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Drug Development and Industrial Pharmacy, 28(5), 523–531 (2002)

RESEARCH PAPER

A New Rapidly Absorbed Paracetamol Tablet Containing Sodium Bicarbonate. I. A Four-Way Crossover Study to Compare the Concentration–Time Profile of Paracetamol from the New Paracetamol/Sodium Bicarbonate Tablet and a Conventional Paracetamol Tablet in Fed and Fasted Volunteers

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ABSTRACT

The primary objective of this four-way crossover study was to compare the concentration–time profile of paracetamol from a new rapidly absorbed paracetamol tablet containing sodium bicarbonate (PS) with a conventional paracetamol tablet (P), in a panel of 28 fed and fasted healthy volunteers. The results demonstrated that paracetamol was absorbed more rapidly from tablets containing sodium bicarbonate compared to conventional tablets, as indicated by a shorter t_{max} *in both the fed and fasted state and a higher* C_{max} *in the fasted state. The two*

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formulations were bioequivalent with respect to area under curve (AUC). Food did not affect the extent of absorption from either formulation, as indicated by AUC, however, food did reduce the rate of absorption from both formulations, as indicated by a longer t_{max} *and a lower* C_{max}*. Metabolic activation of paracetamol to its oxidation metabolites, as assessed by combined partial clearances to subsequent secondary metabolites cysteine and mercapturic acid conjugates, indicated that the two formulations were bioequivalent in this respect.*

Key Words: *Bioequivalence; Metabolism; Paracetamol; Rate of absorption*

INTRODUCTION

Paracetamol is a commonly used analgesic and antipyretic drug that has been available over the counter in many counties for more than 40 years. It is widely used as an antipyretic and analgesic for mild to moderate pain states and it is first-line choice for pain relief management and antipyresis in a variety of patients. It has a broad tolerability and is of particular value in the treatment of patients in whom non-steroidal drugs are contraindicated (1).

The rate of paracetamol absorption following oral administration of conventional paracetamol tablets can be variable (2,3). For example, the mean t_{max} following a 1000-mg oral dose of paracetamol was estimated as 0.90 hr, with a standard deviation of 0.51 hr (2). Delayed absorption could lead to a later onset of analgesic action for many patients. Delayed absorption can be overcome by the use of soluble paracetamol tablets, which have been shown to have both a faster rate of absorption (4) and a faster onset of analgesic action (5) compared to conventional tablets. Unfortunately, soluble tablets may not always be convenient, as they have to be dissolved in water prior to administration and furthermore the resulting solution may be unpalatable to some patients. An ideal paracetamol oral dosage form should combine the convenience of a conventional tablet with the speed of onset of an effervescent tablet.

In a previous pharmacokinetic study we demonstrated that inclusion of sodium bicarbonate 630 mg in paracetamol tablets increases the rate of paracetamol absorption relative to conventional tablets (6). However, the study used subjects who were fasted volunteers and there was no attempt to assess whether food affected the rate of absorption from the new formulation. Food has been reported to slow the rate of paracetamol absorption (7), probably as a result of delayed gastric emptying. In a clinical setting patients are likely to have ingested food at varying times before dosing with analgesic medication, and an ideal analgesic should be rapidly absorbed irrespective of the dietary state of the patient.

The primary objective of the present study was to compare the pharmacokinetics of paracetamol from a new rapidly absorbed paracetamol/sodium bicarbonate tablet with a conventional paracetamol tablet in both fasted and fed healthy volunteers. A secondary objective was to assess whether the two formulations were equivalent with respect to the metabolic fate of paracetamol to its oxidation metabolites by comparing the partial clearances to subsequent metabolites, cysteine and mercapturic acid conjugates, over 0–4 hr and 0–12 hr post-dose.

MATERIALS AND METHODS

The formulations evaluated in the study were as follows:

- paracetamol 500 mg/sodium bicarbonate 630 mg tablets (PS), batch number C328.8.003;
- paracetamol 500 mg tablets (P), batch number 1PN 905.

