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Research paper

A five way crossover human volunteer study to compare the pharmacokinetics of paracetamol following oral administration of two commercially available paracetamol tablets and three development tablets containing paracetamol in combination with sodium bicarbonate or calcium carbonate

Tim Grattan[a,*], Rachel Hickman[a], Anne Darby-Dowman[a], Marshall Hayward[b], Malcolm Boyce[c], Steve Warrington[c]

[a]*SmithKline Beecham Consumer Healthcare, Weybridge, Surrey, UK*
[b]*655 Carlene Drive, Bridgewater, NJ, USA*
[c]*Hammersmith Medicines Research, Central Middlesex Hospital, London, UK*

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Abstract

This report concerns a single dose randomized five way crossover study to compare the pharmacokinetics of paracetamol from two commercially available paracetamol (500 mg) tablets and three different development paracetamol (500 mg) tablet formulations containing either sodium bicarbonate (400 mg), sodium bicarbonate (630 mg) or calcium carbonate (375 mg). The results demonstrated that addition of sodium bicarbonate (630 mg) to paracetamol tablets, increased the rate of absorption of paracetamol relative to conventional paracetamol tablets and soluble paracetamol tablets. Addition of sodium bicarbonate (400 mg) to paracetamol tablets increased the absorption rate of paracetamol relative to conventional paracetamol tablets, but there was no difference in the rate of absorption compared to soluble paracetamol tablets. Inclusion of calcium carbonate (375 mg) to paracetamol tablets had no effect on absorption kinetics compared to the conventional paracetamol tablet. The faster absorption observed for the sodium bicarbonate formulations may be as a result of an increase in gastric emptying rate leading to faster transport of paracetamol to the small intestine where absorption takes place.

Keywords: Paracetamol; Sodium bicarbonate; Gastric motility; Pharmacokinetics; Rate of absorption

1. Introduction

Paracetamol is an analgesic and antipyretic drug, effective in relieving mild to moderate pain of a non-visceral origin. In therapeutic doses it is regarded as safe, producing very few therapeutically significant drug interactions [1].

The rate of absorption of paracetamol following oral administration is variable, for example, one previous pharmacokinetic study involving 15 subjects reported a mean t_{max} in plasma of 0.90 h with a standard deviation of 0.51 h following a 1000 mg oral dose [2]. The variability in absorption kinetics could result in a delayed therapeutic effect in some cases. A paracetamol formulation which could increase the overall absorption rate and decrease the variability should have clear advantages over conventional tablets and capsules.

Several different approaches have previously been utilized in an attempt to achieve rapidly absorbed paracetamol solid dose formulations. These include enhancing tablet disintegration rate [3], enhancing drug dissolution rate by utilizing amino acid salts [4] or alkali metal salts [5] of paracetamol and addition of either sorbitol [6] or antacids [7] to paracetamol tablets.

The rate of absorption of paracetamol following oral administration is dependent on gastric emptying rate, with negligible absorption occurring in the stomach whereas absorption in the small intestine is rapid and complete [8]. Inclusion of ingredients that have a prokinetic effect on gastric emptying rate may offer a viable approach to increas-

* Corresponding author. SmithKline Beecham Consumer Healthcare, St Georges Avenue, Weybridge, Surrey, UK. Tel.: +44-1932-822-278; fax: +44-1932-822-326.

E-mail address: tim.j.grattan@sb.com (T. Grattan)

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ing absorption of paracetamol from oral dosage forms. For the purposes of the present study, three different prototype formula containing putative prokinetic agents were produced. The objective of the study was to compare the pharmacokinetics of paracetamol from the three prototype tablets with the two commercially available paracetamol formulations, one of which was a conventional tablet, the other a soluble tablet.

2. Materials and methods

The five formulations evaluated in the study were as follows:

A, paracetamol 500 mg, sodium bicarbonate 630 mg/tablet;
B, paracetamol 500 mg, sodium bicarbonate 400 mg/tablet;
C, paracetamol 500 mg, calcium carbonate 375 mg/tablet;
D, paracetamol 500 mg (Panadol® tablets, batch number T124.6.038, manufactured by SmithKline Beecham Consumer Healthcare, Brentford UK);
E, paracetamol 500 mg, sodium bicarbonate 1342 mg/tablet (Panadol® soluble, batch number NK67, manufacture by SmithKline Beecham Consumer Healthcare, Brentford UK).

