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Bioavailability of a new ketoprofen formulation for once-daily oral administration

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Abstract

A new sustained-release formulation (sustained release Ibifen®) that gradually releases ketoprofen within 24 h and ensures therapeutic plasma concentration for the entire period has been developed. It consists of tableted pH-dependent barrier film-coated ketoprofen granules and was administered at a single dose of 200 mg to 12 volunteers. Ketoprofen plasma profiles were compared with: (1) administration of Orudis retard® 200 capsule (200 mg); (2) two 12-h doses of prompt release Ibifen® capsules (100 mg). In vitro dissolution kinetics and ketoprofen plasma levels were measured by HPLC. Sustained release Ibifen® dissolution rate was constant for 10 h, whereas Orudis retard® 200 dissolution profile presented one higher slope (0–6 h) and a lower one (6–12 h). Both formulations showed a delayed kinetics with respect to prompt release Ibifen®. After sustained release Ibifen® administration, ketoprofen plasma peak, reached within 2 h, remained practically constant for at least 12 h (average 4 μg/ml), which is higher than therapeutic levels. Differently, Orudis retard® 200 produced a delayed, higher C_{max} (5.91 ± 0.66 vs. 4.51 ± 0.65 μg/ml; $P < 0.01$) and disappeared more quickly. In conclusion, sustained release Ibifen® can ensure therapeutic ketoprofen plasma levels for the entire 24 h period, avoiding plasma concentration spikes, with bioavailability similar to other ketoprofen preparations.

Keywords: Anti-inflammatory drug; Ketoprofen; Bioavailability; Sustained release formulations; Pharmacokinetics

1. Introduction

Ketoprofen is a nonsteroidal anti-inflammatory drug with well established analgesic and antipyretic properties (Cathcart et al., 1973; Fossgreen et al., 1976; Julou et al., 1976). In anti-inflammatory models, ketoprofen exerts inhibitory effects on prostaglandin and leukotriene synthesis (Vargaftig and Dao, 1971), as well as antibradykinin effects and lysosomal membrane-stabilizing activity (Stiegler et al., 1995). It is widely used for the treatment of rheumatic disorders, but requires frequent administrations to maintain therapeutic plasma concentrations (Liversidge, 1981). An analgesic effect–concentration relationship has been established: the effect-site rate constant was estimated to be 0.9 h, and the concentration that produced one-half the maxi-

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mum pain intensity difference (PID) was 0.3 μg/ml (Clinical Pharmacology, 2002).

In conventional prompt-release formulations, ketoprofen is rapidly and efficiently absorbed, with peak plasma levels occurring within 0.5–2 h, after which the therapeutic plasma concentration abruptly falls to very low levels. At a single dose of 150 mg, ketoprofen plasma concentration reaches values upto 15–25 μg/ml, which are much higher than the therapeutic active concentration (Upton et al., 1981). The relatively high gastrointestinal concentration and plasma peaks associated with conventional formulations result in increased incidence of side effects and in the need for multiple daily administrations (Graham et al., 1984). When administered with food in the conventional form, the total bioavailability of ketoprofen remains unaltered, while the absorption rate is slowed by 1–2 h (Bannwarth et al., 1988), which, however, is not enough to ensure appropriate therapeutic plasma levels for the entire day.

Several recently developed formulations resist dissolution in the low pH of gastric fluid, and then gradually release the drug at a controlled rate in the higher pH environment of the small intestine. Various approaches have been adopted, including the use of pH-dependent barrier films or capsules dispensed with microgranules, matrix pellets of nanocrystalline ketoprofen, and tablets. The pharmacokinetics and therapeutic efficacy of these controlled-release ketoprofen formulations have been documented both by single-dose and by chronic studies (Houghton et al., 1984a,b; Caruso et al., 1982; Vergote et al., 2001; Le Liboux et al., 1994; Marcolongo et al., 1984; Morley et al., 1984).