Both test products were manufactured by Glaxo SmithKline Consumer Healthcare, Brentford, UK.

The four treatment groups were as follows:

- paracetamol/sodium bicarbonate: two tablets (fed);
- paracetamol/sodium bicarbonate: two tablets (fasted);
- paracetamol: two tablets (fed);
- paracetamol: two tablets (fasted).

Twenty eight Caucasian healthy male ($n = 18$) and female ($n = 10$) non-patient volunteers were recruited from a panel at BIBRA International. They were

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aged between 18 and 50 years and had a body mass index within 15% of ideal body weight and frame size as given by the Metropolitan Life Insurance tables (8). The volunteers were non-smokers and stated that they had not taken any medication within 7 days of the start of the study or at any time during the study. Females were either of non-child-bearing potential or screened negative with a pregnancy test. The study was approved by the local ethics committee and volunteers gave written informed consent before entering the study.

Volunteers were required to attend the study center the evening before each treatment and they remained resident at the study centre for 36 hr thereafter. After fasting overnight each volunteer received one of the four treatments on four separate days according to a randomization schedule based on a four-way Latin square design balanced for carry-over effects (9). There was a washout period of at least 48 hr between each of the doses. On two of the four study days the volunteers ate a standard breakfast 30 min before administration of the study medication. The breakfast comprised one fried egg, a slice of bacon, one slice of toast with 15 g butter and marmalade, 112 g hash potatoes, and 200 mL whole milk.

On each study day the tablets were taken with 100 mL of water. Blood samples were taken via an indwelling cannula pre-dose, then at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 90 min post-dose, then at 2, 3, 4, 6, 8, 12 hr post-dose. Urine collections were made pre-dose and for 24 hr following dosing in four collection periods between 0–4 hr, 4–8 hr, 8–12 hr and 12–24 hr. Two hours after dosing the volunteers drank 200 mL of water, and at 4 hr post-dose they were provided with a standard lunch plus one cup of decaffeinated tea or coffee. After 6 hr they were supplied with decaffeinated tea or coffee ad lib. Further meals were provided at 7 hr and 13 hr post-medication.

Blood samples taken during the study were allowed to stand for 30 min and then centrifuged at 2500 rpm for 5 min. Approximately 1.5 mL of serum was separated from each sample, placed in a polypropylene screw top tube, and stored at −20°C prior to analysis.

All urine collected during the specified collection periods was pooled for each subject and the volume measured. A 5-mL aliquot of each urine sample was retained and stored at −20°C within 3 hr of the end of each study period.

Serum samples (500 μL) were mixed with 30% (v/v) perchloric acid (50 μL) and centrifuged at 13,000 rpm for 5 min. The supernatant was then decanted into autosampler vials prior to analysis. Samples were analyzed by high-performance liquid chromatography (HPLC) using a 150 mm × 4.6 mm i.d. Ultrasphere-5 ODS column maintained at 40°C. The mobile phase consisted of 100 mM potassium dihydrogen phosphate:formic acid:propanol, 98:1:1. The injection volume was 10 μL and the flow rate was set at 2.0 mL/min with detection wavelength 244 nm. The typical elution time for paracetamol was 2.6 min. Quantification of paracetamol was by comparison with standard paracetamol solutions. The limit of reliable quantification was defined as 0.05 μg/mL, values below this level were reported as zero.

Urine samples (100 μL) were mixed with water (800 μL) and an aqueous solution of internal standard which contained 4-fluorophenol 5 mg/mL (100 μL) in glass autosampler vials and then centrifuged prior to analysis. Samples were analyzed by HPLC using a 250 mm × 4.6 mm i.d. Spherisorb-5 ODS 1 column maintained at 40°C. The mobile phase consisted of 0.67% (v/v) acetic acid:methanol:ethyl acetate, 75:25:0.1. The injection volume was 20 μL and the flow rate was set at 1.3 mL/min with detection wavelength 250 nm. The typical elution times were as follows: paracetamol, 4.6 min; paracetamol sulfate, 1.8 min; paracetamol glucuronide, 2.7 min; mercapturic acid conjugate, 5.6 min; cysteine conjugate, 6.4 min; internal standard 10.6 min. Quantification of paracetamol and metabolites was by comparison with the internal standard. The reliable limits of quantification for paracetamol sulfate, paracetamol glucuronide, paracetamol, paracetamol mercapturate and paracetamol glucuronide were 5, 1, 0.1, 0.5, and 0.5 μg/mL, respectively.

