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Bioavailability of Two New Formulations of Paracetamol, Compared With Three Marketed Formulations, in Healthy Volunteers

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SUMMARY

The aim of this study was to compare the main pharmacokinetic characteristics of two new paracetamol formulations, powder sachet and tablet, with that of three commercially available paracetamol formulations: two conventional solid tablets and one effervescent tablet. Twelve healthy volunteers participated in an open, single dose (paracetamol 1000 mg), randomized, five-way, crossover study. Formulations studied included: formulation A: 2 x 500 mg paracetamol tablets (Laboratorios Belmac S.A.); formulation B: 1 x 1000 mg paracetamol powder sachets (Laboratorios Belmac, S.A.); formulation C: 2 x 500 mg paracetamol film-coated tablets (Panadol®, SmithKline Beecham); formulation D: 2 x 500 mg paracetamol tablets (Tylenol®, McNeil); and formulation E: 1 x 1000 mg effervescent paracetamol tablets (Efferalgan®, UPSA). The primary variables were area under the plasma concentration time curve extrapolated to infinity ($AUC_{o-\infty}$), maximum plasma concentration (C_{max}), and time to maximum plasma concentration (t_{max}). Mean $AUC_{o-\infty}$ ranged from 52.6 (B) to 56.3 μg.h/ml (D); mean C_{max} varied between 17.98 (C) and 20.73 μg/ml (E); mean t_{max} ranged from 0.40 (E) to 0.88 h (C); and median $t_{1/2}$ varied between 2.65 (C) and 2.81 h (A). Formulations A, B and E showed significantly shorter t_{max} than formulation C. The t_{max} and C_{max} values found for formulations A and B were very similar to that found for E, an effervescent tablet formulation. In conclusion, the two new formulations of paracetamol tested in this study were absorbed rapidly after a single oral dose in healthy volunteers, similar to an effervescent paracetamol formulation and significantly faster than two ordinary commercialized paracetamol tablets.

Key words: Absorption - Effervescent - Paracetamol - Powder - Tablet - T_{max}

INTRODUCTION

Paracetamol (acetaminophen, *N*-acetyl-paraminophenol, 4-hydroxy-acetanilide) is an analgesic and antipyretic drug effective in relieving mild to moderate pain of a non-visceral origin (1, 2). Paracetamol is rapidly absorbed from the gastrointestinal tract after oral administration, although first-pass metabolism decreases availability to the systemic circulation (3, 4).

Several different approaches have previously been used to achieve a more rapid absorption of paracetamol solid dose formulations. These include enhancement of tablet disintegration rate (5), enhancement of drug dissolution rate by using amino acid salts (6) or alkali metal salts (7) of paracetamol, and the addition of either sorbitol (8) or antacids (9) to paracetamol tablets. The pharmacokinetics of paracetamol in solid or effervescent formulations has been extensively studied (8, 10, 11) but few studies are available on the degree of absorption of paracetamol presented as a powder sachet formulation (12). We have modified the characteristics of paracetamol to obtain a more hydrophilic and soluble powder. The objective of this study was to evaluate the main pharmacokinetic characteristics of two new paracetamol formulations, powder sachet and tablet, based on the modified paracetamol powder described above, and to compare these characteristics with three commercially available paracetamol formulations: two conventional solid tablets and one effervescent tablet.

MATERIALS AND METHODS

This was an open, single dose (paracetamol 1000 mg), randomized, five-way, crossover study. The study was conducted in accordance with the International Conference of Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP), the recommendations of the World Health Organisation, and the Declaration of Helsinki. Prior to study initiation, Ethics Committee approval was obtained and written informed consent was obtained from all participants. Twelve healthy volunteers were included: 8 males and 4 females aged 29 ± 9.7

years. Concomitant medication was not permitted for 14 days prior to or during the trial. Paracetamol was permitted up to 72 h prior to the trial, but could not be used as concomitant medication.