Oral sustained-release formulations need to guarantee therapeutic plasma ketoprofen levels for at least 24 h, thereby, improving the patients' compliance by allowing once-daily oral administration. Inter-individual plasma peak fluctuations should be low and bioavailability must be similar to that of the conventional active principle administered at the same dose. Herein, we describe the development and optimization of a new once-daily oral formulation characterized by gradual fractional release of the active ingredient over a 12 h period. The formulation was designed to produce therapeutic ketoprofen plasma levels about 60 min after administration and to maintain a steady-state plasma level for at least 12–14 h, prior to very gradual disappearance. This would ensure ketoprofen plasma levels associated with analgesic activity greater than 0.7 μg/ml (Houghton et al., 1984a) even after 24 h. The new formulation, named Ibifen® 'compresse a rilascio prolungato' (200 mg) consists of a tablet coated with cellulose acetophtalate and dibuthylphtalate that confers mild gastroresistance. Release is then controlled by granulation with hydroxypropylmethylcellulose (HPMC) and polyvinilpyrrolidone (PVP).

We compared the in vitro dissolution rate of the new sustained release formulation with that of a commercially available controlled release formulation (Orudis retard® 200), using the official dissolution test. A single dose of the new formulation was then orally administered to 12 healthy volunteers and ketoprofen plasma levels were compared with those obtained in the same subjects either after administration of one equimolar dose of Orudis retard® 200, or after two 12-h administrations of prompt release Ibifen® (100 mg). The study was an open acute format and the three formulations were randomly administered. In vitro dissolution kinetics and ketoprofen plasma levels were determined by high performance liquid chromatography (HPLC) with an ultraviolet detector. Pharmacokinetics parameters, including time to peak (t_{max}), maximum plasma concentration (C_{max}) and area under the curve (AUC) were calculated, and the results compared.

2. Materials and methods

2.1. Chemicals

Ketoprofen was supplied by SIMS (Scandicci, Florence, Italy); Fenoprofen calcium salt by Sigma Chemical Co. (St. Louis, MO, USA); (HPLC)-grade acetonitrile by Carlo Erba (Milan, Italy). Deionized water was purified by a Milli-Q System (Waters, Milford, MA, USA). all other chemicals and solvents used were of the highest purity commercially available.

2.2. Drugs

Three different ketoprofen formulations were studied: (1) the newly developed sustained release formulation Ibifen® 'compresse a rilascio prolungato' (200 mg, Istituto Biochimico Italiano, Milan, Italy); composition described below; (2) Orudis retard® 200 'capsule a rilascio prolungato' (200 mg, Rhone-Poulenc Rorer, Milan, Italy), used as a comparative sustained release drug (this formulation, developed to obtain sustained release of the active ingredient consists of coated granules dispensed in a gelatin hard capsule, the excipients being sucrose, yeast, silica colloidal, lac, ethyl cellulose and talc, as reported by the manufacturer, which describes it as a sustained release formulation; 3) prompt release Ibifen® 'capsule rigide' (100 mg, Istituto Biochimico Italiano, Milan, Italy) used as a prompt release reference formulation.

2.3. Sustained release Ibifen® preparation

The new formulation consists of tablets coated with cellulose acetophtalate and dibuthylphtalate. The coating confers mild gastroresistance, controlling release during the first 2 h; subsequently, the release is controlled by granulation with HPMC and PVP. Fifty parts of HPMC K4M and 60 parts of mannitol were added to 100 parts of ketoprofen. The mixture was loaded in the basket of a fluid-bed granulator (PAG from ICO, Modena, Italy) and sprayed with a solution of PVP in water (20%) at 60 °C. In the same equipment, the granulate was air-dried for 45 min at 60 °C until water content lower than 2%. The granulate was unloaded and mixed with magnesium stearate (1 part) and colloidal silica (0.5 part) in a mixer. This final mixture was tableted with a Manesty Unipress in tablets of 11 mm diameter, 463 mg each. Cellulose acetophtalate (2.5 kg) was added to acetone (22.5 l) and stirred until complete dissolution. After addition and complete dissolution of dibuthylphtalate (0.5 kg), ethyl alcohol (25 l) was added. Tablets were loaded in a coating pan (GS, Bologna, Italy) and the above-mentioned solution was sprayed. The lab-scale process has been optimized and comparable performance has been obtained on large-scale production. Since the formulation has now been approved by the Italian Ministry of Health and is commercially available, the overall production and the related analytical controls follow the GMP and GLP procedures indicated by the European Commission. Content in active substance was analyzed by HPLC and calculated in 200 mg tablets. In particular, 10 tablets were triturated and weighted exactly; about 225 mg of obtained powder were put in a 100 ml flask, diluted with the eluent and shaken for 10 min. Two milliliters of the filtered solution were properly diluted with the HPLC mobile phase and submitted to HPLC analysis as reported below.