The values derived from the analysis of QC samples during the study indicated that the determination of all five metabolites was within the ICH guidelines of ±15% accuracy and precision at the levels encountered in the vast majority of study samples, with any discrepancies at relatively low levels having little or no effect on the reported parameters.

The pharmacokinetic analysis was performed using a model-independent software program (PK Solutions 2.0, Summit Research Services, Montrose, CO, USA).

The areas under the concentration–time curves from dosing to the time point (*tn*) of the last

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non-zero value (AUC_{0-tn}) were calculated by the linear trapezoidal method. The area from the last measured concentration (*tn*) to infinity ($AUC_{tn-\infty}$) was calculated by dividing the predicted value of the concentration at time (*tn*) by the elimination rate constant. The elimination rate constant and elimination half-life were calculated from non-linear regression of the terminal portion of the serum concentration–time curve. Partial clearances were calculated by dividing metabolite recovery in urine (0–4 or 0–12 hr) by the corresponding AUC of the paracetamol.

A linear analysis of variance (ANOVA) model was used to analyze the logarithmically transformed AUC, C_{max}, and partial clearance (CL). The model incorporated factors for subject, session, formulation, first-order carry-over, and sex. First-order carry-over was dropped from the statistical model when it was found to be insignificant. A similar ANOVA model was used to analyze the logarithmically transformed partial clearance of oxidation metabolites. The differences between treatments were evaluated by Tukey's post hoc analysis (SPSS vers. 10).

For the tests designed to demonstrate bioequivalence, the null hypothesis was that there is a difference between the formulations. For the assessments of the food effect on rate of absorption, the null hypothesis was no difference between formulations.

Residual variances from the ANOVAs were used to calculate confidence intervals for the difference in formulation means on the log scale; 90% confidence intervals were used for the assessment of bioequivalence with respect to AUC, C_{max}, and partial clearance of different metabolites. These were then back-transformed to give the relative values of the parameters (and confidence intervals) for the paracetamol/sodium bicarbonate formulation to the corresponding paracetamol formulation in the fed and fasted state and for the ratios of the fed and fasted states for each formulation. Half-life was similarly analyzed but was not logarithmically transformed. Values of t_{max} were analyzed non-parametrically by the Wilcoxon matched-pairs, signed-ranks test.

RESULTS

Twenty seven volunteers completed the study, one volunteer dropped out after completing just one leg of the study. Only subjects who completed the study were included in the pharmacokinetic analysis. Both treatments were well tolerated. Eight subjects reported a total of 10 adverse events during the study. None of these events were serious and none were considered related to the study formulations.

Mean paracetamol serum concentration vs. time for each of the four legs of the study is shown in Fig. 1. The pharmacokinetic parameters and partial clearances to metabolites for each of the treatments are shown in Table 1. Pharmacokinetic parameter ratios and confidence intervals for AUC, C_{max}, and t_{max} are detailed in Table 2. The ratios of partial clearances are shown in Table 3 together with their confidence intervals. Box plots for parameters related to oxidative and non-oxidative metabolism of paracetamol are shown in Fig. 2. The results of ANOVA for AUC and C_{max} indicated significant subject, treatment, and period effects. There was no significant gender effect for partial clearance or C_{max}, although AUC was 25% greater in females compared to males ($p < .0001$).