The following formulations were administered: formulation A: 2 x 500 mg paracetamol tablets (Laboratorios Belmac S.A.); formulation B: 1 x 1000 mg paracetamol powder sachets (Laboratorios Belmac, S.A); formulation C: 2 x 500 mg paracetamol film-coated tablets (Panadol®, SmithKline Beecham); formulation D: 2 x 500 mg paracetamol tablets (Tylenol®, McNeil); and formulation E: 1 x 1000 mg effervescent paracetamol tablets (Efferalgan®, UPSA). Volunteers were required to fast overnight for at least 10 h prior to dosing on the study day. During the overnight fast, water could be taken *ad libitum*, up to 1 h predosing. Each volunteer was given a single oral dose of one of the test or reference medications at approximately 08:00 h. In three of the five treatment periods, tablets were swallowed, without chewing or crushing, with 250 ml of water. In the other two treatment periods, powder sachets or effervescent tablets, the medication was diluted in 250 ml water. A mouth check was carried out to ensure the medication was swallowed. The five formulations were given to each volunteer in random order, separated by a washout period of at least 3 days.

Blood samples of 5 ml were drawn at each of the following times by means of an indwelling catheter or venipuncture: predose, and at 15 min, 30 min, 45 min, 1 h, 1 h 20 min, 1 h 40 min, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h and 24 h postdosing (n = 14 blood samples per period). The total volume of blood taken over the entire study did not exceed 450 ml. The blood samples were collected into labeled lithium-heparin tubes (Sarstedt, Germany) and centrifuged at 3,000 rpm for 10 min at 4 ºC in a refrigerated centrifuge. Plasma samples were frozen immediately and stored at –20 ºC until analyzed.

Plasma concentrations of paracetamol were measured using a sensitive, specific, validated liquid chromatographic with UV detection and theophylline (T-1633, Sigma-Aldrich Chemicals) as internal standard solution. Human plasma samples (50 µl), internal standard solution (10 µl, 1 mg/ml), reagent grade water (10 µl) and 6% perchloric acid solution (100 µl) were mixed in polypropylene tubes and centrifuged at 3500 rpm for 8 min. Then, 130 µl was transferred to a HPLC vial insert. A MAX-RP 80A, 150 x 4.6 mm ID (Phenomenex) HPLC column was used, with a C18 (ODS), 4 x 3 mm ID (Phenomenex) HPLC guard column. The mobile phase consisted of 50 mM phosphate buffer (pH 2.2):acetonitrile, 93: 7 v/v with a run-time of 7 min and a flow rate of 1.2 ml/min. The validation range was 0.25-160 µg/ml; the highest concentration of paracetamol found was 32.65 µg/ml. Accuracy ranged from –0.8 to –5.0%, and precision from 9.5 to 3.8%, at the lowest and highest concentrations, respectively.

