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Servicio de Investigación de Farmacología Clínica, Hospital General de México, Mexico City, Mexico

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ABSTRACT: We conducted a randomized, crossover study in 23 healthy young female volunteers to compare the bioavailability of two brands of meloxicam (7.5 mg) tablets and to obtain pharmacokinetic parameters of this molecule in Mexican population not reported previously. Two tablets (15 mg) were administered as a single dose on 2 treatment days separated by a 1-week washout period. After dosing, serial blood samples were collected for a period of 72 h. Plasma harvested was analyzed for meloxicam by a modified and validated high-performance liquid chromatography (HPLC) method previously reported. Pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, k_e, MRT and $t_{1/2}$ were determined from plasma concentrations of both formulations, resulting in a C_{max} 120% larger than and a T_{max} 65% faster than those reported in other populations. AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were statistically tested for bioequivalence after log transformation data in a non-balanced design, and no significant differences were found either in 90% classical confidence interval (90% CI) or in Schuirmann test ($p < 0.05$); thus, we concluded that bioequivalence existed between both formulations. Copyright © 2005 John Wiley & Sons, Ltd.

Key words: meloxicam; bioequivalence; pharmacokinetics; high-performance liquid chromatography (HPLC)

Introduction

Meloxicam (MXC) (CAS 71125-38-7) (4-hydroxy-2-methyl-*N*-[5-methyl-2-thiazolyl]-2H-1,2,-benzothiazine-3-carboxamide-1,1-dioxide) is a non-steroidal, anti-inflammatory drug (NSAID) that blunts prostaglandin synthesis selectively via type-2 cyclooxygenase (COX-2) inhibition, resulting in inflammation relief [1]. Thus, although the Food and Drug Administration (FDA) recognizes the use of MXC in osteoarthritis and rheumatoid arthritis, its use in extra-articular diseases has been extended [2].

Oral or rectal doses of MXC are well-absorbed with absolute bioavailability of 90% [3]. There were no differences in bioavailability when MXC was administered under fasting conditions or following food intake; maximum plasma concentrations (C_{max}) fluctuated from 1.5 to 1.7 μg/ml and reached 9–11 h (T_{max}) after 30 mg was given orally [4]. MXC is bound to serum albumin at a high level (>99%) and readily penetrates into perivascular spaces, showing an apparent volume of distribution between 0.1 and 0.2 L/kg [5]. MXC is extensively metabolized in liver to four physiologically inactive metabolites that are excreted in both urine and faeces. CYP2C9 plays a major role in oxidative metabolism of MXC,

*Correspondence to: Servicio de Investigación de Farmacología Clínica, Unidad Analítica (407), Hospital General de México, Dr Bálmis #148, Col. Doctores, c.p. 06720 México, D.F., México. E-mail: gabmarcelin@hotmail.com

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and to a lesser extent in CYP3A4. Clearance of MXC ranges from 0.4 to 0.7 L/h, while its terminal elimination half-life ($t_{1/2}$) in plasma varies from 13 to 20 h [6,7].

Recently, there has been renewed interest in the clinical use of MXC due to its high efficacy and wide therapeutic applications in addition to its safer toxicological profile with respect to other oxicams and even over recent COX-2 specific inhibitors. The aim of the present work was to determine bioequivalence between two products containing MXC, Promotion® and Mobicox® in young healthy female Mexican volunteers and to ascertain clinically useful pharmacokinetic parameters in our population.

Materials and methods

Study formulation

The test product was Promotion® 7.5 mg tablets (Farmaceúticos Rayere, S.A., Mexico City, Mexico). The reference product was Mobicox® 7.5 mg tablets (Boehringer Ingelheim Promeco, Mexico City, Mexico).

Clinical design

Volunteers

Twenty-four healthy female volunteers participated in the study under the following inclusion criteria: age between 18 and 45 years, nonsmokers or having quit smoking 72 h previous to beginning of study, with body mass index (BMI) between 20 and 29, normal clinical history, normal values in laboratory tests (hematology, blood biochemistry, hepatic function, and urine analysis), and negative results for AIDS, hepatitis types B and C, and pregnancy test. Exclusion criteria included any sickness state 4 weeks prior to study, history of drug addiction, or use of any drug 2 weeks before study initiation. Other exclusion criteria were considered throughout the study such as hypersensitivity toward MXC, loss of two or more samples around C_{max}, or dietetic transgression. Signed informed consent formats were obtained from each volunteer and the study protocol was reviewed and approved by the Ethics Board of the Hospital General de México.

