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Pharmacokinetic profiles of two tablet formulations of piroxicam

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Abstract

There is considerable interest in developing new non-steroidal anti-inflammatory drugs (NSAIDs) formulations with faster onset of analgesic action like fast dissolving tablets. An open-label, randomized, single dose, crossover study with a 18 days washout period was conducted in 16 healthy volunteers to compare the pharmacokinetic profile of 20 mg piroxicam freeze-dried tablet (Proxalyoc®, Cephalon) with that of 20 mg piroxicam capsule (Feldène®, Pfizer).

T_{lag} with freeze-dried tablet was three times shorter than with capsule (21.6 min versus 59.4 min). Mean $AUC_{0–30\,min}$, mean $AUC_{0–1\,h}$, mean plasma concentrations at 15 min, 30 min and 1 h post-dose were significantly higher with the freeze-dried tablet than with the capsule, indicating that piroxicam was more rapidly absorbed from the freeze-dried tablet with higher plasma concentrations achieved at shorter intervals after dosing. The 90% confidence intervals of the ratios of means C_{max}, $AUC_{0–t}$, $AUC_{0–\infty}$ and $T_{1/2}$ all fell within the acceptance range of 0.8–1.25, demonstrating the bioequivalence of the two formulations.

Although the bioavailability of the two formulations was similar, the administration of piroxicam as a freeze-dried tablet gave a much faster absorption rate during the first hour after dosing than the capsule formulation. This faster absorption is an obvious advantage for the treatment of acute episodes of pain.

Keywords: Piroxicam; Bioequivalence; Freeze-dried tablet; Healthy volunteers

1. Introduction

Piroxicam is a well-established non-steroidal anti-inflammatory drug (NSAID) exhibiting anti-inflammatory, analgesic and antipyretic properties. It is widely used in rheumatic diseases because of its potent anti-inflammatory properties and long half-life (about 50 h) offering the convenience of a once-daily administration (Woolf and Radulovic, 1989). In France, the reference-marketed product is Feldène® 10 and 20 mg capsules. Following a single oral administration of a capsule, the maximal concentrations are achieved 2 h post-dose but this time fluctuates between 1 and 6 h depending on each individual. Consequently, there is considerable interest in developing new NSAIDs for-

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mulations with faster onset of analgesic action (Lee and Balfour, 1994; Piscitelli et al., 1998).

A fast dissolving oral formulation of piroxicam (freeze-dried 20 mg tablet) was developed and marketed by Cephalon France (Proxalyoc®). This formulation shows, in addition to the common properties of freeze-dried products (good stability, rapid dispersion or dissolution and release of initial drug properties), the following therapeutic benefits improved bioavailability, improved observance and rapid onset of action (Jaccard and Leyder, 1985; Leyder and Nguyen, 1990). Because the oral mucosa is highly vascularized, drugs that are absorbed through the oral mucosa directly enter the systemic circulation, bypassing the gastrointestinal tract and first-pass metabolism of the liver. This results in a rapid onset of action via a more comfortable and convenient delivery route than the intravenous route (Zhang et al., 2002).

Previous clinical studies showed that a fast-dissolving formulation of piroxicam administered by sublingual route was bioequivalent to the standard capsule formulation (Ronca et al., 1994). Moreover, the onset of analgesic effect was faster than that of classical NSAIDs for the treatment of post-extraction dental pain (Dolci et al., 1993; Selcuk et al., 1998) and acute osteoarthritis flares (Consoli et al., 1994).

The primary aim of this study was to compare the early pharmacokinetic profile (1 h after administration) of the freeze-dried tablet (Proxalyoc®) to the early pharmacokinetic profile of the standard piroxicam capsule (Feldène®).

2. Materials and methods

Sixteen healthy male Caucasian volunteers (aged 18–30 years) were included in the study, after having undergone a thorough medical examination. The clinical trial was performed in accordance with the guidelines set by the World Medical Assembly (Declaration of Helsinki). All volunteers gave written informed consent to participation in the study, after having been informed of the nature and implications of the trial. A total of 16 male healthy subjects completed this study. There were no dropouts. Their mean age was 24.8 ± 3.8 years (range 21–30 years), their mean weight was 72.4 ± 7.3 kg (range 64–84 kg) and their mean height was 180.6 ± 6.7 cm (range 167–192 cm). All cardiovascular measurements and laboratory values at screening were within prescribed limits.

