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RESEARCH ARTICLE

A new rapidly absorbed paediatric paracetamol suspension. A six-way crossover pharmacokinetic study comparing the rate and extent of paracetamol absorption from a new paracetamol suspension with two marketed paediatric formulations

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Abstract

The objective of this study was to compare the rate and extent of paracetamol absorption from the new Paracetamol pediatric suspension (PPS) with two marketed paracetamol suspensions: Children's panadol (CP) and Panodil baby & infant (PBI). The study also assessed the effect on paracetamol absorption of light-calorie, low-fat food consumed 2 h before dosing. Twenty eight male adult volunteers received a single oral dose of 1000 mg of paracetamol from each of three treatments, in both fasted and fed states according to a randomized, single-center, open-label, six-way crossover study design. PPS was bioequivalent to both CP and PBI for $AUC_{0-10\ h}$, AUC_{0-inf} and C_{max} in both fasted and fed state. However, PPS had greater rate of paracetamol absorption and a faster speed of onset. T_{max} for PPS was significantly shorter than for PBI in both fasted ($p = 0.0005$) and fed state ($p = 0.0001$). Median T_{max} for PPS was also 10 min shorter than CP in fasted state. Time to reach minimum effective concentration (MEC) for PPS was significantly shorter than CP and PBI. Early paracetamol exposure of PPS was significantly higher than that of the two existing paracetamol products. Food had a significant effect in the early exposure and onset of therapeutic level of paracetamol from PPS. $AUC_{0-30\ min}$ was significantly higher and time to reach plasma paracetamol at MEC level was significantly shorter than in the fasted state.

Keywords: Paracetamol pediatric suspensions, rate of absorption, minimum effective concentration, bioequivalence, early paracetamol exposure

Introduction

Paracetamol, otherwise known as acetaminophen, is an over-the-counter (OTC) drug for pain relief and fever reduction. Fever and pain in children, especially associated with infections, are very common. Although fever is only a symptom of other illness, an elevated body temperature is associated with discomfort, increased risk of dehydration and seizures. Parental concern over these effects leads to fever being one of the most commonly treated pediatric conditions. Fever is treated with OTC antipyretic drugs such as ibuprofen and paracetamol. Widespread use of paracetamol has shown that it is effective in the reduction of pediatric fever and pain[1–5]. The safety of short-term use of paracetamol is well established in the pediatric population[2–6]. Paracetamol is recommended for use in babies and children aged 1–12 years old for up to 3 days without medical advice[7], The common single dose for children is 10–15 mg/kg

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body weight[8,9] and for adult is 500–1000 mg, with a recommended maximum daily dose of 4000 mg or 60 mg/kg body weight. The World Health Organization (WHO) recommends that paracetamol be given to children with fever higher than 38.5°C (101.3°F)[5,9,10]. Paracetamol, the active ingredient in children's panadol (CP) and panodil baby & infant (PBI) suspensions, is a first-line antipyretic choice because of its proven safety and efficacy profile. Availability of the medication in liquid formulation makes it easy to administer in children and promotes compliance. Although existing pediatric paracetamol suspensions provide antipyretic effect, there is still the need for faster acting products for children. A faster onset time of therapeutic effect would be more beneficial for the pediatric population providing a quicker relief especially in febrile children. The new Paracetamol pediatric suspension (PPS) has been designed to be absorbed more rapidly than existing paracetamol suspension products while maintaining or improving other pharmacokinetic (PK) properties with regard to extent of paracetamol absorption. Two pilot studies conducted previously showed that combination of paracetamol suspension with sorbitol, maltitol, and carbopol in the PPS provided faster absorption and superior PK properties than existing paracetamol liquid formulations[11].

This study was conducted to compare rate of absorption, early onset and exposure and extent of paracetamol absorption of the new PPS (24 mg/mL) with two marketed paracetamol suspensions (CP and PBI) in fasted and fed state. In addition, the study assessed the effect of low-calorie, low-fat food on exposure and extent of paracetamol absorption from PPS and the two marketed paracetamol suspensions and determined the safety and tolerability of all three formulations. Please check the edit in the sentence "In addition, the study…".