Pharmacokinetic variables were calculated using Kinetica 2000® software (Version 4, Innaphase Clinical Information Engineering). The original plasma concentration data were adjusted for the very slight differences in the certified content of paracetamol. No significant discordant values (outlier data) were observed for the pharmacokinetic parameters. The primary variables calculated were the area under the plasma concentration time curve extrapolated to infinity ($AUC_{0-\infty}$), the maximum plasma concentration (C_{max}), and the time to maximum plasma concentration (t_{max}). Secondary variables were the area under the plasma concentration time curve from 0-t h after drug administration ($AUC_{0-tlast}$) and the terminal elimination half-life ($t_{1/2}$), calculated from the terminal rate constant. Differences in the rate and extent of absorption of the different products were further examined by determining the partial area under the plasma concentration time curve in the 15 min, 30 min, 45 min and 1 h after dosing ($AUC_{0-0.25h}$, $AUC_{0-0.5h}$, $AUC_{0-0.75h}$, $AUC_{0-1.0h}$). AUC was calculated using the mixed log linear rule. Using this method the AUC was calculated by the trapezoid method, between the first (data) point and t_{max}, and then by the logarithmic method between t_{max} and the last data point. However, the calculation automatically switched to the trapezoidal method each time the concentration level increased or was equal between two data points. Values below the limit of quantification (LOQ) were assumed to be zero when they occurred before t_{max}. Values below LOQ occurring after t_{max} were ignored for calculation of the terminal regression line. There was interpolation between data points if a value below the limit of quantification, or a missing value, occurred between two values above the LOQ. Extrapolation of AUC was carried out using linear regression on the logarithmic (ln) transformed data points of the curve. Adverse events or abnormal clinical, blood hematological or biochemical values were also recorded. Statistical analyses were carried out using SAS® V. 8.1. (SAS Institute, Cary, NC, USA). SAS PROC GLM was used to calculate p values for the paired t-comparisons of AUC and C_{max} treatment means. EquivTest V. 2.0 (Statistical Solutions, Broadway) was used to compare treatment means of the non-normally distributed t_{max} data, using the Mann-Whitney independent rank sum test. Data are shown with interindividual coefficients of variation (CV).

RESULTS

Mean $AUC_{0-\infty}$ ranged from 52.6 (formulation B) to 56.3 µg.h/ml (formulation D). No significant differences were found between formulations (Table 1). Mean $AUC_{0-tlast}$ showed a similar trend (Table 1). Mean paracetamol plasma concentrations *vs.* time for 24 h following dosing are shown in Figure 1.

Mean C_{max} varied between 17.98 (formulation C) and 20.73 µg/ml (formulation E). No significant differences

TABLE 1. Pharmacokinetic parameters of the 5 formulations studied.

	Formulation				
Parameter	**A**	**B**	**C**	**D**	**E**
$AUC_{0-\infty}$ (µg.h/ml)	55.4 (10.3) [18.6%]	52.6 (12.5) [23.8%]	54.8 (14.4) [26.4%]	56.3 (14.9) [26.5%]	53.4 (11.7) [21.9%]
$AUC_{0\text{-tlast}}$ (µg.h/ml)	53.3 (10.5) [27.6%]	50.8 (12.4) [24.4%]	52.7 (14.5) [27.6%]	53.9 (15.0) [27.8%]	51.8 (11.9) [22.9%]
C_{max} (µg/ml)	20.55 (6.90) [33.6%]	20.24 (6.22) [30.8%]	17.98 (6.21) [34.5%]	19.41 (7.60) [39.2%]	20.73 (5.76) [27.8%]
$t_{1/2}$ (h)*	2.81 (2.41) [65.5%]	2.81 (1.05) [33.9%]	2.65 (0.73) [25.2%]	2.68 (1.58) [47.4%]	2.71 (0.72) [24.9%]

A: 2 x 500 mg paracetamol tablets (Laboratorios Belmac S.A); B: 1 x 1000 mg paracetamol powder sachets (Laboratorios Belmac, S.A.); C: 2 x 500 mg paracetamol film-coated tablets (Panadol®, SmithKline Beecham); D: 2 x 500 mg paracetamol tablets (Tylenol®, McNeil); and E: 1 x 1000 mg effervescent paracetamol tablets (Efferalgan®, UPSA). Data shown are mean with standard deviation (in parentheses) and coefficient of variation [in brackets]. *median values. $AUC_{0-\infty}$: area under the plasma concentration time curve extrapolated to infinity; $AUC_{0\text{-tlast}}$: area under the plasma concentration time curve from 0-t h after drug administration; C_{max}: maximum plasma concentration; $t_{1/2}$: terminal elimination half-life. For all results $n = 12$.