The study was designed as a randomized, open, non-placebo controlled, single dose, crossover study in 16 healthy volunteers. Each subject underwent successively the two study periods in a randomized order according to a crossover design. This study was without direct individual benefit and each subject was considered as his own control. In the first session, the subjects received either one freeze-dried tablet or one capsule of piroxicam. In the second session, they were crossed over to receive the other formulation. The two treatment periods were separated by a washout period of at least 18 days.

Each study session comprised 8 days. The subjects arrived at the Clinical Center on the evening of day 1 and remained in the unit until 24 h after the administration of 20 mg piroxicam. Blood samples were taken at pre-dose (−1 h) and 5, 10, 15, 20, 30 and 45 min, and then 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 72, 120 and 168 h post-dose. Subjects were discharged from the unit on the morning of day 2 and they returned to the Clinical Center at days 4, 6 and 8 in ambulatory conditions for the last three blood samples (72, 120 and 168 h post-dose).

During each hospitalization period, the subjects remained under constant medical surveillance by a physician. During the two study sessions, the subjects maintained daily contact with the clinical investigator and reported any adverse events, whether related or not to the ongoing drug treatment in his opinion. Medication was forbidden over the period starting from 2 weeks before the trial (3 months for enzyme-inducing or inhibiting drugs) and ending 2 days after the study end.

An indwelling catheter was used for blood sampling during day 1, remaining blood samples were obtained by puncture of a forearm vein. The 5 mL of blood were collected in evacuated polypropylene tubes containing sodium heparinate. Immediately after blood collection, the tubes were centrifuged for 10 min at $1500 \times g$ at +4 °C. After centrifugation, at least 2 mL plasma were rapidly transferred into two polypropylene tubes and stored in appropriately labeled freeze resistant bags at −20 °C until sent to the analytical laboratory.

The assay of piroxicam in plasma was performed by a validated high performance liquid chromatography (HPLC) method with UV detection. A Nucleosil C_{18} column (5 μ, 150 × 4.6 mm, Hypersil) and

a mobile phase consisting of an acetonitrile-distilled water–acetic acid (58/38/4, v/v/v) mixture were used. The flow rate was 1 mL/min and the effluent was monitored at 365 nm.

Before any assay, the specificity, the linearity and the repeatability of the method were demonstrated and the limit of quantification and detection were determined. Calibrations curves were linear in the range from 0.1 to 10 μg/mL. The detection limit was 0.03 μg/mL for plasma piroxicam. The limit of quantification (corresponding to the last point of the calibration curve with a coefficient of variation (CV) lower than 10%) was 0.1 μg/mL (CV = 0.74%). Plasma concentrations below the limit of quantification at early time points were set to zero. Plasma levels below the limit of quantification in the terminal samples were excluded from the analysis.

The following early pharmacokinetic parameters were determined for the first hour following administration: the lag time estimated directly from experimental data (T_{lag}), the area under the concentration–time curve from 0 to 30 min and to 1 h post-dose according to the linear trapezoidal method ($AUC_{0–30\,min}$ and $AUC_{0–1\,h}$) and the plasma concentrations measured at 15 min, 30 min and 1 h post-dose ($C_{15\,min}$, $C_{30\,min}$ and $C_{1\,h}$).

For the overall assessment period, the maximum plasma concentration (C_{max}) and the time to reach the maximal plasma concentration (T_{max}) were directly obtained without interpolation from the experimental plasma concentration data as a function of time. The apparent half-life was calculated by application of the equation: $T_{1/2} = \ln 2/z$ (where z corresponds to the elimination rate constant estimated by log-linear regression of the terminal part of the curve). The area under the concentration–time curve ($AUC_{0–t}$) was computed using the linear trapezoidal rule from zero to the last measurable concentration. The extrapolated area under the concentration–time curve ($AUC_{0–inf}$) was calculated by addition of the residual area (Ct/z) to $AUC_{0–t}$, where Ct corresponds to the last measured concentration.