Drug administration and sample collection

The study was carried out with a single 15-mg (two-tablet) dose of MXC; trial design was two treatments, two periods, two sequences, double-blind, crossover, and randomized. Treatment groups were balanced, and volunteers were randomly distributed into product administration sequences. Reference and test products were blinded by an identification code for both clinical and analytical phases of the study. Decode was carried out prior to statistic analysis.

Volunteers entered the study 12 h previous to phase 1 initiation, having dinner at 8:00 p.m. and an overnight fasting period (12 h). The following morning, an indwelling cannula was fixed and a single dose (15 mg MXC) of either tablet (reference or test) was taken with 250 ml water and breakfast. Lunch and dinner were served 6 and 12 h after dose administration. Volunteers left the Research Center after dinner and returned on the mornings of the following 3 days. They reentered phase 2 after 6 days (day prior to second administration) on the same schedule.

Blood samples, approximately 5 ml, were taken through the cannula at 0 h (prior to administration) and at 0.5, 2, 4, 6, 8, 9, 10, 11, 12, 24, 48, and 72 h after dosing. Plasma was separated into labeled criovials and kept frozen at −70°C until chromatographic analysis.

Sample preparation and high-performance liquid chromatography (HPLC) analysis

Sample purification and HPLC conditions used with our modifications were previously reported [8].

Validation assay

Analytic method was validated following criteria established in Mexican regulatory guidelines [9]. Standard calibration curves were constructed by spiking drug-free human-pool plasma with known amount of MXC at concentrations of 100, 500, 1000, 1500, 2000, 2500, and 3000 ng/ml. Quality control points at low, medium, and high levels (300, 1250, and 2250 ng/ml, respectively)

were used to determine absolute recovery and within- and between-day precision and accuracy. Stability, limit of quantification, and selectivity were also evaluated.

Pharmacokinetic analysis

Pharmacokinetic parameters were calculated considering plasma data, a single extravascular (e.v.) dose in a non-compartmental model, using WINNONLIN™ version 3.1 software [10]. Elimination half-life ($t_{1/2}$), area under curve to last measurable concentration (AUC_{0-t}), area under curve extrapolated to infinity ($AUC_{0-\infty}$), mean residence time (MRT), and constant of elimination (k_e) were software outputs. Maximum observed concentration (C_{max}) and time of C_{max} (T_{max}) were experimentally obtained by observation.

Statistical analysis

ANOVA for a standard 2×2 crossover design was used to evaluate fixed effects such as period, sequence, formulation, and carryover. For bioequivalence analysis, AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were considered as primary variables. Decimal logarithm values of these parameters were taken into consideration to construct classic confidence interval at 90% (90% CI) with significance level (α) of 0.05 . Moreover, interval hypothesis based on two one-sided procedures (Schuirmann test) was evaluated, with significance level (α) of 0.05; both data analyses were conducted according to FDA recommendations for establishing bioequivalence [11]. All statistical procedures were also performed using WINNONLIN™ version 3.1 software.

Results and discussion

The original 24 volunteers concluded the study; however, volunteer No. 17 was excluded from statistical analysis because she showed high level of MXC in pre-dose sample of phase 2. As a consequence of this, ANOVA was performed specifying square sum type III for unbalanced groups in WINNONLIN™ software. Volunteers formed a homogeneous population in terms of age (22.17 ± 2.82 years), weight (57.53 ± 6.75 kg), height (1.56 ± 0.06 m) and body mass index (BMI) (23.76 ± 2.18 kg/m^2).

The described analytical method used for measurement of MXC in plasma proved to be as accurate and sensitive as that previously reported [8]. Within-day recovery was 102.25% with a coefficient of variation (CV) of 4.63%, and between-day recovery was 105.7% with a CV of 3.67%. Throughout stability tests, MXC proved to be stable in biological samples for at least two freeze-and-thaw cycles. Moreover, MXC in plasma was stable at room temperature (approximately 20°C) for at least 6 h, and during long-term stability it was stable at −70°C for at least 50 days. In addition, reconstituted samples containing MXC after extraction technique were stable in autosampler for at least 12 h. Finally, during validation other drugs were tested to establish assay selectivity. Heparin, chlorphenamine, acetaminophen, acetylsalicylic acid, and butylhyoscyne showed no interferences with MXC measurement.

