A New High-Absorption-Rate Paracetamol 500-mg Formulation: A Comparative Bioavailability Study in Healthy Volunteers

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ABSTRACT

Background: Paracetamol is often the analgesic or antipyretic of choice, especially for patients for whom salicylates or other nonsteroidal anti-inflammatory drugs are contraindicated.

Objective: The aim of this study was to compare the absorption rate of a new tablet formulation of paracetamol (500 mg) with a reference formulation of paracetamol at the same dose.

Methods: This was a single-center, Phase I, open-label, randomized, 2-period, crossover, single-dose, comparative bioavailability clinical trial. During both study periods, healthy volunteers were given a single oral dose of a more hydrophilic test formulation of paracetamol, or a reference formulation. Fifteen plasma samples were obtained to determine paracetamol concentrations and to calculate kinetic parameters.

Results: The study participants comprised 24 healthy volunteers (12 men, 12 women; mean [SD] age, 22.8 [1.5] years). The pharmacokinetic parameters calculated for the test versus the reference formulation were as follows: median time to maximum concentration ($T_{\max}$), 0.42 versus 0.75 hour; mean (SD) maximum plasma drug concentration ($C_{\max}$), 9.85 (2.40) $\mu\text{g/mL}$ versus 8.33 (2.22) $\mu\text{g/mL}$; and mean (SD) area under the plasma concentration–time curve from time 0 to infinity ($\text{AUC}_{0-\infty}$), 30.16 (8.87) $\mu\text{g} \cdot \text{h/mL}$ versus 28.49 (8.57) $\mu\text{g} \cdot \text{h/mL}$. The 90% CIs of the ratios were as follows: base e logarithm (Ln)-transformed $C_{\max}$, 105.08% to 137.59%; $\text{Ln-AUC}_{0-\infty}$, 102.02% to 110.43%; and the difference in $T_{\max}$, -0.375 to -0.085 hours.

Conclusions: The speed of release and absorption was statistically significantly higher with the test formulation compared with the reference one (evaluated using $T_{\max}$, $C_{\max}$, and $C_{\max}/\text{AUC}$ parameters). This speed is especially

important for a rapid analgesic or antipyretic effect. (*Curr Ther Res Clin Exp.* 2003;64:401–411) Copyright © 2003 Excerpta Medica, Inc.

Key words: pharmacokinetics, bioavailability, paracetamol, healthy volunteers, clinical trial.

INTRODUCTION

Paracetamol is a para-aminophenol derivative with analgesic and antipyretic properties. Due to its good tolerability profile, paracetamol is often the analgesic or antipyretic of choice, especially in patients in whom salicylates or other nonsteroidal anti-inflammatory drugs are contraindicated. It is widely used in several formulations and pharmaceutical presentations¹ that are intended to optimize the use of the medication by good absorption and reduction of secondary effects.

The new (test) formulation* is more hydrophilic and soluble than the reference formulation[†] used in this study, due to its mixture of paracetamol and other pharmaceutical components and the desiccation process of the mixture. Thus, the test formulation allows a more rapid dissolution of the active principal ingredient (paracetamol), which is intended to lead to a more rapid absorption.

The objective of the study was to assess the kinetic differences in the rate of absorption of a new formulation of paracetamol (using the parameter time to maximum concentration [$T_{\max}$] as the principal variable and maximum plasma drug concentration [$C_{\max}$]/area under the plasma concentration–time curve from time 0 to infinity [$AUC_{0-\infty}$] as the secondary variable) compared with the reference formulation.

SUBJECTS AND METHODS

Subjects

The subjects were selected from a group of volunteers from the Clinical Pharmacology Study Unit, Clinical Pharmacology Service, Hospital Clínico San Carlos (Madrid, Spain) and were examined (medical history, vital signs, electrocardiography [ECG], blood analysis [basic profile, cell count, prothrombin time, viral serology], and urinalysis [sediment, drugs, pregnancy test]) to verify their health status and that they met the inclusion criteria, as follows. Men and women aged 18 to 40 years with a body weight of 50 to 100 kg and a body mass index of 18 to 27 kg/m² were eligible for the study if they had no abnormalities on physical examination, ECG, and drug and laboratory analyses (drugs of abuse, hematology count and profile, plasma creatinine, glucose, uric acid, albumin, total calcium, total cholesterol, bilirubin, alkaline phosphatase, and lactate

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†Trademark: Termalgin® (Novartis Pharmaceutical Laboratories S.A., Barcelona, Spain).

dehydrogenase levels; alanine aminotransferase, aspartate aminotransferase, and prothrombin activities; urine sediment; and results of hepatitis and HIV serologic tests). Furthermore, fertile women had to have a negative pregnancy test the day before entering the study and had to use a reliable method of contraception (except oral anovulatory drugs) until the end of the trial.