Calculations were performed by non-compartmental approach using WinNonLin® software, version 3.0.

The early pharmacokinetic parameters: $AUC_{0–30\,min}$, $AUC_{0–1\,h}$, $C_{15\,min}$, $C_{30\,min}$ and $C_{1\,h}$ were compared using the non-parametric test (Mann–Whitney's test). Some values of these parameters were equal to zero, precluding logarithmic transformation for the analysis of variance. Moreover, the values were not normally distributed.

The pharmacokinetic parameters C_{max}, $AUC_{0–t}$, $AUC_{0–inf}$ and $T_{1/2}$ were analyzed by a four-way analysis of variance (ANOVA). The factors of the model were the treatment, the sequence of administration, the subject within sequence and the period. Prior to all analyses C_{max}, $AUC_{0–t}$ and $AUC_{0–inf}$ were log transformed. $T_{1/2}$ was directly analyzed without log transformation.

The 90% confidence intervals for the formulation means ratio, used for the assessment of the bioequivalence of the two formulations were calculated in the standard way. The 95% Westlake's symmetric confidence intervals were also calculated.

T_{lag} and T_{max} were analyzed using the non-parametric Friedmann's test.

3. Results

Tolerance of each medication was excellent over the entire treatment period. A total of two non-serious adverse events occurred in two subjects, namely one episode of rhinitis of discreet intensity and one episode of headache of medium intensity whose relationship to study drug was judged, respectively, by the investigator as excluded or doubtful.

Mean plasma concentrations of piroxicam are depicted in Fig. 1 for the first hour following the administration and in Fig. 2 for the overall assessment period (0–168 h). The first 0–1 h portion of the plasma curves

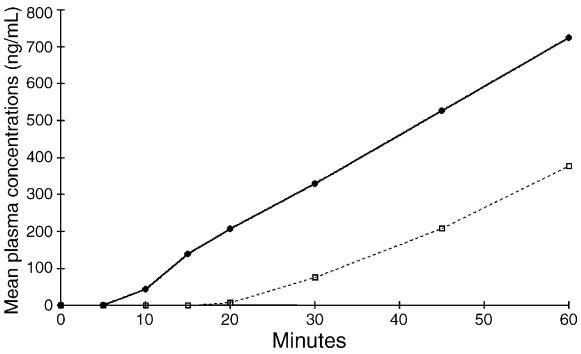

Fig. 1. Mean plasma concentration of piroxicam over the 0–1 h period after single 20 mg oral dose in 16 healthy subjects as one freeze-dried tablet (●) or as one capsule (□) of piroxicam.

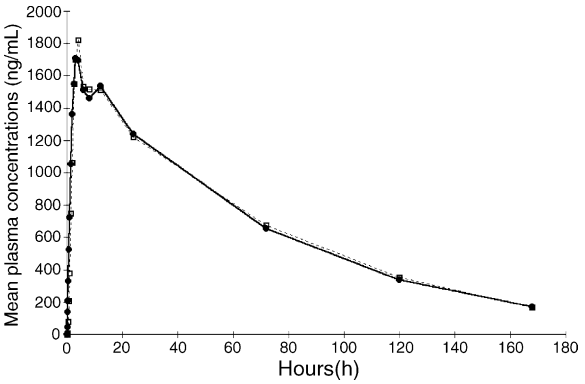

Fig. 2. Mean plasma concentration of piroxicam over the 0–168 h period after single 20 mg oral dose in 16 healthy subjects as one freeze-dried tablet (●) or as one capsule (□) of piroxicam.

(Fig. 1) indicated that piroxicam was more rapidly absorbed from the freeze-dried tablet than from the reference capsule, the peak level was reached within 3 h after administration of the freeze-dried tablet compared to 4 h after the reference capsule. Moreover, the average levels observed from 0.5 to 1 h post-dose were markedly higher after the freeze-dried tablet than after the capsule by factors 4 and 1.9, respectively. Upon completion of the absorption phase, the mean plasma concentration curves corresponding to the two formulations over the 168 h post-dose were virtually super imposable.