For the pharmacokinetic parameters AUC_{0-tn} and $AUC_{0-\infty}$ the 90% confidence limits for the mean ratios for paracetamol/sodium bicarbonate compared to paracetamol in both the fed and fasted states were within the limits of 0.8 to 1.25, indicating that the two formulations were bioequivalent with respect to these parameters. Furthermore, a comparison of the AUC values for each formulation in the fed and fasted state indicated that food had no effect on the extent of paracetamol absorption for either formulation.

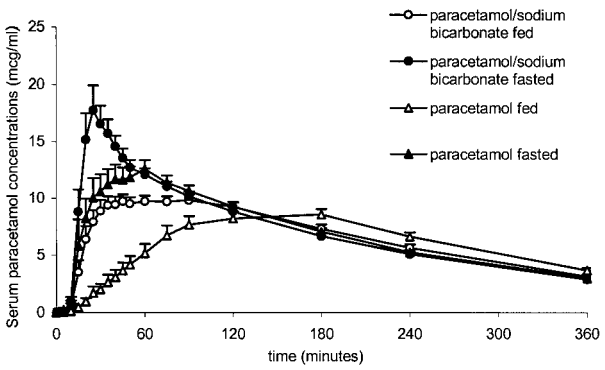

Figure 1. Mean paracetamol serum concentrations for paracetamol/sodium bicarbonate tablets fed, paracetamol/sodium bicarbonate tablets fasted, paracetamol tablets fed, paracetamol tablets fasted.

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Table 1

Summary Statistics for Pharmacokinetic Parameters

	PS Fed	PS Fasted	P Fed	P Fasted
$AUC_{0-\infty}$[a] (μg min/mL)	3284 [800] (1725–5175)	3348 [681] (1951–4685)	3115 [692] (1681–46.81)	3287 [782] (1898–4983)
AUC_{0-tn}[a] (μg min/mL)	3028 [706] (1605–4666)	3166 [645] (1861–4418)	2861 [612] (1593–4297)	3082 [735] (1785–4760)
$T_{1/2}$[a] (min)	175 [22] (144–225)	151 [17] (121–192)	169 [22] (138–234)	160 [18] (134–191)
C_{max}[a] (μg/mL)	13 [4] (5–26)	24 [9] (8–38)	11 [3] (6–16)	18 [10] (8–49)
t_{max}[b] (min)	45 [35] (15–120)	25 [18] (15–90)	120 [47] (35–180)	55 [28] (15–120)
$Cl_{Cys+Mercap}$[a], 0–4 hr (mL/min)	11 [5] (2–23)	10 [3] (6–17)	11 [4] (3–19)	12 [6] (6–33)
$Cl_{Cys+Mercap}$[a], 0–12 hr (mL/min)	22 [7] (11–38)	19 [5] (13–31)	23 [8] (10–44)	20 [8] (13–48)
$Cl_{Glucuronide}$[a], 0–4 hr (mL/min)	90 [9] (30–180)	112 [8] (54–212)	99 [10] (32–265)	112 [8] (58–224)
$Cl_{Glucuronide}$[a], 0–12 hr (mL/min)	150 [12] (47–326)	159 [11] (77–301)	150 [11] (67–302)	161 [12] (86–311)
$Cl_{Sulfate}$[a], 0–4 hr (mL/min)	81 [5] (22–156)	76 [5] (37–133)	78 [6] (0–170)	72 [4] (42–126)
$Cl_{Sulfate}$[a] ,0–12 hr (mL/min)	99 [6] (36–188)	95 [6] (55–167)	101 [6] (48–171)	91 [4] (56–149)

[a]Arithmetic mean [standard deviation] (range).
[b]Median [standard deviation] (range).