Formulation and manufacturing details of formulations A, B and C are given elsewhere [9]. Formulation D and formulation E were both commercially available paracetamol products.

Tablet disintegration and dissolution tests were conducted on the three test formulations A, B and C. Disintegration tests were carried out using the Ph. Eur. method with simulated gastric fluid USP. Dissolution studies were conducted using simulated gastric fluid USP (900 ml) using the USP paddle apparatus with stirrer speed set at 50 rev./min.

Fifteen healthy male non-patient volunteers, were recruited from a panel at Hammersmith Medicines Research Clinical Unit. The volunteers were aged between 18 and 50 years, had a body mass index between 19 and 30. They were non-smokers and had not taken any other medication within 30 days of the start of the study or at any time during the study period. The study was approved by the local ethics committee.

After fasting overnight each volunteer received a two tablet dose of each of the formulations on five separate days according to a randomization schedule based on a five way latin square design balanced for carryover effects [10]. There was a washout period of at least 48 h between each of the doses. On each occasion the tablets were taken with 100 ml of water. In the case of formulation E, the 100 ml of water was used to dissolve the tablets prior to administration. On each study day blood samples were taken via an indwelling cannula pre-dose and then at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75 and 90 min post dose and then at 2, 3, 4, 8, 10 and 12 h post dose. Two hours after dosing the volunteers drank 200 ml of water, and at 4 h post dose they were provided with a standard lunch plus one cup of decaffeinated tea or coffee. After 8 h they were provided with decaffeinated tea or coffee ad lib and an evening meal was provided after 10 h.

Blood samples taken during the study were placed in glass tubes and allowed to stand for 30 min at room temperature prior to centrifugation. Serum was separated from each sample and stored at −20°C prior to analysis.

Paracetamol serum assays were performed using an assay based on liquid/liquid extraction with analysis by HPLC with UV detection. The assay was found to possess the sensitivity and specificity necessary to measure the analyte in serum samples from a clinical pharmacology study.

Serum samples (100 μl), internal standard solution comprising of 4.98 mg of 3-acetaminophenol in methanol 1%/water 99% (100 μl), xris(hydroxymethyl)methylamine (100 μl, 2 M) and ethyl acetate (2 ml) were mixed in a polypropylene tube and then centrifuged at 3500 rev./min for 5 min. The solvent layer was separated and then evaporated to dryness at 60°C and the residue was then redissolved in 500 μl of acetonitrile (5%)/water (95%).

Solvent delivery was achieved using a Shimadzu LC 10AS pump. Sample injection was performed by using a BioRad AS-100 auto injector operated at 10°C and fitted with a 200 μl sample loop. Chromatography was on a 150 × 4.6 mm i.d. Spherisorb ODS2 column. Detection was by UV at 245 nm using a Jasco UVIDEC-100-V detector. The mobile phase consisted of acetonitrile 50 ml, water 950ml containing 0.1%, phosphoric acid (85%) and the flow rate was set at 1 ml/min. The limit of reliable determination was defined as 0.1 μg/ml; values below this value were reported as zero.

The pharmacokinetic analysis was carried out using PCmodfit published by ARTPAC. Area under the concentration time curves from dosing (0) to the time point (tn) of the last non-zero value (AUC_{0-tn}) were calculated by the trapezoidal method. The linear trapezoidal method was used up to the time of the maximum plasma drug concentration (t_{max}) and the logarithmic trapezoidal method was used on the declining serum concentrations from the maximum serum concentration C_{max}. 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 ($t_{1/2}$) were calculated from non-linear regression of the terminal portion of the serum concentration time curve.

Values for t_{max} were compared using the Wilcoxon signed ranks test. AUC_{0-tn}, $AUC_{0-\infty}$ and C_{max} were logarithmically transformed prior to statistical analysis by analysis of variance (ANOVA) taking into account sources of variation due to formulation, subject and study session. The residual variances were used to calculate 90% confidence intervals

for the difference in formulation means on the log scale. These were then back transformed to give point estimates and confidence intervals for the ratios of the three test formulations (A, B and C) to each of the reference formulations (D and E). Untransformed values for the area under the concentration time curve from dosing – 0–20 min (AUC_{0-20}) – and $t_{1/2}$ were analyzed by a similar ANOVA model. The residual variances were used to calculate the significance of differences between formulation means. The 5% level was used for significance testing.