2.4. Dissolution test

In vitro dissolution kinetics studies were performed following standardized and validated (European Pharmacopoeia, 1997) procedures, using a SOTAX AT 6 equipped with six baskets. Prompt release Ibifen®, sustained release Ibifen®, and Orudis retard® 200 dissolution kinetics were studied at a pH 7.5 under the same experimental and instrumental conditions. One liter of 0.1 M phosphate buffer solution, pH 7.5, was put in each container at a constant temperature of 37 ± 0.5 °C. A tablet was introduced into the container and rotated at 150 rpm. At scheduled times, 5 ml of the solution were collected, filtered and diluted 1/10 v/v with phosphate buffer solution. Absorbance was measured at 260 nm. A ketoprofen standard solution in the same buffer was used for external calibration. Dissolution tests were performed on 24 tablets prepared in four separate periods over 1 year, and the reported results are the mean value $\pm$ S.D.

2.5. Studied subjects

Twelve male volunteers aged 19–35 years, all received a briefing on the purpose and nature of the study before providing written, informed consent. Before administering the first ketoprofen dose, medical examination and biochemical and hematological tests were performed to assess that subjects were healthy, while urine was screened

for drugs or abuse. During the study, all volunteers consumed a light standard diet containing about 1200 calories per day. No other medication was used for 2 weeks prior to dosing. The local Medical Ethics Committee approved the study protocol and the written informed consent form.

2.6. Study design

For each subject, the study comprised three 1 day periods, one for each formulation, separated by a 1 week washout period. In particular, one dose was administered at 08:00 h of either sustained release Ibifen® (200 mg) or Orudis retard® 200 (200 mg) (Ollagnier et al., 1987), while two oral administrations (at 08:00 and 20:00 h) were performed for prompt release Ibifen® capsules (100 mg). Blood samples were collected immediately before administration and at 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 h after administration of the controlled-release formulations, while at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 12.5, 13, 13.5, 14, 15, 16, 18, 20 and 24 h after administration of the prompt release formulation. Plasma was separated by centrifugation and stored at −40 °C until analysis.

2.7. Plasma ketoprofen analysis

Plasma standards (1 ml) were prepared by adding the appropriate ketoprofen solution to drug-free plasma, to give a concentration range of 0.075–20 μg/ml. Calibration and clinical plasma samples were processed and submitted to HPLC analysis in an identical manner. A modified version of the extraction procedure of Satterwhite and Boudinot (Satterwhite and Boudinot, 1988) was used. In brief, internal standard solution (60 μl of 55 μg/ml fenoprofen calcium salt in methanol) was added to 1 ml of plasma, which was then acidified with 0.2 ml of 1 M phosphate buffer, pH 2.0. The sample was then extracted with diethyl ether (5 ml) and vortex-mixed for 5 min. The upper organic phase was separated and evaporated to dryness at 40 °C under a stream of nitrogen gas. The dry residue was dissolved in 0.3 ml of mobile phase for HPLC analysis.