Table 2

Relative $AUC_{0-\infty}$, C_{max}, and t_{max} and Their Confidence Intervals

Comparison of Formulations[a]	Mean Ratio $AUC_{0-\infty}$ (90% CI)[b]	Mean Ratio C_{max} (90% CI)[b]	Median Difference t_{max} (min) (90% CI)[b]
PS fasted/P fasted tablets	1.02 (0.99,1.04)	1.3 (1.14,1.48)	−20 (−29,−14)
PS fed/P fed tablets	1.05 (1.02,1.08)	1.16 (1.01,1.33)	−67.5 (−82,−55)
PS fed/PS fasted tablets	0.98 (0.96,1.00)	0.56 (0.50,0.63)	23.5 (9,63)
P fed/P fasted tablets	0.95 (0.92,0.97)	0.64 (0.56,0.73)	75 (55,102)

[a]P = paracetamol, PS = paracetamol/sodium bicarbonate.
[b]CI=confidence interval.

The apparent elimination half-life of paracetamol for paracetamol/sodium bicarbonate tablets was significantly shorter than for paracetamol tablets in the fasted state, but there was no significant difference in the fed state. Food increased the apparent half-life for both formulations.

Paracetamol/sodium bicarbonate tablets had a significantly higher C_{max} than paracetamol tablets in the fasted state but not in the fed state, and food significantly reduced the C_{max} for both formulations. The t_{max} for paracetamol/sodium bicarbonate was significantly shorter compared to paracetamol in both the fed and fasted states, and food significantly increased the t_{max} for both formulations.

With the exception of the paracetamol tablets fed vs. fasted comparison for 0–4 hr, the 90% confidence intervals for partial clearance of oxidation metabolites were within the limits of 0.8 to 1.25, indicating that the two formulations were bioequivalent in this respect. With respect to glucuronide and sulfate metabolites, the two formulations were bioequivalent, although there was a food effect between 0 and 4 hr on partial CL for glucuronide metabolite for both formulations, and between 0 and 4 hr on partial CL of sulfate metabolite for the paracetamol/bicarbonate sodium tablet (Table 3).

DISCUSSION

In an earlier study (6) we demonstrated that paracetamol was absorbed faster from tablets

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Table 3

Relative Partial CL (0–4 and 0–12 hr) to Oxidation Metabolites (Assessed by Subsequent Secondary Metabolism to Cysteine and Mercapturate Conjugates) and Other Main Metabolites Together with Their 90% Confidence Intervals

Comparison of Formulations[a]	Ratio (90% CI)	
	(0–4 hr)	(0–12 hr)
Cysteine and mercapturate conjugates		
PS fasted/P fasted	0.92 (0.81,1.05)	0.97 (0.90,1.05)
PS fed/P fed	1.01 (0.88,1.15)	0.97 (0.90,1.05)
PS fed/PS fasted	0.99 (0.86,1.13)	1.13 (1.05,1.22)
P fed/P fasted	0.90 (0.79,1.03)	1.12 (1.04,1.21)
Glucuronide		
PS fasted/P fasted	1.00 (0.85,1.18)	1.01 (0.92,1.12)
PS fed/P fed	1.04 (0.88,1.22)	1.00 (0.91,1.10)
PS fed/PS fasted	0.83 (0.71,0.98)	0.91 (0.83,1.01)
P fed/P fasted	0.80 (0.68,0.94)	0.92 (0.84,1.02)
Sulfate		
PS fasted/P fasted	0.95 (0.80,1.13)	1.02 (0.87,1.11)
PS fed/P fed	0.99 (0.83,1.19)	1.02 (0.90,1.15)
PS fed/PS fasted	1.08 (0.91,1.30)	1.07 (0.95,1.21)
P fed/P fasted	1.04 (0.87,1.24)	1.03 (0.92,1.17)

[a]P = paracetamol, PS = paracetamol/sodium bicarbonate.

containing sodium bicarbonate 630 mg relative to conventional paracetamol tablets in a panel of 15 fasted volunteers. Results from the present study confirm that in fasted volunteers faster absorption is achieved from tablets containing sodium bicarbonate compared to conventional paracetamol tablets, as demonstrated by a shorter t_{max} and a higher C_{max}. Furthermore, in the fed state, the t_{max} for paracetamol/sodium bicarbonate tablets was significantly shorter than for paracetamol tablets. The C_{max} was also numerically higher for paracetamol/sodium bicarbonate tablets, but failed to reach significance ($p = .0612$). As expected, food slowed down the rate of absorption from both formulations, although the increase in the median value of the t_{max} for paracetamol/sodium bicarbonate tablets was only 20 min, whereas for paracetamol tablets the increase in median t_{max} was 67.5 min.