Concentration-time value profiles of the 23 volunteers for the two formulations are shown in Figure 1, indicating that plasma drug concentrations of both brands were quite similar and that final samples were sufficient for calculating >80% of $AUC_{0-\infty}$. All calculated pharmacokinetic parameters of both brands of MXC tablets are summarized in Table 1; as can be observed, 90% CI for all compared parameters (ratios of $AUC_{0-\infty}$, AUC_{0-t}, C_{max}) were contained in the

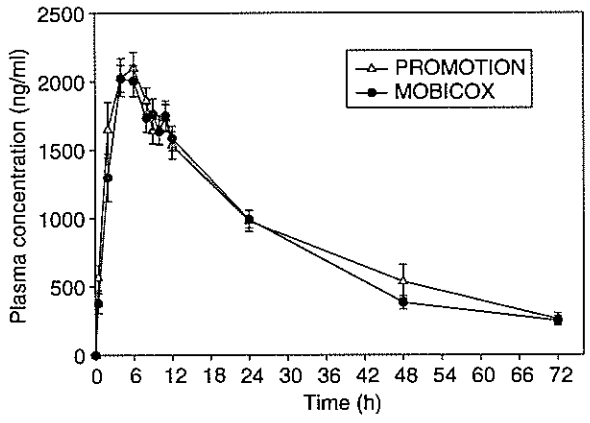

Figure 1. Plasma concentration profiles of meloxicam tablets after single oral administration of 15 mg of two brands in 23 young female healthy volunteers

Table 1. Pharmacokinetic parameters of both brands of meloxicam tablets

Pharmacokinetic parameter	Promotion® (test)	Mobicox® (reference)	90% CI[a] (80–125%)	Schuirmann test[a] ($p1$ and $p2 < 0.05$)
AUC_{0-t} (ng h/ml)	61230.18 ± 21526.7	55446.74 ± 17246.6	85.17–100.92	0.0035 0.00001
$AUC_{0-\infty}$ (ng h/ml)	68811.59 ± 26696.03	62730.05 ± 21315.40	86.18–99.68	0.0011 0.00001
C_{max} (ng/ml)	2559.75 ± 538.7	2290.66 ± 581.5	82.91–97.31	0.0107 0.00001
T_{max} (h)	4.365 ± 1.17	5.129 ± 1.12		
$t_{1/2}$ (h)	19.953 ± 1.05	19.050 ± 1.04		
MRT (h)	20.76 ± 1.22	19.72 ± 0.894		
k_e (ng/ml h)	0.0386 ± 0.0023	0.0421 ± 0.0025		

Values are given as mean ± standard error.
[a]Statistics were applied on decimal logarithm-transformed data; $n = 23$.

80–125% interval. Moreover, Schuirmann test for all analyzed parameters showed no significant differences, with statistic power >99% in every tested parameter.

As can be noted in the pharmacokinetic profile, T_{max} was observed 6 h after drug administration; this value agrees with that previous reported by Türck *et al.* [3] but differs from the 10 h reported by Busch *et al.* [4], who also reported no differences in bioavailability of MXC under fasting conditions or when administered with meals.

The most significant difference observed with previous reports was C_{max} values for both formulations, which ranged from 2000 to 2800 ng/ml with oral single dose of 15 mg MXC. Türck *et al.* and Busch *et al.* reported lower C_{max}, between 1500 and 1900 ng/ml, with oral single dose of 30 mg MXC, twice that used in the present work. However, none of the previous works described the type of population under investigation; nevertheless, it has been reported that there exist no differences in bioavailability of MXC due to either cirrhosis [12], renal impairment [13], or gender [14].

Although there is no CYP450 genotype profile of the population employed in the present work, metabolic rate of MXC was very similar, and $t_{\frac{1}{2}}$ agreed with all those previous reported [3,4,7,12–14].

Pharmacokinetic parameters of a specific population obtained in bioequivalence trials should be used to improve therapeutics. In the case of MXC, we must bear in mind that it is capable of inhibiting COX-2 induced during inflammation, but a single overdose or long-term administration could inhibit not only COX-2, but also COX-1, which is more ubiquitous and responsible for regulating many other physiologic processes, having as consequences all the side effects shared by common NSAIDs, such as gastrointestinal ulceration, blockade of platelet aggregation, inhibition of uterine motility, and inhibition of prostaglandin-mediated renal functions [15].

Conclusions

To improve safer therapeutics, the finding of a C_{max} 120% greater than previously reported would be considered an overdose in this type of population, and special care should be taken in

long-term treatments such as with articula diseases, for which MXC is indicated.

Statistical analysis of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ between both brands (7.5 mg meloxicam tablets indicated no significant differences in any compared pharmacokinetic parameters. Therefore, i can be established that Promotion® is bioequivalent to Mobicox® and that both formulation can be considered equally effective and safe i therapeutics in Mexican patients.

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