The HPLC analysis system consisted of two high-pressure pumps (Model 125-S, Beckman, Fullerton, CA, USA), a sample injection valve (Rheodyne Model 7121, Cotati, CA, USA) with 20 μl sample loop, and a variable-wavelength ultraviolet absorbance detector (Model 168, Beckman Fullerton). Ketoprofen and fenoprofen (internal standard) were separated using a reverse phase C-18 column (Ultrasphere, 120 Å, 5 μm, 4.6 × 250 mm, Beckman, Fullerton) at room temperature. The mobile phase consisted of acetonitrile, 0.01 M KH_2PO_4 adjusted to an apparent pH 3.5 with H_3PO_4 (40:60, v/v). Ketoprofen and internal standard were eluted isocratically at a flow-rate of 1 ml/min and monitored at 254 nm. The method produces linear calibration graphs over the range 0.05–50 μg/ml of ketoprofen in plasma. The precision of the assay procedure, evaluated on plasma samples at concentrations of ketoprofen of 0.1, 1 and 10 μg/ml, yielded variation coefficients of 4.5, 3.0 and 2.8%, respectively. Calibration curves were made by fitting ketoprofen to internal standard peak-area ratios with ketoprofen concentration. Unknown samples were quantified by reference to the linear regression equation derived from the standard curve.

2.8. Statistical methods

C_{max} and t_{max} were measured and AUC was calculated by the trapezoid rule from 0 to 24 h for all participants. Each of these measurements was determined in a crossover design using variance analysis. The bioavailability of each formulation was determined and compared by calculating the mean AUCs (Caruso et al., 1982).

3. Results

3.1. Dissolution profile optimization

The proportions of the excipients responsible for sustained release were evaluated with respect to their effect on the resultant dissolution kinetics. Experiments were performed using phosphate buffer (0.1 M, pH 7.5) and following validated procedures and instrumentation. The ratio be-

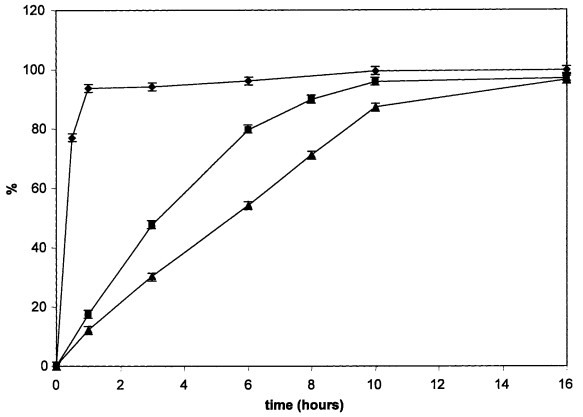

Fig. 1. Dissolution kinetics, obtained following the European Pharmacopoeia (1997) of the newly developed sustained release Ibifen® tablets (▲), Orudis retard® 200 capsules (■), and prompt release Ibifen® capsules (◆). Each point represents mean values ± S.D. of six experiments.

tween mannitol, HPMC and PVP was optimized in order to achieve a complete ketoprofen release (greater than 95%) within 10 h. The optimized excipients proportions in 200 mg ketoprofen tablets were 100, 40 and 120 parts for HPMC, PVP and mannitol, respectively. We observed that reducing the proportion of PVP content from 40 to 20 parts and while raising that of HPMC upto 150 led to a reduction in the drug dissolution kinetics, with only 50–60% of the drug being dissolved after 10 h (data not shown). The identified formulation was, therefore, optimized and used for acute human comparative studies with Orudis retard® (200 mg). This formulation is commercially available, its drug master file has been approved and the overall process for its preparation followed the European guidelines of GMP and GLP.

3.2. Dissolution profile comparison

Fig. 1 shows the dissolution kinetics obtained with the new sustained release Ibifen® formulation, as compared with prompt release Ibifen® and with Orudis retard® 200 capsules. Prompt release Ibifen® formulation dissolved rapidly and efficiently (more than 90% during the first hour) in pH 7.5 buffered solution. By comparison, sustained release Ibifen® exhibited much slower kinetics, characterized by a constant dissolution rate during the entire period, as shown by the slope of the curve; almost 95% of the active ingredient was dissolved after 10 h. Orudis retard® 200 also showed a slower dissolution rate than the plain formulation, but with a different profile than sustained release Ibifen®: the dissolution profile exhibited faster kinetics in the first 6 h period, after which the slope was reduced; after 10 h more than 90% of the drug was dissolved.

