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Single dose pharmacokinetics of fenspiride hydrochloride: phase I clinical trial

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Summary. The absolute bioavailability of fenspiride has been studied in twelve healthy volunteers. It was administered IV and orally in single doses of 80 mg fenspiride hydrochloride according to a randomised crossover pattern.

Following IV administration, the plasma clearance of fenspiride was about 184 ml · min^{-1}, and its apparent volume of distribution was moderately large (215 l).

When given orally as a tablet, fenspiride exhibited fairly slow ab- sorption; the maximum plasma concentration (206 ng · ml^{-1}) was achieved 6 h after administration. The absolute bioavailability was almost complete (90%). The tablet had slow release characteristics. The elimination half-life obtained from the plasma data was 14 to 16 h independent of the route of administration.

Key words: Fenspiride; pharmacokinetics, bioavailability

Fenspiride hydrochloride (Fig. 1) forms whitish-coloured microcrystals, readily soluble in water; its molecular weight is of 297.

Experimentally it has anti-bronchoconstrictor and antiinflammatory properties [1, 2, 3], and in clinical practice, fenspiride improves respiratory function and significantly reduces cough, expectoration and dyspnoea in patients suffering from chronic bronchitis [4, 5, 6]. Recent studies have also shown that fenspiride improves mucociliary transport and gasometric parameters in patients with chronic obstructive pulmonary disease [7, 8, 9].

The adverse effects observed during treatment with fenspiride hydrochloride are few and mild; they are nausea, stomach ache and drowsiness. In a few exceptional cases hypotension and tachycardia have appeared, which can be attributed to its adrenolytic alpha-1 activity [10].

Pharmacokinetic studies carried out in the rat have shown that, the oral absorption of C-14 fenspiride is swift, levels being detected in plasma after 15 min; the principal route of elimination is renal, 70% of the dose being eliminated in the urine [11]. In man, renal excretion of the parent drug and its metabolites is also predominant. The drug is not highly metabolised and the unchanged drug is the main component in human plasma and urine [12].

The objective of the present study was to determine the absolute bioavailability of oral fenspiride hydrochloride administered as a single dose of fenspiride 80 mg tablets, and to monitor its general tolerance in healthy volunteers.

Material and methods

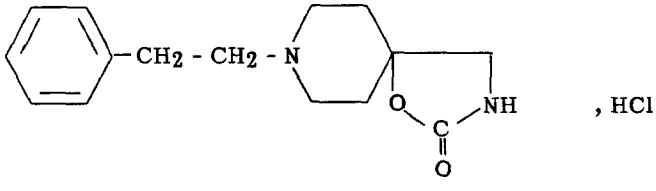
The trial was carried out in 12 healthy male volunteers as a controlled, randomised, cross-over study. The protocol was approved by the local hospital Ethical Committee and was conducted according to the current legal standards for Phase I clinical trials.

All the healthy volunteers gave their written consent after they had received detailed information about the protocol and about side effects that might appear.

Fenspiride hydrochloride (Pneumorel®, Servier, Courbevoie, France) was administered as:

- Treatment A, injectable solution comprising two 5 ml ampoules, each containing 40 mg fenspiride hydrochloride. They were injected intravenously during 2 min. The subject remained supine or seated for 15 min after administration.
- Treatment B. One tablet containing 80 mg fenspiride hydrochloride was swallowed with 150 ml water.

The sequence of administration of each treatment to the subjects was randomly assigned. A wash-out period of at least one week separated the two treatments.



$C_{15}H_{20}N_2O_2$, HCl

M = 260,33 + 36,46 = 296,79

Fig. 1. Fenspiride

Table 1. Arterial blood pressure and heart rate (Mean with (SD)) after oral and IV single doses of 80 mg fenspiride hydrochloride in 12 healthy volunteers

Time (h)	Arterial blood pressure (mm Hg)		Heart rate (beats · min^{-1})
	Systolic	Diastolic	
Intravenous administration			
0	137 (11)	75 (10)	63 (9)
0.25	130 (17)	69 (10)	66 (7)
0.50	128 (16)	71 (11)	65 (5)
1	133 (16)	70 (6)	64 (9)
2	133 (16)	72 (7)	66 (10)
Oral administration			
0	138 (14)	74 (8)	65 (10)
3	134 (17)	69 (14)	76 (13)
6	144 (13)	71 (8)	75 (15)
8	135 (14)	70 (10)	71 (11)

Table 2. Plasma concentrations (Mean with (SD)) of fenspiride (ng · ml^{-1}) after a single dose of 80 mg fenspiride hydrochloride in 12 healthy volunteers