3. Results

The disintegration times for formulations A, B and C were all under 2 min and the dissolution tests demonstrated that all three test formulations complied with the USP with >98% paracetamol dissolved within 30 min.

The pharmacokinetic parameters derived for each of the treatments are shown in Table 1. Point estimates and 90% confidence intervals for $AUC_{0-\infty}$ and C_{max} are shown in Table 2. ANOVA results are shown in Table 3. Mean paracetamol serum concentrations *vs* time for the first 90 min following dosing are shown in Fig. 1. Mean paracetamol serum concentrations with standard errors *vs* time for formulations A and E are shown in Fig. 2.

For the pharmacokinetic parameters AUC_{0-tn} and $AUC_{0-\infty}$ the 90% confidence limits for the mean ratios of each of the three test formulations, A, B and C relative to the two reference formulations D and E, were all within the limits of 0.8–1.25 indicating that formulations A, B and C were bioequivalent to the two control formulations D and E with respect to these parameters. For $t_{1/2}$, there were no statistically significant differences between the three test formulations (A, B and C) and the two controls (D and E).

For C_{max} none of the mean ratios and 90% confidence limits for each of the test formulations A, B and C relative to D and E were within the bioequivalence limits of 0.8–1.25 and with the exception of C relative to D, none were within the wider limits of 0.7–1.43 sometimes used for C_{max}, furthermore, there were significant differences between formulation A and formulation D ($P < 0.002$), formulation A and formulation E ($P < 0.02$) and formulation B and formulation D ($P < 0.02$).

For t_{max} there were significant differences between formulation A and formulation D ($P < 0.01$) and between formulation C and formulation E ($P < 0.02$).

For AUC_{0-20}, the only comparisons conducted were between formulation B and D which were significantly different ($P < 0.01$), D and E which were significantly different ($P < 0.005$) and between A and E where there was no significant difference.

All five treatments were well tolerated. Three subjects reported adverse events, none of these were considered related to the study medication and none were serious.

4. Discussion

Results from the pharmacokinetic analysis clearly show that addition of sodium bicarbonate (630 mg) to paracetamol tablets significantly increased the rate of absorption of paracetamol compared to a conventional tablet as indicated by a shorter t_{max} and higher C_{max} for formulation A compared to formulation D, furthermore the variability in the rate of absorption was reduced as indicated by a lower

Table 1
Paracetamol pharmacokinetic parameters

	Formulation A	Formulation B	Formulation C	Formulation D	Formulation E
AUC_{0-tn}	2647	2691	2545	2477	2540
(μg.min/ml)[a]	[478]	[521]	[521]	[458]	[507]
	(18.04%)	(19.37%)	(20.48%)	(18.52%)	(19.96%)
$AUC_{0-\infty}$	2762	2819	2677	2602	2661
(μg.min/ml)[a]	[522]	[568]	[570]	[503]	[564]
	(18.91%)	(20.15%)	(21.31%)	(19.33%)	(21.19%)
$t_{1/2}$ (min)[a]	158	162	161	159	160
	[14]	[16]	[17]	[16]	[18]
	(8.84%)	(10.22%)	(10.85%)	(9.96%)	(11.57%)
C_{max} (μg/ml)[a]	29.79	26.12	15.37	17.02	19.94
	[9.06]	[10.68]	[5.66]	[6.40]	[6.85]
	(30.42%)	(40.88%)	(36.82%)	(37.58%)	(34.35%)
t_{max} (min)[b]	17.5	22.5 35.33	43.75 47.33	35 45.00	20 24.00
	17.67	[32.37]	[32.34]	[42.84]	[16.17]
	[4.95]	(91.62%)	(68.33%)	(95.21%)	(67.37%)
	(28.03%)				
AUC_{0-20}	245	177	76	70	199
(μg.min/ml)[a]	[132]	[148]	[83]	[60]	[136]
	(53.6%)	(83.7%)	(109.8%)	(85.9%)	(68.1%)

[a] Arithmetic mean [standard deviation] (coefficient of variation).
[b] Median, arithmetic mean [standard deviation] (coefficient of variation).

