Clinical Trials Journal

ISSN 0009 - 9325

an International Publication of
Scientific and Clinical Investigations

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A Controlled Study *vs.* an Injectable Piroxicam Formulation

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Reprinted from: CLIN TRI J 1990; 27 (3): 176–86

Received 5.12.89

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SUMMARY

The analgesic effect and plasma levels of a new oral formulation, sachets of granules of piroxicam complexed with beta-cyclodextrin, were compared with an injectable piroxicam formulation.

Both preparations each contained 20 mg of piroxicam, and were given as a single dose to 24 patients with post-surgical pain, according to a randomized double-blind/double-dummy design for parallel groups. The assessment of the effect on pain and the determination of piroxicam plasma levels were made on Day 1 and after 24, 48, 72 and 96 hours.

In their plasma kinetics, the two formulations did not substantially differ, except for T_{max} which was significantly reduced after being given orally. The effects on pain were superimposable both for speed of action and for duration of the symptom-free period.

Key Words — *Acute post-surgical pain; piroxicam beta-cyclodextrin; injectable piroxicam*

Introduction

Beta-cyclodextrin is a cyclic macromolecule of glucidic origin, made up of seven glucopyranose units, obtained from common starch by enzymic hydrolysis. It is not orally absorbed, but is completely hydrolysed by intestinal amylase.[1,2]

Beta-cyclodextrin is able to complex non-soluble substances by encapsulation, thus improving their molecular scattering and enabling dissolution in acqueous physiological media. The first effect is a more rapid absorption of these

substances, whose maximum plasma concentration (Cmax) is reached much earlier than in non-complexed formulation. Another important effect is the shorter time of contact with the gastro-intestinal mucosa: this can reduce the incidence and severity of mucosal damage, especially for potentially high damaging substances.

The molecular encapsulation of beta-cyclodextrin with piroxicam, a poorly water-soluble non-steroidal anti-inflammatory drug (NSAID), leads to a complexed, readily soluble formulation, with rapid bioavailability[3-5] and with a better gastro-intestinal tolerability,[6,7] compared to the non-complexed parent drug.

The quicker absorption makes therapeutically effective piroxicam levels available in plasma within 30 minutes of administration, resulting in an important anticipation of the analgesic effect, compared to the same administration route of the non-complexed parent drug. Clinical studies carried out on different types of acute pain confirmed the more rapid action of piroxicam complexed with beta-cyclodextrin both by oral and rectal administration.[8-13]

A number of investigators successfully used the piroxicam beta-cyclodextrin complex (Brexin* tablets) in the treatment of orthopaedic post-traumatic and post-surgical pain.[14-16]

The development of a new granular formulation easily dispersible in water appears to improve further the bioavailability of the drug, and make its oral absorption similar to that by injection.

The aim of this study was to verify the bioavailability and the analgesic effect of the granular formulation (sachets) of piroxicam beta-cyclodextrin, compared to an injectable formulation of piroxicam.

Materials and Methods

Twenty-four male patients undergoing orthopaedic surgery for fracture, meniscectomy, arthroprothesis insert, lumbar discectomy, were enrolled in the study.

Exclusion criteria included: gastro-intestinal disease, cardiac, renal and hepatic failure, known hypersensitivity to NSAIDs, body-weight under or over (± 10%) the Italian standard in similar aged males, concomitant or very recent NSAID treatment (any previous treatment with piroxicam must have been stopped at least 15 days before commencing the present trial). Patients under 18 or over 65 years were not admitted to the study. Patients who did not give their written consent were not admitted.

After enrolment, patients underwent surgery and were then treated with a single oral dose of piroxicam beta-cyclodextrin, Brexin* (one 20 mg sachet) or standard formulation of i.m. injectable piroxicam† (one 20 mg ampoule).