Exclusion criteria were smoking (≥ 6 weeks); pregnancy or breastfeeding; a history of alcoholism or drug addiction; consumption of large amounts (> 5 cups/d) of stimulating (xanthines) beverages or drugs that could affect the drug under study during the 2 weeks before the study; regular consumption of any enzyme inhibitors or inducers during the previous month; participation in a clinical trial during the past 2 months or ≥ 4 clinical trials during the past year; history of a clinically important illness or major surgery during the past 3 months; inability to relate to and/or cooperate with the investigators; medication allergy; illnesses or disorders that could affect the absorption, distribution, metabolism, and/or excretion of drugs (eg, malabsorption, edema, and renal or hepatic insufficiency as measured by information from the anamnesis); previous positive serology for hepatitis B or C (not due to immunization) or human immunodeficiency virus infection; blood loss or donation > 200 mL in the 3 months before the trial; blood or blood-derivative transfusion in the past 6 months; and exhausting physical exercise during the previous 72 hours.

All participants provided written informed consent before inclusion in the study.

Methods

This single-center (Clinical Pharmacology Study Unit, Clinical Pharmacology Service, Hospital Clínico San Carlos, Madrid, Spain), Phase I, open-label, randomized, 2-period, crossover, single-dose, comparative bioavailability clinical trial was assessed by the ethics committee at Hospital Clínico San Carlos and was authorized by the Ministry of Health of Spain. It was developed according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines and was audited by an independent quality-control company.

Using kinetic data from a previous pilot study (unpublished data, Belmac Laboratories S.A., 2002) on formulations similar to those in this study, a mean [SD] $T_{\max}$ of 0.44 (0.19) versus 0.88 (0.55) was obtained for the test versus the reference formulation. A sample of 24 subjects would allow a power $> 80\%$ ($\alpha = 0.05$, 2-sided) to show differences in $T_{\max}$ using a nonparametric test, assuming that there were $> 20\%$ of ties (ie, equal values) in the value pairs. This sample size would allow a probability $> 90\%$ of finding differences of 20% in $C_{\max}/AUC_{0-\infty}$ (Student t test, repeated measurements; $\alpha = 0.05$, 2-sided; $\beta = 0.2$). In addition, this sample size would allow us to compare whether the AUC differs by $> 20\%$ between the test and reference formulations.

Subjects were admitted to the unit on 2 occasions for the administration of a single dose of the test or reference paracetamol formulation. To determine paracetamol concentrations and to calculate the pharmacokinetic parameters,

15 blood samples (~7 mL each) were drawn by a nurse through a venous catheter during each period at the following times: baseline (predose) and 10, 20, 30, 40, and 50 minutes and 1, 1.25, 1.5, 2, 4, 6.5, 10, 12, and 14 hours after dosing. The blood was centrifuged at 3000 rpm for 10 minutes at 4°C within 20 minutes after it was drawn. The plasma samples were separated and divided into 2 aliquots of ~1.5 mL each that were then placed in tightly sealed plastic tubes. The labeled samples were frozen at -30°C in a vertical position and stored at this temperature until they were sent for analysis.

The 2 treatment periods were separated by a 7-day washout period.

The subjects were admitted to the unit the night before administration of the drug. They fasted from 10 PM the day before administration until 2 hours after administration for water and 4 hours for food. Subjects followed a xanthine-free diet during the 2 days before the study and during the study. Subjects remained seated for the first 2 hours after drug administration.

Formulations

The test and reference formulations were 500-mg tablets administered orally. The medication was taken with 200 mL of water. The drugs were administered by a nurse.

Drug Analysis

For paracetamol analysis, 250-μL plasma aliquots were thawed at room temperature and processed after the addition of theobromine as the internal standard. A calibration curve was analyzed for each set of samples. Samples were extracted with 2.5 mL of ethyl acetate, and a 50-μL aliquot was injected into the chromatographic system. This system consisted of a Waters 515 HPLC Pump® (Waters Corporation, Milford, Massachusetts), a Waters 717Plus Autosampler®, and a Waters 486 Tunable Absorbance Detector®. Separation was carried out using a Beckman reversed-phase Ultrasphere-ODS® (octadecylsilane) column (25 cm × 4.6 mm, 5-μm particle size) (Beckman, Toronto, Canada) with a mobile phase consisting of an acetonitrile–water ratio of 12:88 at a flow rate of 1 mL/min. The UV detector was operated at 237 nm.