The early mean pharmacokinetic parameters after administration of one freeze-dried tablet or one capsule of piroxicam are shown in Table 1. The mean (±S.E.M.) T_{lag} with the freeze-dried tablet was 0.36 ± 0.04 h. This was significantly shorter than the value observed with the capsule formulation: 0.99 ± 0.10 h ($p = 0.001$ by Friedmann's test). The $AUC_{0–30\,min}$ and $AUC_{0–1\,h}$ values with the freeze-dried tablet (68.58 ± 17.73 and 331.69 ± 53.73 ng h/mL, respectively) were significantly higher than that of the capsule formulation (7.49 ± 5.09 and 116.58 ± 44.71 ng h/mL; $p = 0.0001$ and 0.001, respectively). The mean plasma piroxicam concentrations observed, respectively, at 15 min, 30 min and 1 h post-dose ($C_{15\,min}$, $C_{30\,min}$ and $C_{1\,h}$) were markedly higher with the freeze-dried tablet than with the capsule formulation (by a factor 4.3 at 30 min: 328.75 ± 62.10 ng/mL versus 76.25 ± 56.73 ng/mL and a factor 1.9 at 1 h: 724.00 ± 98.09 ng/mL versus 377.63 ± 102.76 ng/mL). The Mann–Whitney's test showed a significant difference between the two formulations for $C_{15\,min}$, $C_{30\,min}$ and $C_{1\,h}$ ($p = 0.0035$, $p = 0.0001$ and $p = 0.0114$, respectively).

The pharmacokinetic parameters for the overall assessment period are shown in Table 2. The mean values of the time to reach peak plasma concentration of piroxicam were similar for the freeze-dried tablet formulation and the capsule formulation (4.78 ± 0.75 h versus 5.22 ± 0.73 h). The Friedmann's test demonstrated no significant difference between the two formulations for this parameter. The maximum mean plasma concentration with the freeze-dried tablet was 1812.00 ± 80.76 ng/mL. This value was not significantly different from the value of 1900.31 ± 96.20 ng/mL observed with the capsule formulation (ANOVA). Similarly, the $AUC_{0–t}$, $AUC_{0–inf}$ and $T_{1/2}$ values (49.44 ± 5.35 h versus 53.11 ± 4.54 h) did not significantly differ between the two formulations according to the results of the analysis of variance (Table 2).

Table 1
Early plasma pharmacokinetic parameters of piroxicam after a single dose of piroxicam 20 mg as one freeze-dried tablet or as one reference capsule in 16 healthy subjects

Parameter mean ± S.E.M. (mininum–maximum)	Freeze-dried tablet	Capsule	*p*-Value
T_{lag} (h)	0.36 ± 0.04 (0.17–0.75)	0.99 ± 0.10 (0.33–1.50)	0.001 (Friedmann's test)
$AUC_{0–30\,min}$ (ng h/mL)	68.58 ± 17.73 (0–261.24)	7.49 ± 5.09 (0–76.33)	0.0001 (Mann–Whitney's test)
$AUC_{0–1\,h}$ (ng h/mL)	331.69 ± 53.73 (77.13–845.49)	116.58 ± 44.71 (0–666.33)	0.001 (Mann–Whitney's test)
$C_{15\,min}$ (ng/mL)	138.06 ± 53.51 (0–734.00)	0.00 (0–0)	0.0035 (Mann–Whitney's test)
$C_{30\,min}$ (ng/mL)	328.75 ± 62.10 (0–930.00)	76.25 ± 56.73 (0–898.00)	0.0001 (Mann–Whitney's test)
$C_{1\,h}$ (ng/mL)	724.00 ± 98.09 (197.00–1566.00)	377.63 ± 102.76 (0–1294.00)	0.0114 (Mann–Whitney's test)

S.E.M., standard error of the mean; T_{lag}, lag time estimated directly from experimental data; $AUC_{0–30\,min}$, area under the plasma concentration–time curve from 0 to 30 min after administration; $AUC_{0–1\,h}$, area under the plasma concentration–time curve from 0 min to 1 h after administration; $C_{15\,min}$, $C_{30\,min}$ and $C_{1\,h}$, plasma concentrations measured 15 min, 30 min and 1 h, respectively, after administration.