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* *Brexin® (Chiesi Farmaceutici) and Cicladol®(Master Pharma);*
† *Feldene® (Pfizer)*

Patients were randomly assigned to treatment in double-blind/double-dummy conditions.

After opening the treatment code at the end of the study, the two groups were seen to be homogeneous for age, body-weight and height (Table I).

TABLE I

Patient details

	Piroxicam beta-cyclodextrin oral formulation	Piroxicam injectable formulation	Student's paired t-test
No. of Patients	12	12	
Age *(yrs)* Mean ± SD range	49.50 ± 14.42 22-62	44.80 ± 12.79 28-60	NS
Weight *(Kg)* Mean ± SD range	72.33 ± 6.51 65-80	74.25 ± 5.20 67-85	NS
Height *(cm)* Mean ± SD range	173.00 ± 4.80 165-180	173.17 ± 5.60 165-180	NS

The treatment took place on the morning of the day after surgery had been performed. Pain assessment was made at baseline and 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 hours after treatment. Pain intensity (PI) was assessed by a rating scale ranging from 0 to 4 (0 = no pain, 1 = mild, 2 = moderate, 3 = severe, 4 = unbearable). Pain-relief (PAR) was evaluated at the same time according to the following score: 1 = no improvement, 2 = slight improvement, 3 = good improvement, 4 = total pain-relief.

The patients were also requested to give a self-evaluation of pain after 0.5, 1, 2, 4 and 6 hours according to a vertical analogue visual scale (VAS).

PID (difference between the basal pain score and the score at the different times), SPID (sums of PID) and TOTPAR (sums of PAR) were determined.

Tolerability was monitored from the start of treatment until the end of the trial. Adverse reactions spontaneously declared by the patients, as well as objective symptoms such as cardiovascular disorders, skin reactions or hardening in the injection site were recorded.

Blood samples were taken by venous puncture from the forearm at the following times: pre-dose, 0.25, 0.5, 1, 2, 4, 8, 24, 48, 72 and 96 hours. The blood samples were collected into heparinized test tubes and immediately centrifuged (10 minutes at 3500 rpm) and the plasma was stored at –20°C until assayed. Piroxicam was determined according to a standardized high performance liquid chromatographic method in Chiesi Pharmacokinetics Laboratory.[17,18]

Samples of plasma (1 ml) were acidified (0.2 ml 1N HCl), 4 µg of isoxicam (internal standard) were added and the samples were then extracted with toluene (2 x 5 ml).

The organic phases were evaporated to dryness and the residue was dissolved with 150 µl of tetrahydrofuran. A portion of the solution (20 µl) was analysed by HPLC equipped with a Li Chrosorb RP18 10 µm column (250 x 5 mm ID) and elution was performed in isocratic conditions at a flow rate of 2 ml/min with a mixture of acetonitrile, monobasic ammonium phosphate, and phosphoric acid 55 : 22.5 : 22.5 v/v/v, respectively. Ultraviolet (UV) detection was carried out at 340 nm. The mean coefficient of variation (CV%) of the method evaluated in the linearity range (0.5–10 µg/ml) was 4.6%

Pharmacokinetic Analysis

The maximum plasma concentration (C_{max}), and the time to achieve C_{max} (T_{max}), were directly obtained from the experimental data, without interpolation. The area under the plasma piroxicam time curve (AUC) from 0 to T, where T is the time at which the last detectable piroxicam plasma level is found, was calculated by the linear trapezoidal rule. AUC ($0 - \infty$) was calculated by the addition of AUC (0–T) to the product C(T)/K el. C(T) is the concentration at time T and K el is the apparent terminal plasma elimination rate constant derived from the ordinary least squares regression of the log-linear plot of piroxicam plasma levels against time. The elimination half-life (t 1/2 el) was determined as: ln2/K el.