The method showed good linearity over the studied range (0.5–20.0 μg/mL). The limit of quantification was 0.5 μg/mL. Interday precision (expressed as the coefficient of variation [CV] for specific added concentrations) and accuracy (expressed as a percentage error of the measured and true concentrations) were better than 9.4% and 5.3%, respectively. Intraday precision and accuracy were better than 5.7% and -5.6%, respectively.

Analyses of drug concentrations were performed by MCC-Analítica (Barcelona, Spain), according to Good Laboratory Practice standards.

Pharmacokinetic Analysis

Pharmacokinetic parameters were calculated from the drug plasma concentration curve against the real time of extraction for each patient using a noncompartmental module of the application WinNonlin® version 3.1 (Pharsight Corporation,

Palo Alto, California). AUC was calculated using the trapezoidal method until the last measurable concentration (AUC_{last}). $AUC_{0-\infty}$ was calculated by adding AUC_{last} to the extrapolated AUC, which was calculated by dividing the plasma drug concentration at time t by K_e (where K_e is the elimination-rate constant derived from the semilogarithmic plot of plasma concentration versus time [visual inspection of the final part of the plasma concentration–time curve was used to identify the elimination phase]). C_{max} and T_{max} were derived directly from the study data. The other pharmacokinetic parameters assessed were plasma half-life ($t_{1/2} = 0.693/K_e$) and mean residence time (MRT) of the compound in the body.

Tolerability Assessment

Adverse events were recorded. Changes in blood pressure, body temperature, electrocardiography, and clinical examination also were recorded for the tolerability assessment.

Statistical Analysis

Analysis of variance (ANOVA) was performed for $AUC_{0-\infty}$, AUC_{last} , C_{max} , and $C_{max}/AUC_{0-\infty}$, and for their base e logarithm (Ln) transformations, which included the terms *formulation*, *period*, *sequence*, and *volunteer-sequence*. CIs were set at 90% (classical method) of the ratios of the dependent variables for each formulation (WinNonlin 3.1). Statistical significance was set at $P < 0.05$ (2 sided).

For T_{max} , a nonparametric contrast was made using the Wilcoxon rank sum test, as well as a calculation of the CI of the median of the differences, using Tryarcus® (StatsDirect Ltd., Sale, United Kingdom).

RESULTS

A total of 24 healthy volunteers (12 men, 12 women; mean [SD] age, 22.8 [1.5] years) were studied. The demographic characteristics of the patients are shown in Table I.

The individual data and mean values of the plasma concentration–time curves of paracetamol are given in Figures 1 and 2, respectively. Tables II and III show the descriptive statistics of the pharmacokinetic parameters of both formulations and a comparative analysis of the data, respectively. ANOVA did not show any period-effect, and the extrapolated AUC was a small fraction of $AUC_{0-\infty}$.

Median T_{max} for the test versus the reference formulation was 0.42 versus 0.75 hour. No significant deviations occurred. The median difference in T_{max} (the main variable) between the test and reference formulations was -0.25 hour (90% CI, -0.375 to -0.085) (Table III). Thus, C_{max} was reached ~ 15 minutes sooner with the test formulation than with the reference formulation; the difference was statistically significant ($P < 0.001$). The variability of T_{max} was greater in the reference formulation; the CV for the reference compared with the test formulation was 77.05% versus 58.31%.

Table I. Demographic characteristics of the study participants (N = 24).

Characteristic	Value
Age, y	
Mean (SD)	22.8 (1.5)
Median	23.0
Range	19.0–25.0
Sex, no (%)	
Men	12 (50)
Women	12 (50)
Body weight, kg	
Mean (SD)	64.8 (10.9)
Median	67.0
Range	50.0–85.0
Height, cm	
Mean (SD)	169.3 (9.5)
Median	169.5
Range	152.0–192.0
Body mass index, kg/m ²	
Mean (SD)	22.4 (2.3)
Median	22.6
Range	19.0–25.9

The mean (SD) $C_{\max}/AUC_{0-\infty}$, analyzed as a secondary indicator of the rate of absorption, was greater for the test formulation (0.34 [0.11] vs 0.30 [0.08]), with a ratio for $\text{Ln-}C_{\max}/AUC_{0-\infty}$ of 113.29%. The difference at 5% 2-sided for this parameter did not reach statistical significance (95% CI, 98.67%–130.07%), although it was significant at 90% CI (101.05%–127.01%) (Figure 1). Mean (SD) $C_{\max}$ of the test and reference formulations appeared to be somewhat different (9.85 [2.40] $\mu\text{g/mL}$ vs 8.33 [2.22] $\mu\text{g/mL}$), with a ratio for $\text{Ln-}C_{\max}$ of 120.24% (90% CI, 105.08%–137.59%) (Table III).