Table 2
Plasma pharmacokinetic parameters of piroxicam for the overall assessment period after a single dose of piroxicam 20 mg as one freeze-dried tablet or as one reference capsule in 16 healthy subjects

Parameter mean ± S.E.M. (minimum–maximum)	Freeze-dried tablet	Capsule	*p*-Value	Point estimate CI 90% Westlake test
T_{max} (h)	4.78 ± 0.75 (2.5–12.00)	5.22 ± 0.73 (2.5–12.00)	NS (Friedmann's test)	Not applicable
C_{max} (ng/mL)	1812.00 ± 80.76 (1256.00–2247.00)	1900.31 ± 96.20 (1383.00–2830.00)	NS ANOVA	95.50 (90.27–101.03) (90.26–109.74)
AUC_{0-t} (ng h/mL)	113250.31 ± 10877.47 (53063.26–224792.29)	113432.74 ± 12470.01 (22722.25–232752.88)	NS ANOVA	104.71 (92.63–118.35) (81.51–118.49)
AUC_{0-inf} (ng h/mL)	134967.12 ± 18298.18 (62833.12–363134.39)	135031.35 ± 17066.12 (35043.26–327994.30)	NS ANOVA	101.49 (91.90–112.08) (87.22–112.78)
$T_{1/2}$ (h)	49.44 ± 5.35 (27.31–114.70)	53.11 ± 4.54 (26.47–100.48)	NS ANOVA	93.10 (82.33–103.86) (82.29–117.71)

S.E.M., standard error of the mean; T_{max}, time to reach maximum plasma concentration; C_{max}, maximum piroxicam plasma concentration observed; AUC_{0-t}, area under the plasma concentration–time curve up to last measurable concentration; AUC_{0-inf}, area under the plasma concentration–time curve extrapolated to infinity; $T_{1/2}$, half-life; CI, confidence interval.

The 90% confidence intervals for test/reference ratio were (90.27–101.03) for C_{max}, (92.63–118.35) for AUC_{0-t}, (91.90–112.08) for AUC_{0-inf} and (82.33–103.86) for $T_{1/2}$ showing the bioequivalence of the two formulations in terms of bioavailability. These results were confirmed by the values of 95% confidence symmetrical intervals of Westlake (Table 2).

4. Discussion

This trial was designed to compare the pharmacokinetic profile of piroxicam either given by sublingual and oral route (freeze-dried tablet) or by oral route only (capsule) during the first hour following the administration in 16 healthy male subjects.

A trend to a faster absorption of piroxicam with a fast dissolving formulation in comparison with the classical capsule formulation was shown in previous bioequivalence studies (Mueller et al., 1992; Dolci et al., 1993; Ronca et al., 1994). In order to demonstrate a faster absorption of piroxicam with the freeze-dried tablet, particularly during the first hour after administration, several blood samples were taken within 1 h post-dose in this study. The overall sampling time schedule was based on the previous knowledge of the pharmacokinetic profile of piroxicam given as a single dose of 20 mg in healthy volunteers (Woolf and Radulovic, 1989; Lee and Balfour, 1994).

The analysis of early pharmacokinetic parameters confirmed that the administration of piroxicam by sublingual route then by oral route (the saliva being swallowed) gave a faster absorption rate of piroxicam than with the oral capsule. Indeed, a 4.3-fold greater mean plasma piroxicam concentration was achieved as soon as 30 min after administration of the freeze-dried tablet. This increase in the absorption rate is slightly higher than the one obtained previously with an inclusion complex formulation of piroxicam (Deroubaix et al., 1995).

A statistically significant difference was revealed for all early pharmacokinetic parameters (T_{lag}, $AUC_{0-30\,min}$, $AUC_{0-1\,h}$, $C_{15\,min}$, $C_{30\,min}$ and $C_{1\,h}$). The mean T_{lag} observed with the freeze-dried tablet was three times lower than the one observed with the capsule (21.6 min with the freeze-dried tablet against 59.4 min with the capsule). The mean area under the curve between T_0 and $T_{30\,min}$ was more than nine times

higher with the freeze-dried tablet than with the capsule and the mean area under the curve between T_0 and $T_{1\,h}$, was more than 2.8 times higher indicating a marked difference in absorption profile. These results are in line with those of previous clinical studies comparing the fast dissolving formulation to the capsule formulation of piroxicam (Dolci et al., 1993; Consoli et al., 1994).