The absorption rate was calculated from the percent absorbed-time plot using the Wagner-Nelson method.[19]

Statistical Analysis

The homogeneity of the two groups for age, weight and height was assessed by the Student's paired t-test. Multiple ANOVA was used to evaluate the PI, PAR and patient's self-evaluation of pain from differences within treatment, while the comparison between treatments was made according to the Wilcoxon's 2-samples test.

Pharmacokinetic parameters were statistically evaluated according to the non-paired t-test and the Mann-Whitney U-test. This non-parametric test was also used to verify differences between the percentages of drug absorbed, as the formulations have the same bioavailability (AUC 0-∞). Differences were considered significant when p was less than 0.05.

Results

Analgesic Activity

According to the physician's evaluation PI was significantly reduced in both groups ($p < 0.001$). The analgesic effect started 15–30 minutes after administration, reached its maximum after 8 hours and lasted 24 hours (Figure 1). Patient's evaluation was similar, and a statistically significant reduction of pain was evident four hours after drug administration (Figure 2), $p < 0.001$.

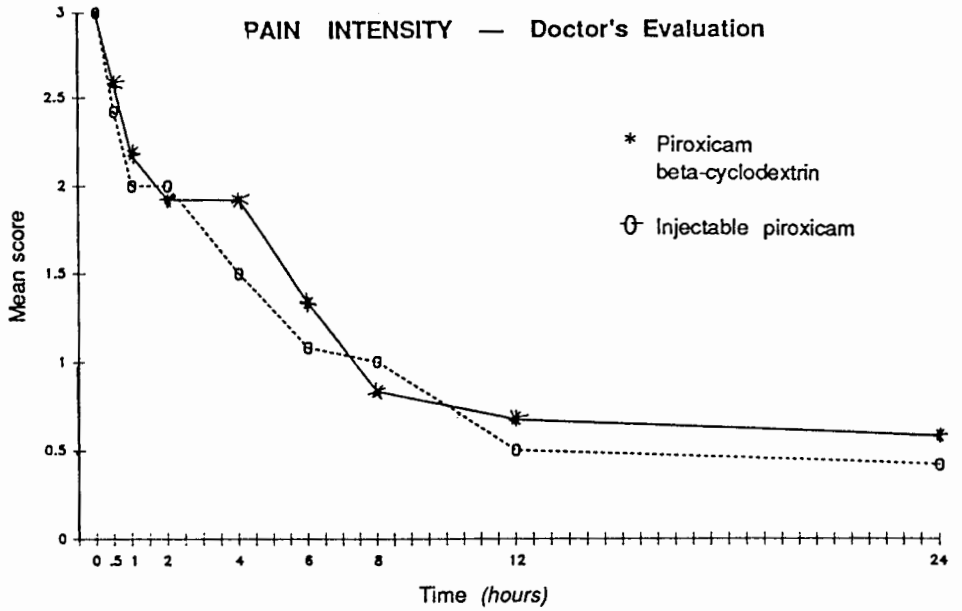


Figure 1. Pain intensity (PI) according to doctor's evaluation up to 24 hours after oral administration of 1 sachet of piroxicam beta-cyclodextrin, or i.m. injection of 1 ampoule of piroxicam.