Subjects and methods

Study participants

Eligible subjects were healthy volunteers, aged 18–55 years old, non-vegetarian, non-smokers, with a body mass index (BMI) of 18.5–24.9 kg/m^2. Participants were excluded if they had recurrent disease that could have affected the action, absorption or disposition of the study medication or clinical or laboratory assessments, or any other illness likely to prevent completion of the study. No blood donations were allowed within 3 months of the screening visit. Subjects could not take any medications within 14 days of the start of the study or regularly use any drugs known to induce or inhibit hepatic drug metabolism within 30 days prior to study dosing. This study was conducted under the guidance of good clinical practice[12] at one site in Northern Ireland in June–July 2008. All subjects provided written consent according to the declaration of Helsinki[13].

Study design

This was a pivotal, single-center, single-dose, open-label, randomized, six-way crossover, PK study. Subjects were screened for eligibility within 15 days prior to dosing. Subjects received each of the three study treatments in both fasted and fed states in a randomized order (according to a computer generated randomization schedule) during a 7 day/6 night residential period at the study site. There was a 24 h washout period between each dose. Paracetamol has a mean plasma half-life of about 2.3 h[7]. Considering that the recommended washout period between dosing arms need to be at least 10 half-lives, a washout period of 24 h between doses is therefore sufficient. Blood sampling took place pre-dose, and at various time points from 10 min to 10 h post-dose.

All subjects fasted overnight from midnight prior to each dosing day. In the fed state, subjects were given a light-calorie, low-fat breakfast 2.5 h prior to dosing that had to be consumed within 30 min. Under these conditions it is likely that the stomach will be in transition between fed and fasted states, described also as 'semi-fed' state[14]. According to the regulatory agencies,[15–16] this is not a complete 'fed' state. However, this phase was chosen primarily for a better differentiation of products. Previous studies[11,17,18,19] show that paracetamol products can differentiate better in feeding state 2.5 h after starting of the meal than in the fed state (0.5 h after starting of the meal). Also, this feeding state was aimed to mimic as much as possible the common actual use of products.

All study treatments were performed in the morning. No fluids were consumed 2 h before or after dosing. No food was consumed for 4 h after dosing. Subjects were only allowed to eat standard meals and have drinks supplied by the study site.

The study products were supplied by the Clinical Supply Department, GlaxoSmithKline Consumer Healthcare. The test product was New PPS (24 mg/mL paracetamol), Batch No. GSK5594B011 manufactured according to Good Manufacturing Practice (GMP). The reference products were Children's Panadol® 1–5 Years color free suspension (24 mg/mL paracetamol) sourced from Ermington, Australia, Batch No. 111858 and Panodil® Baby & Infant Paracetamol Oral Suspension (24 mg/mL paracetamol) sourced from Herouville, France, Batch No. 7012 and manufactured according to GMP. All three study formulations contained 24 mg/mL of paracetamol, therefore a dose of 42 mL was approximately equivalent to 1000 mg paracetamol. Subjects received a single 42 mL oral dose (1008 mg paracetamol) of one of the study treatments per dosing day. The study formulations were administered at the appropriate volume orally via an oral dosing syringe by a physician or an appropriate member of the study site staff. Subjects had to remain in an upright position for 2 h post-dose.

Blood samples were taken 1 h prior to administration of the drug and then every 10 min following administration for the first hour, then at 75, 90 and 120 min and hourly thereafter for up to 10 h. Periodic 2-hourly checks were conducted to measure safety (physical examination, electrocardiogram, vital signs, clinical laboratory assessments, and adverse events (AE) questioning).

Plasma samples were analyzed by MDS Pharma Services Switzerland AG. Concentrations of paracetamol in plasma samples were determined by validated liquid chromatography mass spectrometry (LC-MS) methods.

Statistical methods

Sample size

A total of 28 subjects were planned to be randomized in order to reach a target of 24 subjects completing all six arms of the study. This sample size was considered sufficient to provide adequate information for bioequivalence and other analysis in compliance with the Committee for Proprietary Medicinal Products[20,21].

PK endpoints

The primary variables were area under the plasma concentration time curve from 0 to 10 h ($AUC_{0\text{–}10\ h}$), area under the plasma concentration time curve from 0 and extrapolated to infinity ($AUC_{0\text{–}inf}$) and maximum plasma concentration (C_{max}). These parameters were used to assess bioequivalence between PPS and the two marketed paracetamol suspensions[20,22]. To prove bioequivalence in each feeding state, confirm European Regulatory requirements, analysis were performed separately in fasted and fed state[21].