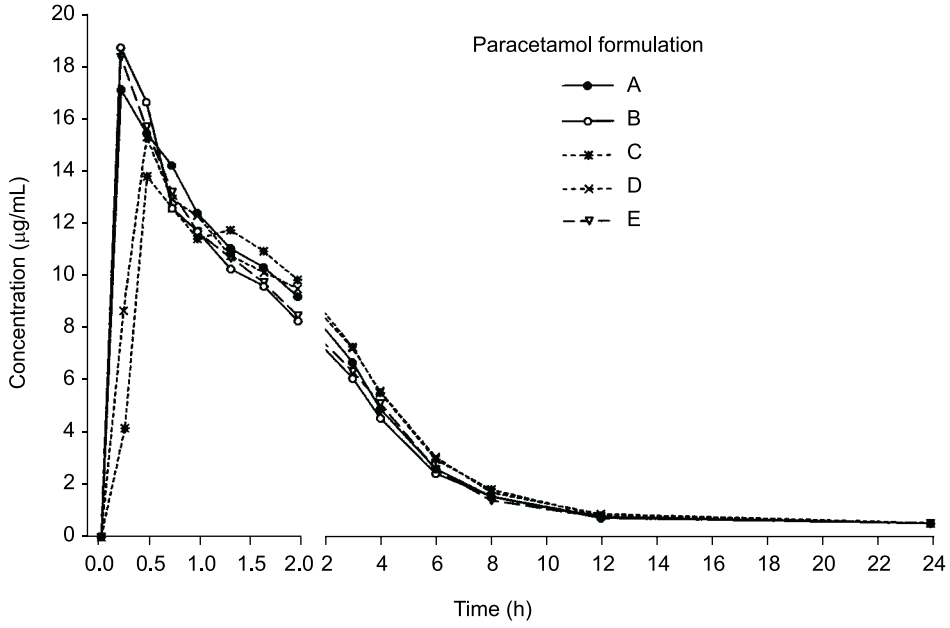

FIG. 1. Paracetamol plasma concentration *vs*. time curves (arithmetic mean data) following oral administration of 1000 mg of the following test formulations: A: 2 x 500 mg tablets (Laboratorios Belmac, S.A.) B: 1 x 1000 mg powder sachets (Laboratorios Belmac, S.A.), C: 2 x 500 mg film-coated tablets (Panadol®, SmithKline Beecham), D: 2 x 500 mg film-coated tablets (Tylenol®, McNeil), and E: 1 x 1000 mg effervescent tablet (Efferalgan®, UPSA).

were found between formulations (Table 1). Nevertheless, the mean C_{max} values found for formulations A and B were very similar to those found for E, an effervescent tablet formulation. Mean plasma paracetamol concentrations 15 min after ingestion ($C_{0.25h}$) were significantly greater for formulations A and B than for formulations C and D (Tables 3 and 4).

Mean t_{max} ranged from 0.40 (formulation E) to 0.88 h (formulation C). Formulations A, B and E showed significantly shorter t_{max} than formulation C (Table 2). Once again, the t_{max} values found for formulations A and B were very similar to those found for E, an effervescent tablet formulation.

Median $t_{1/2}$ varied between 2.65 (formulation C) and 2.81 h (formulation A). No significant differences were found between formulations (Table 1).

Results for the partial area under the plasma concentration curve ($AUC_{0-0.25h}$, $AUC_{0-0.5h}$, $AUC_{0-0.75h}$, $AUC_{0-1.0h}$) showed that formulations A and B were significantly more extensively absorbed than formulation C in the first hour, and significantly more extensively absorbed than formulation D in the first 30 min, following ingestion (Tables 3 and 4).

Total individual drug exposure over the whole study was 5 g (1000 mg in 5 treatment periods). No clinically significant alterations in vital signs, physical findings or hematology/biochemistry results were found in any of

TABLE 2. Summary t_{max} data (h) for the 5 formulations studied.