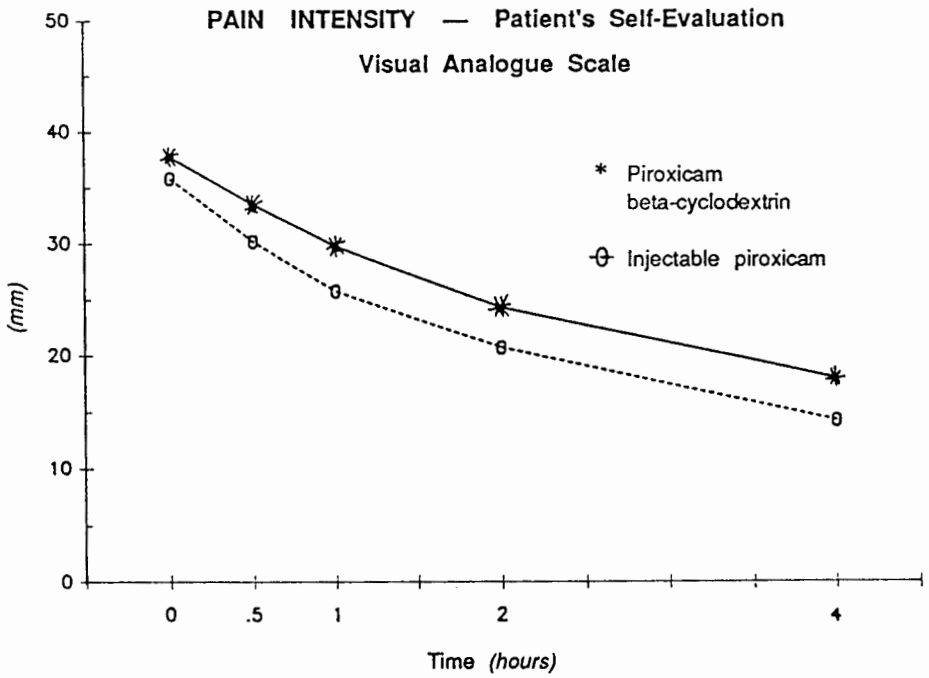


Figure 2. Pain intensity according to patient's self-evaluation by VAS, up to four hours after oral administration of 1 sachet of piroxicam beta-cyclodextrin or i.m. injection of 1 ampoule of piroxicam.

PID curves were also superimposable: they increased quickly and their peaks were reached between eight and 24 hours (Figure 3).

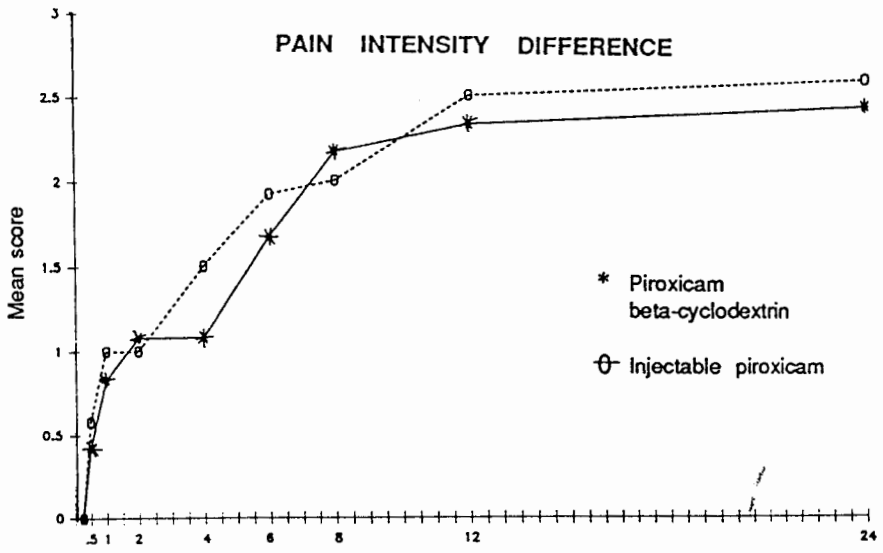


Figure 3. PID trend up to 24 hours after administration.

The evaluation of the improvement of PAR ($p < 0.01$) further confirmed the good analgesic efficacy of the treatment (Figure 4).