Secondary PK endpoints included: time to reach maximum plasma paracetamol concentration (T_{max}), time to reach plasma paracetamol concentration equal or greater than 4 μg/mL ($T_{c\geq 4\ \mu g/mL}$) and area under the plasma paracetamol concentration versus time curve from 0 to 30 min ($AUC_{0\text{–}30\ min}$) and from 0 to 60 min ($AUC_{0\text{–}60\ min}$). In addition to T_{max} that measures the overall rate of paracetamol absorption, $T_{c\geq 4\ \mu g/mL}$ was used to measure speed of onset as the level of 4 μg/mL is considered to be the minimum effective concentration (MEC) for therapeutic effect of paracetamol. In addition, $AUC_{0\text{–}30\ min}$ and $AUC_{0\text{–}60\ min}$ were used to assess the rate of early paracetamol exposure and bring additional evidence on early speed of paracetamol absorption. The PK endpoints measuring extent of paracetamol absorption were derived from plasma paracetamol concentration and elapsed time data using the non-compartmental model of analysis in WinNonlin v. 4.0[23]. Time parameters, i.e. $T_{c\geq 4\ \mu g/mL}$ and T_{max} were calculated directly from observed plasma paracetamol concentration.

Analyses were performed on the intent-to-treat (ITT) population. The ITT population included all subjects that received at least one treatment in at least one feeding state. $AUC_{0\text{–}inf}$, $AUC_{0\text{–}10\ h}$, and C_{max} were log-transformed (natural log) and analyzed based on a linear mixed-effects model using PROC MIXED of SAS v. 8.2[24]. Treatment and period were included in the model as fixed effects while subjects as random effect. Treatment comparisons for bioequivalence were done *post-hoc*. The residual variance from the model was used to construct 90% confidence intervals of differences between least square (LS) means of treatments. Differences between LS means were back-transformed to obtain point estimates (ratios) and confidence intervals. Bioequivalence was accepted if the 90% confidence interval ($p = 0.1$) for the treatment LS mean ratio was within the range 0.80–1.25[20,21]. Food effect on primary variables was based on the same model as for bioequivalence except that all treatments in both fasted and fed states were included in the analysis. Overall food effect (all treatments in fasted state vs. all treatments in the fed state) and food effect for each treatment were calculated *post-hoc* by performing appropriate multiple comparisons at 5% significance level. $AUC_{0\text{–}30\ min}$ and $AUC_{0\text{–}60\ min}$ did not satisfy the normality assumption of analysis of variance (Shapiro–Wilk's normality test was significant at $p < 0.01$). Therefore, these parameters were analyzed non-parametrically, using Proc Univariate of SAS v.8.2[24] with Wilcoxon signed rank test[25] for median of differences between treatments across subjects. Similarly T_{max} assessed by median time, was analyzed the same way using Wilcoxon signed rank test. Similar to primary endpoints, analyses of the secondary endpoints were performed separately for each feeding state. $T_{c\geq 4\ \mu g/mL}$ was analysed with a two-sided *t*-test for the mean of differences between treatments across subjects (testing if mean of differences was greater than zero). Analysis for this variable was conducted *post-hoc* and for fed state only. Testing on all secondary endpoints was done at 5% significance level.

Analyses for food effect on secondary endpoints were performed in a similar way as for formulation effects by testing median of differences (fast–fed) for each formulation separately at 5% significance level.

Assessment of safety was based on the number of AEs reported by all subjects following dosing with the study treatments. Safety population included all subjects who received treatment regardless of whether they were included in the PK analyses. AEs were summarized by treatment group and coded using MedDRA Version 11.0[26].

Results

Subjects

Of the 88 subjects screened, 28 were randomized and 26 completed successfully all study treatments. There were 2 dropouts, one because of an AE (contusion in both elbows that was not related to the study treatments) and the other one withdrew the informed consent. Two periods (PPS in the fasted state and CP in the fed state) were completed by all 28 subjects; three periods (CP in the fasted state and PBI in the fasted and fed states) were completed by 27 subjects; one period (PPS in the fed state) was completed by 26 subjects. Although there were slight changes in the number of subjects from period to period, the total number of subjects in any period was higher than the required sample size of 24 subjects, providing sufficient statistical power for each treatment comparison. All 28 subjects were included in the analyses of demographics, PK variables and safety. All of the

Table 1. Summary statistics for pharmacokinetic parameters.