Formulation	Mean	Min-Max	Median
A (2 x 500 mg paracetamol tablets; Laboratorios Belmac S.A)	0.44 (0.19) [43.1%]	0.25-0.75	0.50
B (1 x 1000 mg paracetamol powder sachets; Laboratorios Belmac, S.A.)	0.44 (0.28) [65.0%]	0.25-1.00	0.25
C (2 x 500 mg paracetamol film-coated tablets; Panadol®, SmithKline Beecham)	0.88 (0.55) [62.1%]	0.50-2.00	0.50
D (2 x 500 mg paracetamol tablets; Tylenol®, McNeil)	0.80 (0.76) [95.8%]	0.25-3.00	0.50
E (1 x 1000 mg effervescent paracetamol tablets; Efferalgan®, UPSA)	0.40 (0.17) [42.2%]	0.25-0.75	0.38

Mean data are shown as arithmetic means with standard deviation (in parentheses) and coefficient of variation [in brackets]. *n* = 12.

TABLE 3. Further pharmacokinetic parameters of the 5 formulations studied.

	Formulation				
Parameter	A	B	C	D	E
$AUC_{0\text{-}0.25h}$ (µg.h/ml)	2.16 (1.26) [58.5%]	2.36 (1.01) [42.83%]	0.55 (0.71) [129.92%]	1.07 (1.35) [125.73%]	2.31 (0.90) [38.88%]
$AUC_{0\text{-}0.50h}$ (µg.h/ml)	6.16 (2.89) [46.99%]	6.73 (2.46) [36.61%]	2.78 (2.25) [80.75%]	4.02 (2.93) [72.88%]	6.48 (1.69) [26.06%]
$AUC_{0\text{-}0.75h}$ (µg.h/ml)	9.45 (3.70) [39.09%]	10.32 (3.08) [29.84%]	6.04 (3.95) [65.51%]	7.48 (3.82) [51.10%]	9.72 (2.15) [22.11%]
$AUC_{0\text{-}1.0h}$ (µg.h/ml)	13.14 (3.70) [28.15%]	13.33 (3.41) [25.58%]	9.01 (5.12) [56.88%]	10.61 (4.45) [41.91%]	13.21 (2.40) [18.17%]
$C_{0.25h}$ (µg/ml)	17.02 (10.11) [59.40%]	18.63 (8.09) [43.40%]	4.14 (5.71) [137.76%]	8.60 (10.55) [122.69%]	18.25 (7.19) [39.41%]

A: 2 x 500 mg paracetamol tablets (Laboratorios Belmac S.A.); B: 1 x 1000 mg paracetamol powder sachets (Laboratorios Belmac, S.A.); C: 2 x 500 mg paracetamol film-coated tablets (Panadol®, SmithKline Beecham); D: 2 x 500 mg paracetamol tablets (Tylenol®, McNeil); and E: 1 x 1000 mg effervescent paracetamol tablets (Efferalgan®, UPSA). Data shown are mean with standard deviation (in parentheses) and coefficient of variation [in brackets]. $AUC_{0\text{-}0.25h}$: area under the plasma concentration time curve 15 min after dosing; $AUC_{0\text{-}0.5h}$: area under the plasma concentration time curve 30 min after dosing; $AUC_{0\text{-}0.75h}$: area under the plasma concentration time curve 45 min after dosing; $AUC_{0\text{-}1.0h}$: area under the plasma concentration time curve one hour after dosing; $C_{0.25h}$: plasma concentration at 15 min after dosing. For all results *n* = 12.

the volunteers. One case of mild dyspepsia found after administration of formulation C was considered to be possibly related to treatment. Overall, paracetamol treatment was safe and well-tolerated by healthy volunteers at a dose of 1000 mg.