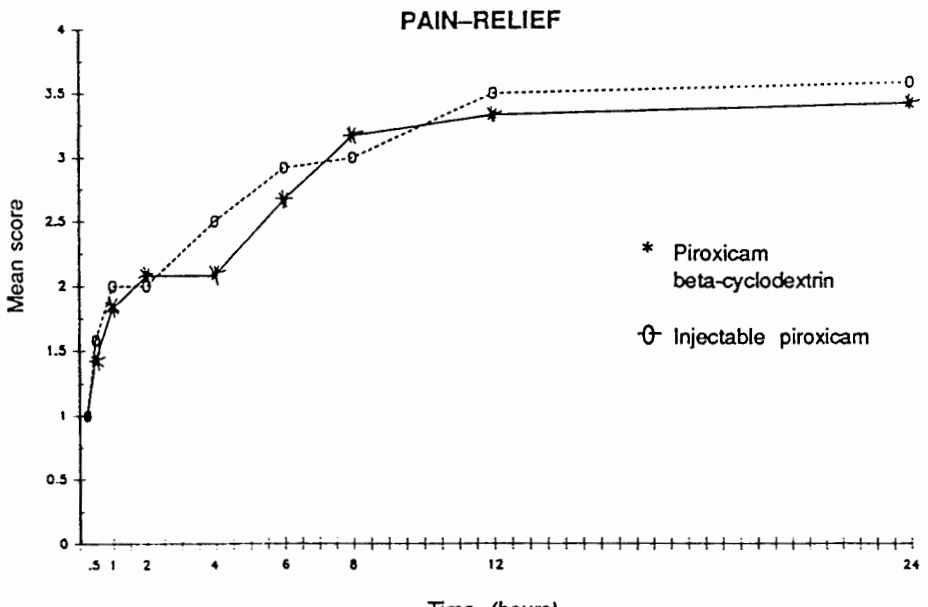


Figure 4. Analgesic effect (PAR) up to 24 hours after administration.

Statistical comparison "between treatments" showed no differences between oral and injectable formulation.

Pharmacokinetics

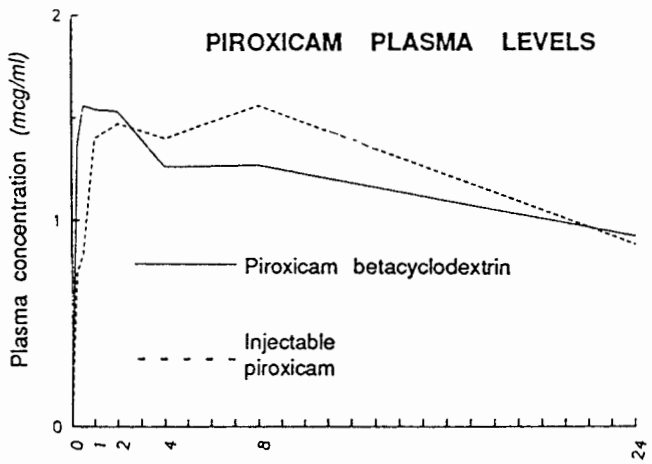
Piroxicam biovailability is identical for both oral and injectable formulations: AUC values (0-∞) were 102.80 ± 11.88 μg.h/ml and 106.17 ± 16.52 μg.h/ml, respectively (Table II). Plasma concentrations (Figure 5) indicated a more rapid absorption for the oral formulation with a significant T_{max} reduction ($p < 0.05$): absorption rate, evaluated according to Wagner-Nelson's method (Table III and Figure 6), showed significant differences after 15 and 30 minutes from administration. However the AUC (0-2 h) value was almost the same for both treatments, as well as the other piroxicam pharmacokinetic parameters (Table II).

TABLE II

Piroxicam pharmacokinetic parameters (mean ± SEM) determined in two different groups of patients (n = 12 each group) after oral and parenteral treatments

Parameter	Piroxicam beta-cyclodextrin *(1 x 20 mg sachet)*	Piroxicam *(1 x 20mg i.m. ampoule)*	P
C_{max} *(μg/ml)*	2.10 ± 0.23	1.88 ± 0.17	NS
T_{max} *(h)*	1.06 ± 0.32	3.65 ± 0.84	* < 0.05
AUC (0–∞) *(μg.h/ml)*	102.80 ± 11.88	106.17 ± 16.52	NS
AUC (0–2 h) *(μg.h/ml)*	2.85 ± 0.19	2.28 ± 0.24	NS
K el *(L/h)*	0.014 ± 0.001	0.017 ± 0.002	NS
t 1/2 el *(h)*	54.80 ± 5.60	53.00 ± 10.30	NS