Moreover, the AUCs of the two formulations for the overall assessment period were similar indicating that their bioavailability was comparable. The bioequivalence of the formulations (freeze-dried tablet and capsule) was established by the assessment of the 90% confidence intervals.

Similar results were obtained with the inclusion complex of piroxicam showing an increase of the absorption rate of piroxicam whilst other pharmacokinetic characteristics remained unchanged (Deroubaix et al., 1995).

In summary, although the bioavailability of the two formulations was similar, the administration of piroxicam given as a freeze-dried tablet gave a much faster absorption rate during the first hour after dosing than the capsule formulation. This faster absorption is an obvious advantage for the treatment of acute episodes of pain.

References

Consoli, G., Covelli, M., Di Matteo, L., Marcolongo, R., Tirri, G., La Montagna, G., Pipitone, V., 1994. Piroxicam compresse sublinguali a rapida dissoluzione vs. naprossene nel trattamento dell'osteoartrosi riacutizzata [Fast-dissolving sublingual tablets of piroxicam versus naproxen in the treatment of recurrent acute osteoarthrosis. Multicenter clinical trial]. Minerva Med. 85, 89–96.

Deroubaix, X., Stockis, A., Allemon, A.M., Lebacq, E., Acerbi, D., Ventura, P., 1995. Oral bioavailability of CHF1194, an inclusion complex of piroxicam and β-cyclodextrin, in healthy subjects under single dose and steady state conditions. Eur. J. Clin. Pharmacol. 47, 531–536.

Dolci, G., Ripari, M., Pacifici, L., Umile, A., 1993. Analgesic efficacy and the tolerance for piroxicam-beta-cyclodextrin compared to piroxicam, paracetamol and placebo in the treatment of postextraction dental pain. Minerva Stomatol. 42, 235–241.

Jaccard, T.T., Leyder, J., 1985. Une nouvelle forme galénique: le lyoc [A new galenic form: lyoc]. Ann. Pharm. Fr. 43, 123–131.

Lee, C.R., Balfour, J.A., 1994. Piroxicam-β-cyclodextrin a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in rheumatic diseases and pain states. Drugs 48, 907–929.

Leyder, J., Nguyen, T., 1990. Le lyophilisat oral: une innovation galénique [The oral lyophilisate: a galenic innovation]. Moniteur Hospitalier 22, 4–8.

Mueller, B.A., Rex, D.K., Figueroa, N., Greene, P., Brater, D.C., 1992. A pharmacokinetic and endoscopic comparison of an oral and an experimental buccal piroxicam formulation. Pharmacotherapy 12, 93–97.

Piscitelli, D.A., Bigora, S., Propst, C., Goskonda, S., Schwartz, P., Lesko, L.J., Augsburger, L., Young, D., 1998. The impact of formulation and process changes on in vitro dissolution and the bioequivalence of piroxicam capsules. Pharm. Dev. Technol. 3, 443–452.

Ronca, F., Palmieri, L., Ronca, G., 1994. Effetto della formulazione e della via di somministrazione sulla velocità di assorbimento del piroxicam [Effect of the formulation and the route of administration on the rate of absorption of piroxicam]. Basi Raz. Ter. 24, 1–6.

Selcuk, E., Gomel, M., Apaydin, S., Kose, T., Tuglular, I., 1998. The postoperative analgesic efficacy and safety of piroxicam (FDDF) and naproxen sodium. Int. J. Clin. Pharmacol. Ther. Res. 18, 9–21.

Woolf, T.F., Radulovic, L.L., 1989. Oxicams: metabolic disposition in man and animals. Drug Metab. Rev. 21, 255–276.

Zhang, H., Zhang, J., Streisand, J.B., 2002. Oral mucosal drug delivery: clinical pharmacokinetics and therapeutic applications. Clin. Pharmacokinet. 41, 661–680.