Table 2
Point estimates and 90% confidence intervals and significance for $AUC_{0-\infty}$, C_{max} and t_{max}[a]

New/reference formulation	Mean ratio $AUC_{0-\infty}$	Mean ratio C_{max}	Median difference t_{max}
A:D	1.05 (0.99–1.11) ns	1.75 (1.32–2.31) $P < 0.002$	−18.7 (−37.5–−5) $P < 0.01$
A:E	1.05 (1.00–1.11) ns	1.43 (1.13–1.82) $P < 0.02$	−2.5 (−15–0) ns
B:D	1.06 (1.01–1.11) ns	1.46 (1.15–1.85) $P < 0.02$	−7.5 (−20–2.5) ns
B:E	1.07 (1.01–1.12) $P < 0.05$	1.19 (0.94–1.52) ns	5.0 (0–27.5) ns
C:D	1.03 (0.98–1.09) ns	0.90 (0.71–1.15) ns	3.8 (−17.5–25.0) ns
C:E	1.04 (0.98–1.11) ns	0.74 (0.56–0.98) ns	21.2 (10–35) $P < 0.02$

[a] ns, not significant ($P > 0.05$).

standard deviation and coefficient of variation (CV) for t_{max} with formulation A (CV 28.03%) compared to formulation D (CV 95.21%). Addition of sodium bicarbonate (400 mg) appeared to have a modest effect on the rate of paracetamol absorption, the C_{max} for formulation B was significantly higher than for formulation D and although t_{max} was numerically lower the difference was not significant, furthermore the variability in the rate of paracetamol absorption from formulation B was comparable to formulation D, the CVs for t_{max} were 91.62 and 95.21%, respectively. A comparison of results obtained for formulation C and formulation D showed that inclusion of calcium carbonate had no effect on variability or rate of paracetamol absorption.

The faster rate of paracetamol absorption observed for formulation A and B compared to formulation D was probably as a result of an increase in gastric emptying rate, although other factors such as increased in vivo dissolution rate may have made a contribution. The effect of various solutes including sodium bicarbonate on gastric emptying rate has been extensively studied by Hunt [11] who investigated the effects of liquid meals containing various levels of sodium bicarbonate and other solutes on gastric emptying rate in healthy volunteers. Gastric emptying rate increased with increasing concentrations of sodium bicarbonate up to a maximum which occurred with solutions which were approximately isotonic (i.e. 150 mM), further increases in concentration resulted in subsequent decreases in gastric emptying rate, hypertonic solutions (250–500 mM) appeared to inhibit gastric emptying in a dose dependent manner. The results from the present study clearly indicate that paracetamol was absorbed faster from formulation A than from formulation D, as indicated by a shorter t_{max} and a higher C_{max}. Paracetamol was also absorbed faster from formulation B compared to formulation D, as indicated by a significantly higher C_{max} and AUC_{0-20}, although there was no significant difference in t_{max} and numerical values for C_{max} and AUC_{0-20} were lower than those observed for formulation A. These results suggest that the effect of sodium bicarbonate on paracetamol absorption rate may possibly be dose dependent. The level of sodium bicarbonate selected for formula A was 630 mg (7.5 mmol)/tablet, therefore two tablets dissolved in 100 ml of water should produce a 150 mM solution. This is approximately the same concentration that has previously been shown to have a maximal effect on gastric emptying rate [11].

One remarkable observation, was the significantly higher C_{max} observed for formulation A compared to formulation E (the soluble paracetamol formulation), which suggests that the faster absorption rate seen for formulation A was not dissolution rate related. One possible explanation for the observed difference is that the soluble paracetamol formulation used in this study contained 1342 mg of sodium bicarbonate/tablet, which is more than double the amount used in formulation A. Two soluble tablets dissolved in 100 ml of water result in a solution that is approximately 300 mM with respect to sodium bicarbonate. At this concentration sodium bicarbonate may have a reduced effect on gastric motility compared to an isotonic solution [11]. Another contributing factor to the slower absorption observed for the soluble tablets could be the citric acid used in the formulation (925 mg/tablet). Citric acid has been shown to retard gastric

Table 3
ANOVA tables for $AUC_{0-\infty}$ and C_{max}

Source of variation	Mean square $AUC_{0-\infty}$	Mean square C_{max}
Subject	0.1670 ($F = 34.49$)	0.3896 ($F = 3.58$)
Period	0.0044 ($F = 0.90$)	0.0247 ($F = 0.23$)
Treatment	0.0107 ($F = 2.20$)	0.7594 ($F = 6.98$)
Carryover	0.0032 ($F = 0.67$)	0.0753 ($F = 0.69$)
Error	0.0048	0.1087