* *Mann-Whitney U-test*



Mean values *(n = 12)*

Figure 5. Piroxicam plasma levels after oral administration of 1 sachet of piroxicam beta-cyclodextrin or i.m. injection of 1 ampoule of piroxicam, respectively.

TABLE III

Wagner-Nelson cumulative absorption; % of dose (mean ± SEM)

Time *(h)*	Piroxicam beta-cyclodextrin *(1 x 20 mg sachet)*	Piroxicam *(1 x 20mg i.m. ampoule)*	P
0.25	72.8 ± 9.9	42.1 ± 9.8	< 0.05
0.50	82.4 ± 9.7	51.7 ± 9.1	< 0.05
1.00	94.5 ± 2.7	84.7 ± 5.3	NS
2.00	97.4 ± 1.1	85.9 ± 6.8	NS
4.00	92.6 ± 3.4	90.4 ± 5.2	NS
8.00	97.1 ± 1.6	95.7 ± 3.6	NS

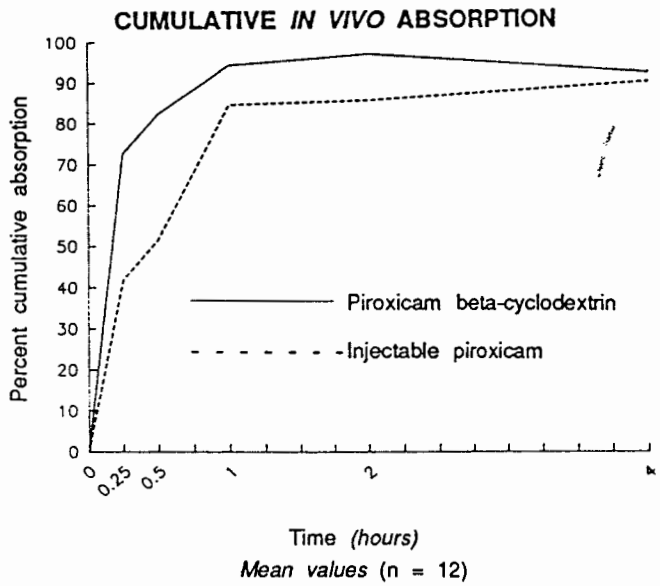


Figure 6. Percentage cumulative absorption of piroxicam up to four hours from oral administration of 1 sachet of piroxicam beta-cyclodextrin or i.m. injection of 1 ampoule of piroxicam, respectively.

Adverse Reactions

Slight pyrosis and gastralgia occurred in one patient treated with piroxicam beta-cyclodextrin four hours after administration; both symptoms disappeared spontaneously after eight hours. Two patients in the injectable piroxicam group complained of the same side-effects: the symptoms appeared after 24 hours and disappeared six to eight hours later.

One patient in the injectable formulation group suffered from a skin reaction on his hands and shoulders: the symptom appeared 12 hours after injection and disappeared spontaneously within six hours.

Discussion

Oral absorption of a solid formulation of piroxicam is enhanced by the

inclusion with the macromolecule beta-cyclodextrin to form piroxicam beta-cyclodextrin inclusion compound.[20] The water-soluble granular formulation allows a further improvement in the absorption rate, and makes it similar to that of an injectable formulation. This result is no doubt very interesting for an oral formulation, since the analgesic effect obtained with the oral administration was superimposable on the injectable formulation (Figure 7) with respect to intensity, rapidity of onset and duration. The systemic and gastric tolerability of the new oral formulation was good: only one patient (8.3%) complained of adverse reactions compared to three (25%) patients treated with injectable piroxicam.