Previous studies have indicated that following oral administration of paracetamol AUC increases more than proportionately to dose (10,11), and this may be attributable to saturation of the phase II metabolic pathways. If this were the case, then the higher paracetamol plasma levels observed for paracetamol/sodium bicarbonate tablets could produce a transitory saturation of either sulfate or glucuronide metabolic pathways, leading to an increase in oxidative metabolism via cytochrome P450 microsomes, which would result in an increased production of the intermediate toxic metabolite, *N*-acetyl-*p*-benzoquinoneimine, which would be converted to cysteine and mercapturic acid conjugates. However, results from partial metabolic clearances 0–4 or 0–12 hr post-dose show that the two formulations were equivalent with respect to the formation of oxidation metabolites in both the fed and fasted state. These results indicate that the faster rate of absorption seen for paracetamol/sodium bicarbonate tablets has no significant effect on the oxidation metabolic pathway for paracetamol, which is responsible for hepatotoxicity following paracetamol overdose.

At this stage it is not known whether the increase in absorption rate and higher maximum plasma concentrations observed following tablets containing sodium bicarbonate will have any clinically significant effect on the onset of analgesic action or peak analgesic effect. However, Moeller et al. (5) have recently demonstrated a faster onset of analgesic action following effervescent paracetamol tablets compared to standard paracetamol tablets in patients following dental surgery. Furthermore, in

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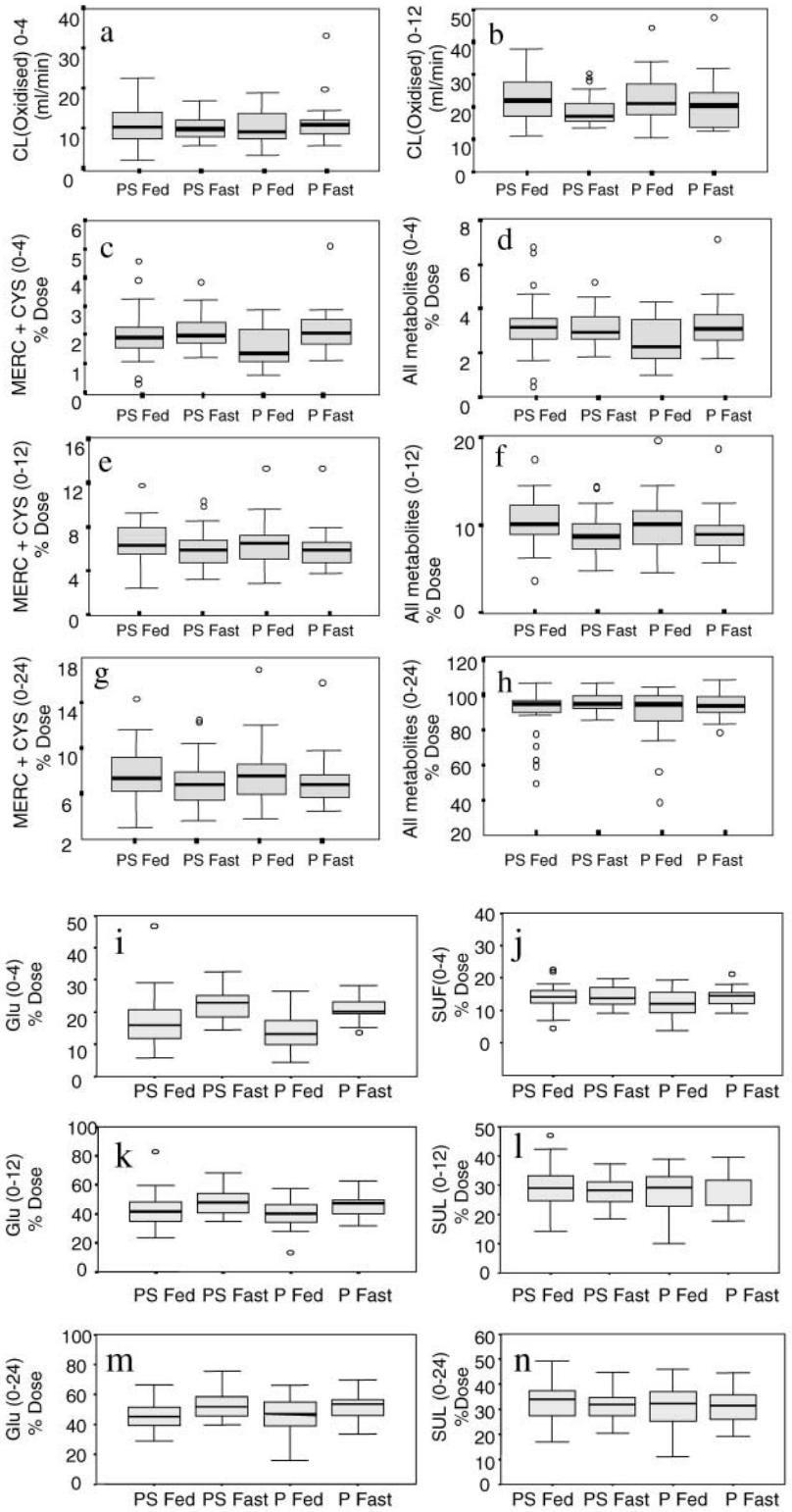