DISCUSSION AND CONCLUSION

The main finding of the present study was the short time to maximal plasma concentration of paracetamol (t_{max}) observed for the two new formulations tested. It is relevant that both new paracetamol formulations were absorbed as rapidly as the effervescent formulation; the new powder sachet and the new tablet formulation exhibited a shorter time to C_{max} for paracetamol when compared with the other solid tablets tested. In the case of formulation C (Panadol®, SmithKline Beecham), this difference was statistically significant. Absence of significant differences in $AUC_{0\text{-}\infty}$ or $AUC_{0\text{-}tlast}$ confirmed similarity regarding the extent of paracetamol absorption for all formulations tested. However, partial AUC results ($AUC_{0\text{-}0.25h}$, $AUC_{0\text{-}0.5h}$, $AUC_{0\text{-}0.75h}$, $AUC_{0\text{-}1.0h}$) indicated a greater extent of absorption for formulations A and B in the first hour after ingestion compared with formulations C and D. Mean C_{max} ranged from 17.98 to 20.73 µg/ml, which is well within the effective analgesic plasma concentration suggested for paracetamol of 10.6-34.8 µg/ml (13). The new paracetamol formulations were within this concentration range 15 min after dosing; these formulations exhibited mean C_{max} values slightly higher than those for the marketed solid tablets and comparable to the commercialized effervescent tablet. Median $t_{1/2}$ varied between 2.65 and 2.81 h, which is consistent with previously published results (14).

In clinical practice, paracetamol is usually administered at a dose of 1000 mg every 4-6 h. Onset of analgesia has been estimated to occur between 15 and 90 min; this varies depending on the formulation used (15). More rapid absorption may result in earlier onset of analgesia in the clinical setting of acute pain (15, 16). We have found only one previously published study comparing the paracetamol absorption rate between solid and effervescent tablets (10). This earlier study showed a t_{max} of 0.45 h for the effervescent paracetamol and 0.75 h for the solid tablet formulation. The results reported here are very similar, with mean t_{max} values of 0.40 h and 0.88 h observed for the effervescent and the solid tablets, respectively. Importantly, the mean t_{max} of 0.44 h found for the two new formulations was almost half that found for the marketed solid tablets. The plasma concentration curves (Fig. 1) were not bell shaped or flattened around

TABLE 4. Summary statistics for inter-treatment comparisons.

Parameter	Comparison	*p* value
t_{max}	A *vs.* C*	0.0142
	B *vs.* C*	0.0057
	E *vs.* C*	0.0034
$AUC_{0\text{-}0.25h}$ (μg.h/ml)	A *vs.* C	0.0009
	B *vs.* C	0.0001
	A *vs.* D	0.0532
	B *vs.* D	0.0144
$AUC_{0\text{-}0.50h}$ (μg.h/ml)	A *vs.* C	0.0042
	B *vs.* C	0.0005
	A *vs.* D	0.0859
	B *vs.* D	0.0227
$AUC_{0\text{-}0.75h}$ (μg.h/ml)	A *vs.* C	0.0397
	B *vs.* C	0.0072
$AUC_{0\text{-}1.0h}$ (μg.h/ml)	A *vs.* C	0.0338
	B *vs.* C	0.0235
$C_{0.25h}$ (μg/ml)	A *vs.* C	0.0009
	B *vs.* C	0.0001
	A *vs.* D	0.0586
	B *vs.* D	0.0159

A: 2 x 500 mg paracetamol tablets (Laboratorios Belmac S.A); B: 1 x 1000 mg paracetamol powder sachets (Laboratorios Belmac, S.A.); C: 2 x 500 mg paracetamol film-coated tablets (Panadol®, SmithKline Beecham); D: 2 x 500 mg paracetamol tablets (Tylenol®, McNeil); E: 1 x 1000 mg effervescent paracetamol tablets (Efferalgan®, UPSA). *Mann-Whitney independent rank sum test. n = 12.

C_{max}, reinforcing the evidence for faster absorption of the two new formulations.

In conclusion, the two new formulations of paracetamol tested in this study, powder sachets and solid tablets, were rapidly absorbed after a single oral dose in healthy volunteers, similar to an effervescent paracetamol formulation and faster than two other ordinary commercialized paracetamol tablets.

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