Time (h)	Intravenous administration	Oral administration
0	BLQ	BLQ
0.25	383 (86)	ND
0.5	353 (58)	10 (12)
1	333 (40)	78 (35)
2	318 (38)	126 (32)
3	302 (36)	ND
4	281 (32)	184 (30)
5	ND	196 (26)
6	259 (34)	198 (31)
7	ND	190 (29)
8	224 (27)	189 (28)
12	185 (33)	174 (26)
24	93 (34)	109 (23)
36	54 (24)	62 (23)
48	29 (17)	35 (15)
72	12 (10)	13 (8)
96	4 (4)	5 (4)
120	3 (2)	3 (2)
168	BLQ	BLQ

BLQ, Below limit of quantitation (2 ng · ml^{-1}); ND, Not determined

Table 3. Pharmacokinetic parameters (Mean with (SD)) of fenspiride after a single dose of 80 mg fenspiride hydrochloride in 12 healthy volunteers

Parameters	Intravenous route	Oral route
C_{max} (ng · ml^{-1})	–	206 ± 28
t_{max} (h)	–	5.9 ± 1.2
AUC (μg · ml^{-1} · h)	6.73 (1.78)	6.03 (1.44)
CL (ml · min^{-1})	184 (42)	–
V (l)	215 (33)	–
F (%)	–	90.3 (9.4)
$t_{1/2a}$ (h)	–	1.5 (0.4)
$t_{1/2}$ (h)	14 (4)	16 (3)

The drug was administered after at least a 10 h fast. A meal was supplied 4 h after administration of the drug. The volunteers did not take alcohol during the 24 h preceding and the 48 h following administration, and they remained at the investigation centre for 12 h after drug administration, under medical control.

Venous blood samples 10 ml were taken either from a flexible cannula (first 12 h) or by separate venepunctures (later times). Blood was collected in heparinised tubes according to the following timetables:

- Treatment A: basal and after 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120 and 168 h
- Treatment B: basal and after 0.5, 1, 2, 4, 5, 6, 7, 8, 12, 24, 36, 48, 72, 96, 120 and 168 h.

Heart rate and arterial blood pressure were monitored before and after drug administration. An electrocardiogram was performed 15 min and 6 h after IV and PO administration, respectively. General tolerance was assessed by free questioning about possible adverse effects after each administration.

The blood samples were centrifuged immediately after sampling at 4000 rpm for 10 min. Plasma was separated and two aliquots were kept in polypropylene tubes at −20 °C. The plasma fenspiride concentration was determined by HPLC [13]. This specific method allowed quantitation of fenspiride in plasma at concentrations between 2 and 100 ng · ml^{-1} with electrochemical detection, and between 10 and 1000 ng · ml^{-1} with ultraviolet detection. The precision of the methods was 15 % and 2.9 %, respectively, at the limit of quantitation. An excellent correlation was obtained between the concentrations measured by the two detection modes in the range 10–100 ng · ml^{-1}.

The plasma concentration curve of each subject after intravenous and oral administration of 80 mg fenspiride hydrochloride was plotted as function of time, and was fitted to a polyexponential function by non-linear regression analysis using NONLIN software [14]. A polyexponential adjustment was applied to the data obtained after intravenous and oral administration of the drug using Akaike's information criterion (AIC).

Except for the absorption and elimination half-lives corresponding to each increasing or decreasing phase ($t_{1/2}$), which were calculated by the above method, other parameters were estimated by a non compartmental method:

- for Treatment A, the area under plasma concentration time curve (AUC_{IV}), the apparent volume of distribution (V) and the total clearance (CL).
- for Treatment B, the maximum plasma concentration (C_{max}) and the corresponding time (t_{max}), the area under plasma concentration time curve (AUC_{PO}), and the absolute bioavailability (f).

Results

The mean age of the volunteers was 21.7 (2.4) y (range 19–27 y), the mean weight was 72.0 (5.8) kg (60–80 kg) and the mean height was 176.8 (6.6) cm (167–185 cm).

The heart rate and systolic and diastolic arterial pressure measurements after IV and oral fenspiride hydrochloride are set out in Table 1. A slight but significant decrease in systolic arterial blood pressure occurred 30 min after IV administration of the drug. A fall was also observed 3 h after ingestion of the drug, but this was not statistically significant.

Tolerance to fenspiride was good. The only noteworthy adverse effect was the appearance of a slight drowsiness in 9 of the 12 healthy volunteers. It appeared 2 h after IV administration and lasted 2–3 h, without any alteration in sleep or attentiveness of the subjects.