Figure 2. Box plots for parameters related to oxidative and non-oxidative metabolism of paracetamol.

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a previous study (6) we have demonstrated that the rate of drug absorption following paracetamol tablets containing sodium bicarbonate 630 mg is faster than the rate of absorption following administration of conventional paracetamol tablets, and at least as fast as soluble paracetamol tablets. Neilsen et al. (12) compared the analgesic efficacy of two single oral doses of immediate release paracetamol (500 mg and 1000 mg) and sustained release paracetamol (2000 mg) in healthy volunteers, using painful laser stimulation. Both 500 mg and 1000 mg immediate release paracetamol were more effective than placebo from 1 to 5 hr after administration, whereas the 2000 mg sustained release paracetamol was not significantly superior to placebo at any time, despite mean maximum paracetamol plasma concentrations in excess of those obtained for the 500 mg immediate release product. The authors concluded that the rate of increase in plasma concentration may be important in the alleviation of acute (laser-induced) pain. Luthy et al. (13) compared the spinal nociceptive reflex (R-III) and subjective pain assessment following 4 g of paracetamol given as four short infusions every 6 hr, with 4 g of paracetamol given as a continuous infusion over 24 hr in a double blind placebo controlled crossover study using 12 healthy volunteers. Paracetamol when given as a continuous infusion was no more effective than placebo (13), whereas paracetamol administered rapidly produced significant analgesia with a peak effect at 2 hr. The AUCs for paracetamol plasma concentration were similar for both active treatments. The report concludes that only rapid administration of paracetamol produces sufficiently high plasma levels at the peak to induce an effective passage of the drug to the central nervous system and cause a significant analgesic effect. From this brief review of the relevant literature it appears likely that the faster rate of paracetamol absorption from paracetamol/sodium bicarbonate tablets will bring the clinical benefit of a faster onset of analgesic action and possibly a greater peak analgesic effect.

ACKNOWLEDGMENTS

The authors wish to thank P. Bell at the University of Canterbury for the synthesis of paracetamol cysteine and paracetamol mercapturic acid conjugates. *Note*: The paracetamol/sodium bicarbonate formulation in this study is marketed by GSK Consumer Healthcare as Panodil Zapp (Denmark, Sweden) and Panadol Actifast (UK).

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