The mean (SD) $AUC_{0-\infty}$ (extent of absorption) was similar for the test versus the reference formulation (30.16 [8.87] $\mu\text{g} \cdot \text{h/mL}$ vs 28.49 [8.57] $\mu\text{g} \cdot \text{h/mL}$). The ratio of $\text{Ln-}AUC_{0-\infty}$ was 106.14% (90% CI, 102.02%–110.43%). The result was similar for $\text{Ln-}AUC_{\text{last}}$ (90% CI, 102.52%–112.57%) (Table III). The results for $t_{1/2}$ and MRT are shown in Table II.

No adverse events were recorded. No significant changes were found in clinical chemistry or physical findings (eg, blood pressure, temperature, heart rate, ECG).

DISCUSSION

The similarity between $AUC_{0-\infty}$ and AUC_{last} , as well as the fact that most of the last determinations were undetectable, confirmed that the planned sampling

Figure 1. Plasma concentration–time curves of the paracetamol (A) test and (B) reference formulations for each of the study participants ($N = 24$).

times were appropriate to describe the extent of the absorption of paracetamol for both formulations. After receiving the test formulation, 2 patients reached $C_{\max}$ by the first sampling time (even though this was done only 10 minutes after administration), so $T_{\max} < 10$ minutes could be assumed for these patients. This fact corroborates the high absorption rate of the test formulation. $T_{\max}$ of the reference formulation was in accordance with that of Ström et al² ($T_{\max} = 0.9$ h), Rawlins et al³ ($T_{\max} = 0.5$ – 1 h), and Rygnestad et al⁴ ($T_{\max} = 0.75$ h).

Figure 2. Mean plasma concentration–time curves of the paracetamol test and reference formulations.

Rates of release and absorption ($T_{\max}$ and $C_{\max}/AUC_{0-\infty}$) were more rapid for the test formulation than the reference formulation, which was the goal of this new formulation. $T_{\max}$ is considered a clinically significant variable, despite the fact that it is not easy to prove differences when its value is <1 hour. $C_{\max}$ was reached earlier with the test formulation. The secondary variable, $C_{\max}/AUC_{0-\infty}$, did not differ significantly between the 2 formulations' alpha level of 0.05 (95% CI), although the difference was significant for a 1-sided alpha level of 0.05 (90% CI). This can be explained by the variability of this parameter and by the fact that absorption was slightly, although not significantly, greater for the test formulation than for the reference formulation. The higher variability occurs not only in $T_{\max}$, but also in each of the extraction times from the first half of the curve. The $T_{\max}$ CV and the graphic representation of the individual plasma concentrations of each formulation corroborate this difference in variability.

Stocker and Montgomery⁵ found that plasma drug concentrations of 10 to 20 µg/mL were associated with antipyretic and analgesic effects. In another study⁶ comparing a sustained-release formulation with an immediate-release formulation, only the immediate-release formulation produced an analgesic effect, probably due to the rate of absorption and $C_{\max}$ reached. This finding supports the hypothesis that the faster the absorption rate and the greater the $C_{\max}$, the sooner and better the analgesic effect. Furthermore, other studies^{7,8} have shown a delay in hypoalgesia with respect to the paracetamol $C_{\max}$ for

Table II. The kinetic parameters of the reference and test formulations of paracetamol in 24 healthy subjects.

