Single and multiple dose pharmacokinetics of a new NSAID (droxicam) in healthy volunteers

L. MARTINEZ, J. SANCHEZ, R. ROSER, J. GARCIA-BARBAL, R. SAGARRA, and A. BARTLETT

Departments of Clinical Research and Biochemistry, Laboratorios Dr. Esteve, S.A., Barcelona, Spain

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SUMMARY

The pharmacokinetics of droxicam, both as a single 10 mg dose and as a multidose regimen of 10 mg/day for 20 consecutive days, have been studied in healthy volunteers. The study was performed in two separate groups of volunteers. Following a single dose the Cmax was 0.82 ± 0.15 μg/ml, the Tmax was achieved at 6.1 ± 3.5 h, the elimination half life was 65.7 ± 17.6 h, the Cl/F was 2.04 ± 0.53 ml/min, the Vd/F was 11.0 ± 1.7 l and the AUC∞ was 86.9 ± 24.6 μgh/ml, which was similar to results reported in other study from piroxicam (10 mg). Following multiple doses the Cmed(ss) was 2.06 ± 0.42 μg/ml, the Tmax(ss) was 8.2 ± 6.0 h, the elimination half life was 41.4 ± 12.4 h, the Cl/F was 3.30 ± 0.63 ml/min, the Vd/F was 11.8 ± 4.3 l and the AUC∞ was 52.4 ± 11.3 μgh/ml. The differences encountered between single and multiple dose administration in elimination kinetics are due to the wide interpersonal variation described for the elimination half life of piroxicam. It may be concluded from these results that absorption, elimination and bioavailability kinetics of droxicam are independent of the administered dose.

INTRODUCTION

Droxicam

(5-methyl-3-(2-pyridyl)-2H,5H-1,3-oxazino[5,6-c][1,2]
1-benzothiazine-2,4-(3H)-dione 6,6-dioxide) is a new non steroidal antiinflammatory drug which is a prodrug of piroxicam, with an activity of the same order of magnitude but an experimental ulcerogenic effect ten times less than that of piroxicam (1-5). Pharmacokinetic studies in rat, dog and man have shown that the bioavailability of droxicam is equivalent to that of piroxicam, but with delayed absorption kinetics due to the process of transformation of droxicam to piroxicam in the gastrointestinal tract (6, 7). Bioavailability of droxicam in human volunteers was not affected by possible variations in the gastric transit (8). Human studies were performed as a comparison between droxicam and piroxicam at a dosage of 20 mg/day for 20 consecutive days (7). Since, however, epidemiological studies from the FDA have suggested that occasionally, particularly in the elderly, piroxicam should be administered at a dosage of 10 mg/day (9), we believed it necessary to study droxicam pharmacokinetics at this 10 mg dosage, both on single and repeated administration, in healthy volunteers.

MATERIALS AND METHODS

Subjects

Fourteen healthy male volunteers participated in the study. In the single dose group, the age of the subjects was 22 ± 4 years (mean ± SD, range, 18–30) and their
mean bodyweight 60.9 ± 8.8 kg (range, 49.5–74.8 kg). In the multiple dose group, their age was 28 ± 5 years (range, 23–37) and the mean bodyweight 68.2 ± 4.3 kg (range, 60.0–74.0 kg). The volunteers were judged normal on the basis of a prestudy medical history, physical examination, clinical laboratory tests and ECG. No other drugs were allowed for one month before and during the study period.

**Ethical considerations**

The study was carried out under the supervision of an Institutional Review Board and had been granted approval by the health authorities. Written informed consent was obtained from all subjects.

**Study design**

The study was carried out simultaneously in two separate groups of volunteers. The first group received one 10 mg droxicam capsule (Lab. Dr. Esteve, S.A.), whilst the second group received a 10 mg capsule daily for 20 consecutive days.

The drug was administered daily at the same time, with 125 ml of water and a light standard meal, following four hour’s fasting. Compliance was assured by ingestion in presence of the investigator. Consumption of alcohol or caffeine was forbidden throughout the course of the study.

Blood samples were obtained at the following times: single dose: 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 36, 48, 72, 96 and 120 h; multiple dose: 72, 120, 168, 216, 240, 264, 266, 270, 288, 312, 314, 318, 336, 360, 362, 366, 384, 408, 410, 414, 420, 432, and 456 h. Additional samples were taken at 2, 4, 6, 8, 10, 12, 24, 30, 36, 48, 54, and 60 h after the last dose was given. Heparin (1% w/v) was added to all blood samples at a ratio of 1:50 to prevent clotting. The samples were immediately centrifuged at 3000 g for 15 min and the plasma obtained was kept deep-frozen (−25°C) until analyzed.

**Analytical method**

Since droxicam is transformed into piroxicam in the gastrointestinal tract and plasma levels of unchanged droxicam are not found (7), only plasma piroxicam concentrations were determined in all the volunteers. The extraction and analytical technique employed for determination of piroxicam in plasma samples followed a specific HPLC method (7, 10).

**Pharmacokinetic analysis**

The piroxicam plasma concentration—time data obtained after single or multiple oral dose....

![Graph](image)