PK parameter	PPS fasted	PPS fed	CP fasted	CP fed	PBI fasted	PBI fed
$AUC_{0\text{-}30\ min}$ (μg·hr/mL)[1]	1.75 (0.93)	2.78 (1.39)	1.67 (1.57)	2.00 (1.35)	1.30 (0.97)	1.37 (1.14)
$AUC_{0\text{-}60\ min}$ (μg·hr/mL)[1]	6.62 (2.21)	8.06 (2.69)	6.05 (2.75)	7.10 (2.51)	4.86 (2.43)	5.76 (2.44)
$AUC_{0\text{-}10\ h}$ (μg·hr/mL)[2]	47.0 (8.34)	45.7 (7.73)	45.9 (7.74)	43.9 (8.09)	45.5 (8.55)	44.4 (8.44)
$AUC_{0\text{-}inf}$ (μg·hr/mL)[2]	51.7 (10.2)	50.2 (9.34)	50.6 (9.50)	48.6 (10.0)	50.3 (10.3)	49.1 (10.4)
C_{max} (μg/mL)[2]	12.2 (2.28)	11.5 (1.93)	13.3 (2.19)	11.4 (2.00)	11.0 (2.23)	11.0 (2.23)
T_{max} (h)[1]	0.86 (0.49)	0.78 (0.46)	1.00 (0.40)	0.84 (0.59)	1.28 (0.66)	1.25 (0.68)

[1]Median (SD).
[2]Mean (Standard deviation).
CP, children's panadol; PBI, panodil baby & infant; PK, pharmacokinetic properties; PPS, paracetamol pediatric suspension.

Table 2. Bioequivalence and food effect for $AUC_{0\text{-}10}$, $AUC_{0\text{-}inf}$ and C_{max}.

	Mean ratio[1] (Confidence intervals or *p* values)[2]		
Comparison	$AUC_{0\text{-}10\ h}$	$AUC_{0\text{-}inf}$	C_{max}
Bioequivalence comparisons			
PPS fasted/CP fasted	1.04 (1.02, 1.06)	1.04 (1.02, 1.05)	1.01 (0.95, 1.06)
PPS fed/CP fed	1.04 (1.02, 1.06)	1.03 (1.01, 1.06)	1.02 (0.97, 1.08)
PPS fasted/PBI fasted	1.05 (1.03, 1.07)	1.05 (1.03, 1.06)	1.12 (1.06, 1.18)
PPS fed/PBI fed	1.04 (1.02, 1.07)	1.04 (1.01, 1.06)	1.06 (1.01, 1.12)
Food effect			
Overall (fasted vs. fed)	1.09 (0.0001)	1.09 (0.0004)	1.14 (0.0416)
PPS fasted/PPS fed	1.03 (0.0150)	1.03 (0.0137)	1.06 (0.1197)
CP fasted/CP fed	1.03 (0.0110)	1.03 (0.0364)	1.07 (0.0545)
PBI fasted/PBI fed	1.02 (0.0606)	1.02 (0.0899)	1.0 (0.9529)

[1]Ratio is the exponentiated difference between least square means of log-transformed variables.
[2]90% confidence intervals were used to test for bioequivalence, whereas *p* values based on a 5% level t-test were used for food effect.
CP, children's panadol; PBI, panodil baby & infant; PPS, paracetamol pediatric suspension.

Table 3. Effect of formulation and food on T_{max}, $AUC_{0\text{-}30}$, $AUC_{0\text{-}60}$.