The mean plasma concentrations after IV and oral administration of the two galenic formulations of fenspiride hydrochloride to the 12 healthy volunteers are specified in Table 2. The plasma concentration-time profiles are illustrated in Fig. 2. The pharmacokinetic

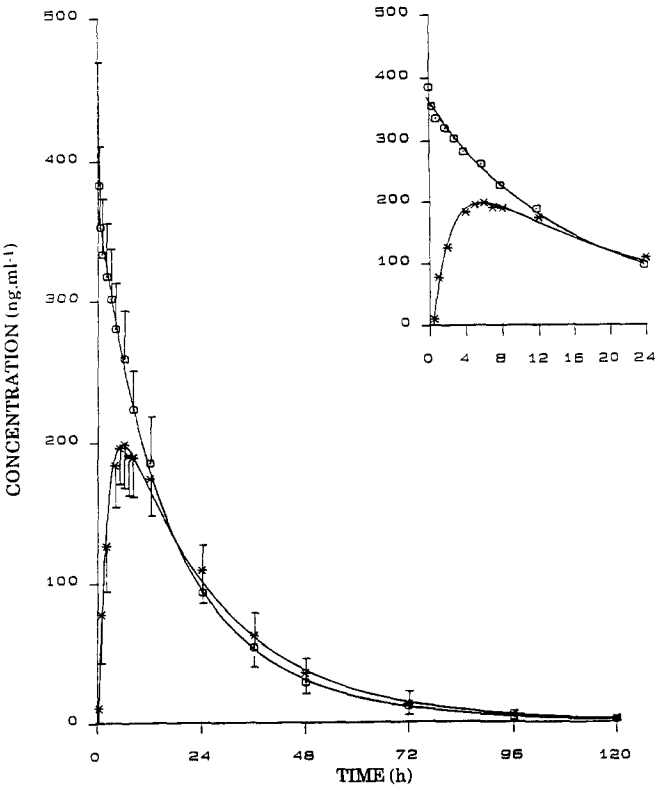


Fig. 2. Mean plasma concentration-time curves of fenspiride after a single dose of 80 mg fenspiride hydrochloride IV (o) and as tablets given orally (*). The parts of the curves up to 24 h are expanded in the insert

parameters calculated for both treatments are described in Table 3.

After a single dose of fenspiride hydrochloride 80 mg IV, the plasma concentration-time profiles showed minor differences between subjects. In 4 of them, elimination followed a biexponential curve, with a rapid decrease in plasma concentration in the first 2 h followed by a slower decline, with a terminal half-life ranging between 11.5 and 13.4 h. In most subjects, the plasma concentration followed a monoexponential curve after a plateau lasting up to 0.5–1 h. The elimination half-life $t_{1/2}$ calculated for all subjects was 14 (4) h, the volume of distribution (V) was 215 (33) l and plasma clearance (CL) was 184 (42) $ml \cdot min^{-1}$. The mean AUC was 6.73 (1.78) $\mu g \cdot ml^{-1} \cdot h$.

After oral administration of a single 80 mg dose of fenspiride hydrochloride, the maximum plasma concentration of 206 (28) $ng \cdot ml^{-1}$ was reached after 5.9 (1.2) h. The lag-time varied from 0.1 to 1.5 h and the absorption half-life was estimated to be 1.5 (0.4) h. Twelve hours after oral administration, the plasma concentration began to decline markedly, with a mean elimination half-life of 16 (3) h. The mean AUC was 6.03 (1.44) $\mu g \cdot ml^{-1} \cdot h$.

The absolute bioavailability, calculated as the ratio of the AUCs extrapolated to infinity after oral and intravenous administration, was 90 (9)%. It is noteworthy that the observed AUC (0–120 h) represented 98% of that extrapolated to infinity for both treatments, which confirms the validity of the calculated bioavailability.

Discussion

The bioavailability of fenspiride hydrochloride tablets by the oral route was almost complete (90%). The result is in agreement with that obtained by the use of ^{14}C fenspiride solution in man, when the bioavailability of the drug was 100% after oral administration [16]. It is consistent with the fact that the drug is not highly metabolised in humans [12].

The absorption of fenspiride hydrochloride from tablets was slow compared to that observed from the solution, the latter producing the maximum plasma concentration about 1 h after administration (12); with the tablet, the maximum plasma concentration was reached between 4 and 8 h (mean t_{max} 5.9 (1.2) h), and a sustained plateau rather than a pronounced peak was observed. This result is consistent with in vitro dissolution data obtained with the tablet, which showed a sustained release spread over more than 10 h.

The mean AUC was 6.73 (1.78) $\mu g \cdot ml^{-1} \cdot h$ and 6.03 (1.44) $\mu g \cdot ml^{-1} \cdot h$, respectively, after IV and oral administration; the corresponding coefficients of variation were 26 and 24%. This result indicates that liberation of the drug from the solid tablet form did not lead to any additional variability in the pharmacokinetic behaviour of fenspiride in comparison to IV administration.

The elimination half-life of fenspiride was in the same range after both the IV and oral routes of administration, namely 14 (4) h and 16 (3) h, respectively.

Thus, the present study in 12 healthy volunteers has shown that the bioavailability of fenspiride administered orally as 80 mg tablets was very high (90 (9)%). The tablet used had the characteristics of a slow release formulation.

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