Parameter	Mean (SD)	CV%	Median	Range	Geometric Mean	Harmonic Mean
T_{max} , h						
Test	0.51 (0.30)	58.31	0.42	0.17–1.50	0.45	0.40
Reference	0.98 (0.75)	77.05	0.75	0.33–4.00	0.82	0.73
$C_{max}/AUC_{0-\infty}$, h^{-1}						
Test	0.34 (0.11)	31.32	0.32	0.22–0.62	0.33	0.32
Reference	0.30 (0.08)	27.01	0.28	0.17–0.53	0.29	0.28
C_{max} , $\mu g/mL$						
Test	9.85 (2.40)	24.37	9.54	6.15–15.47	9.57	9.30
Reference	8.33 (2.22)	26.69	8.68	2.49–12.50	7.96	7.44
$AUC_{0-\infty}$, $\mu g \cdot h/mL$						
Test	30.16 (8.87)	29.41	27.47	17.53–54.06	29.00	27.93
Reference	28.49 (8.57)	30.07	27.18	14.34–51.56	27.33	26.19
AUC_{last} , $\mu g \cdot h/mL$						
Test	27.70 (9.01)	32.54	25.08	15.79–51.31	26.40	25.21
Reference	25.92 (8.72)	33.64	24.83	11.98–48.57	24.57	23.24
MRT_{∞} , h						
Test	3.39 (0.59)	17.46	3.17	2.49–4.59	3.34	3.29
Reference	3.66 (0.72)	19.77	3.72	2.46–5.61	3.59	3.53
$t_{1/2}$, h						
Test	2.27 (0.43)	18.99	2.17	1.70–3.28	2.23	2.20
Reference	2.30 (0.46)	19.85	2.21	1.67–3.13	2.26	2.21

CV = coefficient of variation; T_{max} = time to maximum plasma drug concentration (C_{max}); $C_{max}/AUC_{0-\infty}$ = C_{max} /area under the plasma concentration–time curve (AUC) from time 0 to infinity; AUC_{last} = AUC calculated until the last measurable concentration; MRT_{∞} = mean residence time extrapolated to infinity; $t_{1/2}$ = half-life.

pharmacokinetic/pharmacodynamic reasons and that a reduction of the T_{max} of this drug increased the effect.

Taking into account the tolerability of paracetamol doses far exceeding the dose we studied and the parallel course of plasma drug concentrations with respect to the reference formulation at the elimination phase of the curve, a higher risk due to C_{max} , dose dumping, or higher redosing is not expected.

Due to the chemical characteristics and poor solubility of paracetamol, it is important to have formulations available that allow a greater absorption rate.

Table III. Comparative analysis of the pharmacokinetic parameters (original and base e logarithm-transformed) of paracetamol reference and test formulations.

Parameter	Difference, Median, h	Difference, 90% CI, h	Difference, 90% CI with Respect to Mean of Reference Form, %
$T_{\max}$	-0.25*	-0.375 to -0.085	61.57 to -91.29
Parameter	Difference, Mean (SE)	Ratio (90% CI), %	
$C_{\max}$, $\mu\text{g/mL}$	1.52 (0.61)	118.26 (105.74–130.77)	
$\text{AUC}_{0-\infty}$, $\mu\text{g} \cdot \text{h/mL}$	1.67 (0.68)	105.85 (101.77–109.94)	
AUC_{last} , $\mu\text{g} \cdot \text{h/mL}$	1.77 (0.71)	106.84 (102.12–111.55)	
$C_{\max}/\text{AUC}_{0-\infty}$, h^{-1}	0.04 (0.02)	114.40 (100.29–127.98)	
$\text{Ln-}C_{\max}$	0.18 (0.08)	120.24 (105.08–137.59)	
$\text{Ln-AUC}_{0-\infty}$	0.06 (0.02)	106.14 (102.02–110.43)	
$\text{Ln-AUC}_{\text{last}}$	0.07 (0.03)	107.43 (102.52–112.57)	
$\text{Ln-}C_{\max}/\text{AUC}_{0-\infty}$	0.12 (0.07)	113.29 (101.05–127.01)	

$T_{\max}$ = time to maximum plasma drug concentration; $C_{\max}$ = maximum plasma drug concentration; $\text{AUC}_{0-\infty}$ = area under the plasma concentration–time curve from time 0 to infinity; AUC_{last} = AUC calculated until the last measurable concentration.

* $P < 0.001$ (2-sided, Wilcoxon rank sum test).

Although assessing analgesic effects was not the aim of this study, the differences between the formulations exceeded the usual $\pm 20\%$ interval of bioequivalence (ie, the interval for nonclinically relevant differences). Therefore, in terms of a relationship between drug concentrations and effects, a faster and better effect might be expected with this new formulation. Nevertheless, these facts have not yet been proved clinically, and a comparative efficacy Phase III trial should be carried out to determine whether the new formulation has better efficacy.

CONCLUSIONS

The speed of release and absorption was statistically significantly higher with the test formulation compared with the reference one (evaluated using $T_{\max}$, $C_{\max}$, and $C_{\max}/\text{AUC}$ parameters). This speed is especially important for a rapid analgesic or antipyretic effect.

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