in the urine have been highly overestimated due to rapid hydrolysis of conjugates in the urine (4). Therefore the problem of a potential hydrolysis of pirazolac glucuronide in the urine was reinvestigated. Analysis of urine immediately after its collection (within 15 minutes) revealed only very small concentrations of unchanged drug in the urine (Table IV). The concentration ratio of unchanged drug over glucuronide increased with the length of the collection interval.

Table V. Hydrolysis of Pirazolac Glucuronide in Urine as a Function of Time During Incubation of the 9–22 h Urine Fraction at 37 °C and 4 °C (*). (PAA = pirazolac).

Time after incubation (h)	PAA (μg/ml)	PAA-glucuronide (μg PAA-equiv./ml)
0	9	164
1	13	165
2	16	157
4	19	154
24	59	112
24*	15	161

Incubation of urine samples at 37 °C led to 6-fold increase in free pirazolac during 24 hours. Even at 4 °C a 1.7-fold rise of free pirazolac was observed (Table V).

Discussion

It was the aim of the present study to investigate the pharmacokinetics of pirazolac as a function of the dose. Maximum pirazolac concentration in plasma (C_{max}), the area under the plasma level curve (AUC), the terminal half-life in plasma ($t_{½}$), the total plasma clearance (CL) and urinary excretion rate and cumulative excretion of total pirazolac were determined as pharmacokinetic parameters. The dosages used in the present study cover the therapeutic doses.

Bioavailability of Pirazolac at Different Doses

In a previous study with 3 male and 3 female volunteers 50 mg pirazolac was administered intravenously and orally as

a solution of the sodium salt, and AUC values of 42.1 ± 9.2 μg · h/ml (i.v.) and 44.2 ± 8.7 μg · h/ml (p.o.) were determined (3). Oral administration of the same dose as a crystalline suspension of the free acid in the present study led to AUC values of 56.8 ± 16.4 μg · h/ml, indicating that pirazolac was completely absorbed and bioavailable at this dose level. The AUC and C_{max} values increased in proportion to the dose administered. Hence, complete systemic availability of pirazolac up to oral doses of at least 600 mg was demonstrated.

Dose Dependency of other Pharmacokinetic Parameters

All other parameters investigated – terminal plasma half-life, total plasma clearance[3] and urinary excretion – proved to be independent of the dose. The terminal plasma half-life of 17.5 ± 2.7 hours in young healthy volunteers (age range 18–35 years) agreed with the terminal half-life in elderly subjects (age range 56–68 years) of 16.7 ± 3.5 hours determined previously (3).

[3] It is justified to calculate clearance after oral administration since pirazolac was completely available systemically (F = 1).

The total plasma clearance of pirazolac corrected by body weight was determined as 0.32 ± 0.03 ml/min/kg for males and 0.25 ± 0.03 ml/min/kg for females. In elderly subjects as total plasma clearance of 0.26 ± 0.02 ml/min/kg has been reported (3). The slightly higher clearance of pirazolac in males in this study is reflected in a slightly higher urinary excretion rate for total pirazolac. However, to detect small sex differences in pharmacokinetics of pirazolac a larger number of volunteers has to be studied.

Stability of Pirazolac Glucuronide in Urine

Previously it has been reported that approximately 10% of the dose administered is excreted renally as the unchanged drug independent of the route of administration (3). Present results show that pirazolac glucuronide hydrolyzes in human urine as shown for other NSAIDS like ketoprofen and naproxen (4). It has to be assumed that the amount of pirazolac excreted unchanged is very small and the data reported (4) primarily reflect the duration of frozen sample storage between collection and assay along with the urine collection schedules employed and the speed of clinical and analytical procedures.

Consequences for Therapy

Pirazolac is completely absorbed and systemically available at all doses investigated. No "first pass" effect which often leads to widely varying plasma levels was observed. The biotransformation of pirazolac is simple including only a phase II reaction (glucuronidation). No mixed function oxygenase reactions are involved which could lead to interactions with other drugs at the site of biotransformation. The pharmacokinetics of pirazolac were linear up to the highest therapeutic doses. All these properties of pirazolac should guarantee reliable and predictable plasma levels during long-term treatment of patients.

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