3.3. Plasma ketoprofen pharmacokinetics

Table 1 reports mean values of pharmacokinetic parameters obtained when the three studied formulations were administered to 12 volunteers, as reported above. Fig. 2 shows mean ketoprofen plasma concentration with respect to time. After administration of prompt release Ibifen® (100 mg), peak plasma levels were reached at relatively high levels (C_{max}, 8–12 μg/ml) within 1.5–2 h, followed by a rapid exponential decrease plasma

Table 1
Pharmacokinetic parameters (mean ± S.D.) observed in 12 volunteers after single oral doses of sustained release Ibifen® and Orudis retard® 200 (both 200 mg), and two 12-h doses of prompt release Ibifen® (100 mg)

Pharmacokinetics parameters	Sustained release Ibifen® (200 mg)	Orudis retard® 200 (200 mg)	Prompt release Ibifen® (100 mg)
C_{max} (μg/ml)	4.51 (± 0.65)	5.91 (± 0.66)	10.52 (± 1.43) 12.80 (± 4.22)[a]
t_{max} (h)	2.28 (± 0.32)	4.17 (± 0.42)	1.38 (± 0.48) 1.46 (± 0.52)[a]
AUC (μg h/ml)	62.64 (± 12.67)	60.25 (± 9.82)	66.33 (± 11.78)[a]

[a] Values refer to the 0–24 h period with two administrations of prompt release Ibifen® (100 mg each).

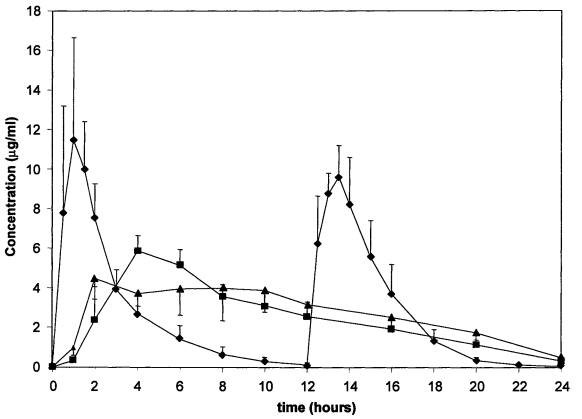

Fig. 2. Mean plasma ketoprofen concentrations in 12 healthy subjects after: (▲) single oral administration of the new sustained release Ibifen® formulation (200 mg); (■) single oral administration of Orudis retard® 200 (200 mg); (◆) two 12-h oral administrations of prompt release Ibifen® (100 mg).

$t_{1/2}$; repeated administration after 12 h produced similar results. By comparison, single administration of sustained release Ibifen® (200 mg) produced a significantly lower ($P < 0.01$) and delayed ketoprofen plasma concentration peak: a steady-state plasma ketoprofen level was reached after 2 h, remained practically constant at a mean value of about 4 μg/ml for at least 10–12 h, and then slowly decreased during the 24 h period. The S.D.s associated with ketoprofen plasma mean concentrations at all the studied times are very low with coefficient of variation less than 20%.

After administration of an equivalent dose of Orudis retard® 200, ketoprofen plasma profiles differed from those obtained with sustained release Ibifen® administration, as shown in Fig. 2. The maximum plasma peak was significantly higher (C_{max}, 5.91 vs. 4.51 μg/ml; $P < 0.01$) and was reached later (t_{max}, 4.17 vs. 2.28 h; $P < 0.01$). Over the last 6 h of the 24 h period, the mean ketoprofen plasma level obtained after administration of sustained release Ibifen® was significantly higher than that obtained after Orudis retard® 200 administration ($P < 0.05$). These data indicate that sustained release Ibifen® produces longer lasting steady-state plasma levels and more effectively maintains adequate therapeutic plasma concentrations. Sustained release Ibifen® and Orudis retard® 200 bioavailabilities were similar and only slightly lower ($P = \text{NS}$) as compared with the sum of the AUC obtained after two successive administrations of prompt release Ibifen® (Table 1).