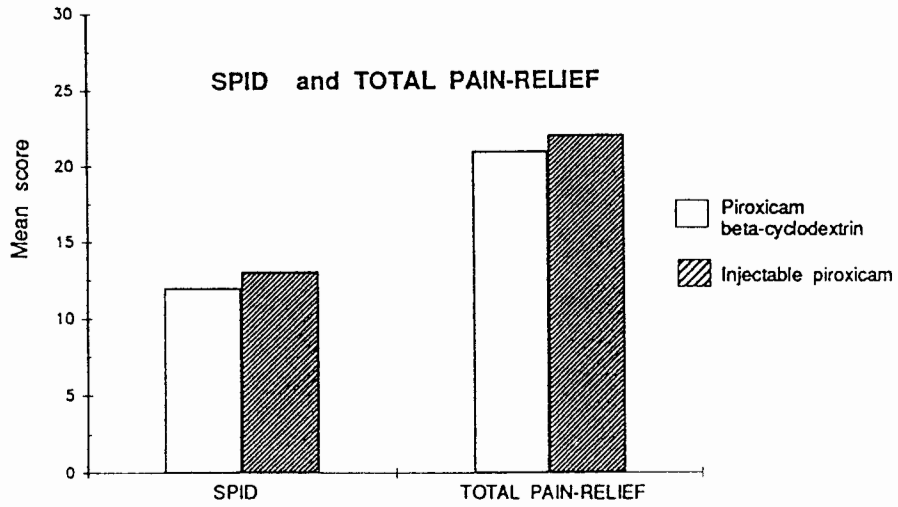


Figure 7. Cumulative analgesic effect (SPID and TOTPAR) after oral administration of 1 sachet of piroxicam beta-cyclodextrin or i.m. injection of 1 ampoule of piroxicam, respectively.

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RESUME

On a comparé l'effet analgésique et les taux plasmatiques de la nouvelle formulation orale de piroxicam associé à une bêta-cyclodextrine, qui se présente en sachets de granules, avec la forme injectable du composé.

Les deux préparations contiennent 20 mg de piroxicam. On les a administrées en dose unique à 24 patients souffrant de douleurs post-opératoires au cours d'une étude randomisée parallèle menée en double insu. On a déterminé l'effet analgésique et les taux plasmatiques du composé au cours du premier jour et après 24, 48, 72 et 96 heures.

Sur le plan de la cinétique plasmatique, on n'a pas observé de différence notable entre les deux formulations, à l'exception de l'excrétion tubulaire maximale qui est significativement moindre après une administration orale. Les effets analgésiques sont identiques en ce qui concerne la vitesse et la durée d'action.

ZUSAMMENFASSUNG

Die schmerzlindernde Wirkung und die Plasmaspiegel einer neuen oralen Formulierung, Beutel mit Körnchen von Piroxicam, angelagert mit Beta-Zyklodextrin, wurden mit einer injizierbaren Piroxicam-Formulierung verglichen.

Beide Präparate enthielten jeweils 20 mg Piroxicam und wurden als eine einzelne Dosis an 24 Patienten mit postoperativem Schmerz entsprechend einem willkürlich verteilten doppelt-blinden/ doppelt-Plazebo-Muster für Parallelgruppen gegeben. Die Beurteilung der Wirkung auf den Schmerz und die Bestimmung der Piroxicam Plasma Spiegel wurden an Tag 1 und nach 24, 48, 72 und 96 Stunden durchgeführt.

In ihrer Plasmakinetik unterschieden sich die beiden Formulierungen nicht erheblich, außer für T_{max}, das nach oraler Verabreichung signifikant reduziert wurde. Die Wirkungen auf den Schmerz waren sowohl für die Geschwindigkeit des Wirkungseintritts als auch für die Dauer der symptomfreien Periode überlagerbar.