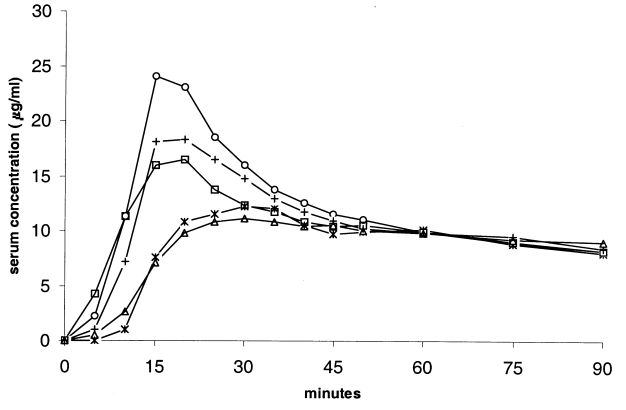

Fig. 1. Mean paracetamol serum concentrations for formulation A (○), formulation B (+), formulation C (△), formulation D (*) and formulation E (□).

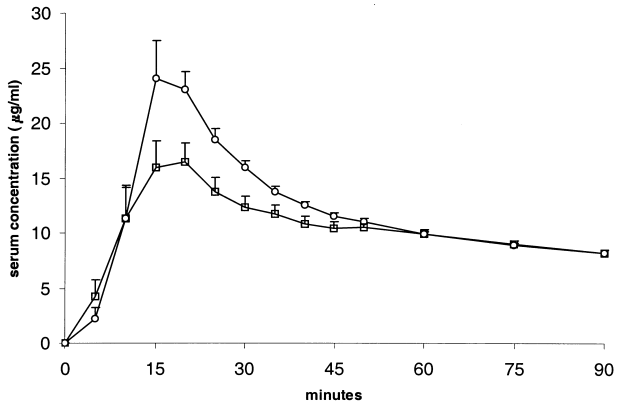

Fig. 2. Mean paracetamol serum concentrations for formulation A (○), formulation E (□). Error bars represent standard error.

emptying [12] and this may partially negate the prokinetic effect of the sodium bicarbonate.

A previous report has suggested that co-administration of any antacid, such as calcium carbonate, with paracetamol may increase the rate of absorption of paracetamol [7]. Results from this study show that calcium carbonate has no effects on paracetamol pharmacokinetics as there were no significant differences between formulation C and formulation D for any of the pharmacokinetic parameters measured. This suggests that the increase in rate of paracetamol absorption seen with sodium bicarbonate is not a general property of all antacids, and sodium bicarbonate may possibly be unique in this respect.

It is possible that the faster absorption seen for the sodium bicarbonate formulations in this study may in part be due to some effects other than induced gastric emptying, for example, an increased in vivo dissolution rate. However, all three test tablets used in this study had a disintegration time of under 2 min, and complied with the EP and USP monographs for tablet dissolution. (i.e. $>$ 90% dissolved after 30 min). Another contributing factor to the faster paracetamol absorption seen for the sodium bicarbonate formulations could be due to a change in the non-ionized/ionized ratio of paracetamol in the stomach lumen which could effect the permeability of paracetamol with respect to the gastric mucous or gastrointestinal epithelium. The pH of a 100 mM solution of sodium bicarbonate has been reported as 8.3 [13] and it is unlikely the pH of the stomach contents following a two tablet dose of formulation A will exceed this value given the dilution and neutralization effect from gastric fluid. Assuming a value of 9.5 for the pKa of paracetamol [14], no more than 6% of the drug should be in the ionized form within the stomach lumen following a two tablet dose of formulation A. Under the acidic conditions normally encountered in the stomach, the degree of ionization of paracetamol following a two tablet dose of formulation D is likely to be negligible. Further work is ongoing to establish whether an increase in degree of ionisation of paracetamol contributes to the faster absorption seen with formulation A.

Recent reports [15,16] have suggested that the increased drug absorption rates observed due to in vivo carbonation may be as a result of an alteration in permeability of gastrointestinal tract epithelium or an alteration of the permeability of gastrointestinal mucus. However, neither of these mechanisms can adequately explain the enhanced speed of absorption seen for formulations A and B, as there was no increase in paracetamol absorption observed when administered with calcium carbonate which also provides a source for in vivo carbonation in the acidic environment of the stomach.

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