4. Discussion

The aim of the present investigation was the development of a new sustained-release formulation for once-daily oral ketoprofen administration, characterized by constant fractional intestinal drug release to ensure therapeutic activity for 24 h. Particular attention was given to the achievement of adequate plasma levels in the last 8–10 h of the 24 h period. In order to improve patients' compliance during chronic administration, tablets were selected as the pharmaceutical form, since they are easier to swallow. The formulation has been optimized taking into account inter-individual variability caused by differences in intestinal motility and transit time. Gradual drug release and dissolution were obtained by calibrating the technical and physical properties of the developed tablets.

In particular, the optimized proportions of HPMC, PVP and mannitol were able to ensure a gradual drug release. HMPC swelling capacity is crucial in determining the ketoprofen release from the tablet. Our results showed that sustained release Ibifen® in vitro dissolution kinetics exhibited a constant dissolution rate for almost 10 h, as a result of optimized formulation in terms of PVP, HPMC and mannitol proportion and of tablet disgregation properties. By contrast, the dissolution kinetics of Orudis retard® 200 were characterized by two slopes, being much faster during the first 4 h. A reduced surface area with respect to the granules contained in Orudis retard® 200 accounts for the more gradual release achieved with the new sustained release Ibifen® formulation.

In vitro dissolution data were in agreement with in vivo plasma ketoprofen kinetics profiles obtained for both formulations. Sustained release Ibifen® (200 mg) oral administration produced a plasma steady-state ketoprofen level, which was

achieved within 2 h after administration and maintained for about 12–14 h. This agrees with the constant drug release observed in the in vitro dissolution tests with the sustained release Ibifen® formulation. By contrast, the plasma ketoprofen kinetics of Orudis retard® 200 were characterized by delayed higher C_{max}, with a subsequent decrease in ketoprofen plasma levels after 8 h (Fig. 2). As compared with Orudis retard® 200, sustained release Ibifen® administration produced a lower C_{max} (4.51 vs. 5.91 μg/ml), which, however, was reached earlier (2.28 vs. 4.17 h) and maintained for a longer time. Indeed, whereas sustained release Ibifen® allowed a steady-state level to be maintained for at least 10–12 h, the plasma levels obtained after administration of Orudis retard® 200 progressively fell to give lower ketoprofen levels after 16 h.

It has been reported that the analgesic effect of the ketoprofen is achieved with plasma concentrations above 0.7–1 μg/ml (Houghton et al., 1984a). Our results show that the newly developed sustained release Ibifen® formulation is able to produce therapeutic mean plasma ketoprofen levels 2 h earlier than Orudis retard® 200. This difference can be explained by taking into account the faster elimination rate observed after administration of Orudis retard® 200 with respect to that of sustained release Ibifen®. During a 24 h period after administration, mean ketoprofen plasma levels never fell to 2 μg/ml with the sustained release Ibifen® formulation, whereas with Orudis retard® 200 they sometimes fell below the therapeutic threshold during the final 6–8 h. This implies that adequate ketoprofen therapeutic plasma levels were maintained throughout the 24 h period only after sustained release Ibifen® oral administration. Indeed, the minimum plasma ketoprofen levels recorded by us after sustained release Ibifen® administration were always higher than the C_{max} (1–2 μg/ml) reported after a single oral administration of prompt release ketoprofen (25 mg) (Stiegler et al., 1995).

These data indicate that the new sustained release Ibifen® formulation is able to ensure constant release of the active component for a longer period than the previously described controlled release formulation Orudis retard® 200, thus, guaranteeing the efficacy of once-daily 200 mg ketoprofen administration. The drug development approach was to optimize a formulation with constant fractional dissolution kinetics. Results obtained in vitro were fully predictive of the in vivo behavior, as confirmed by ketoprofen plasma profiles. Sustained release Ibifen® formulation displayed similar biovailability to plain ketoprofen, while producing a much lower peak plasma concentration and a marked sustained release effect. The mean AUC values obtained with sustained release Ibifen® were similar to those obtained with Orudis retard® 200 and with other previously described formulations (Houghton et al., 1984a,b; Caruso et al., 1982; Le Liboux et al., 1994; Morley et al., 1984).

The new formulation pharmacokinetics should prompt chronic clinical studies that could lead to once-daily dosing, thereby, improving patients' compliance to the treatment.

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