	Median difference[1] (*p* value)		
Comparison	T_{max}	$AUC_{0\text{-}30}$	$AUC_{0\text{-}60}$
Formulation comparison			
PPS fasted vs. CP fasted	−0.17 (0.4668)	−0.17 (0.3340)	−0.18 (0.6909)
PPS fed vs. CP fed	−0.01 (0.1403)	0.50 (0.0078)	1.16 (0.0332)
PPS fasted vs. PBI fasted	−0.34 (0.0005)	0.68 (0.1202)	1.75 (0.0088)
PPS fed vs. PBI fed	−0.50 (0.0001)	1.07 (0.0001)	2.35 (0.0001)
Food effect			
PPS fasted vs. PPS fed	0.17 (0.2265)	−0.84 (0.0021)	−0.89 (0.0816)
CP fasted vs. CP fed	0.17 (0.7972)	−0.31 (0.7258)	−0.25 (0.7258)
PBI fasted vs. PBI fed	−0.002 (0.6398)	−0.13 (0.4668)	−0.04 (0.7435)

[1]Median of differences between treatments across subjects.
[2]*p* value associated with Wilcoxon test for median difference (H_0: Median difference = 0)[25].
CP, children's panadol PBI, panodil baby & infant; PPS, paracetamol pediatric suspension.

28 subjects were Caucasian males with a mean age of 22.6 years (range: 18–39 years) and mean BMI of 22.5 kg/m^2 (range: 18.6–24.3 kg/m^2).

PK analyses

Summary statistics for the PK parameters of each of the treatments are shown in Table 1. A summary of results for the bioequivalence analyses of PPS with CP and PBI is given in Table 2. In both fasted and fed states, the exposure of paracetamol for PPS was bioequivalent to both CP and PBI for $AUC_{0\text{-}10\ h}$, $AUC_{0\text{-}inf}$ and C_{max} with the 90% CIs all being within the range 0.80–1.25.

Results of statistical analysis for T_{max}, $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}60\ min}$ in both fasted and fed states are given in Table 3 and results of analysis for time to reach MEC for the fed state are given in Table 4. The rate of paracetamol absorption as measured by T_{max} was greater for PPS as compared to the two existing products. T_{max} for PPS was significantly shorter than for PBI in both fasted ($p = 0.0005$, 20 min shorter) and fed state ($p = 0.0001$, 30 min shorter). Also, T_{max} for PPS was 10 min shorter than that for CP in the fasted state, although this difference was not significant. Besides a higher rate of paracetamol absorption, PPS had a faster speed of onset, i.e. time to reach MEC. PPS was

significantly faster than the other two reference products in reaching MEC or minimum therapeutic level. The mean time to reach plasma paracetamol concentration 4 μg/mL was 17% shorter for PPS as compared to CP ($p = 0.0385$) and 35% shorter as compared to PBI ($p = 0.0012$). When taking PPS in the fed state, 50% of subjects reached this therapeutic level in 10 min or less, as compared to 32% and 7% of subjects when taking CP and PBI, respectively (Table 4). Early paracetamol exposure of PPS was also significantly higher than that of the two existing paracetamol products. In the fasted state, PPS had a significantly greater early exposure for $AUC_{0-60\ min}$ than PBI, only ($p = 0.0088$). In the fed state, PPS had a significantly greater early exposure for $AUC_{0-30\ min}$ and $AUC_{0-60\ min}$ compared to both CP and PBI. A graphical presentation of mean plasma paracetamol concentration by treatment for the first 2 h is given in Figure 1 for fasted state and Figure 2 for fed state. Both of these graphs illustrate a higher rate of early paracetamol exposure for PPS in the first 60 min after treatment, especially in the fed state.

Table 4. Time to reach plasma paracetamol concentration 4 μg/mL ($T_{c\geq 4\ \mu g/mL}$) in fed state.

Comparison	PPS	CP	PBI
$T_{c\geq 4\ \mu g/mL}$ (min): mean (SD)	19.0 (14.0)	23.0 (14)	29.0 (19.0)
Percent of subjects reaching C≥4 μg/mL in 10 min	50	32	7

Formulation comparison	Mean difference	p value[1]
PPS fed vs. CP fed	−4.0	0.0385
PPS fed vs. PBI fed	−10.0	0.0012
PPS fasted vs. PPS fed	−10.0	0.0501

[1]p value from t-test (H_0: Mean difference = 0).
CP, children's panadol PBI, panodil baby & infant; PPS, paracetamol pediatric suspension.

Light-calorie, low-fat food consumed 2 h before dosing had an overall significant effect on each of the primary PK variables: $AUC_{0-10\ h}$ ($p = 0.0001$), AUC_{0-inf} ($p = 0.0004$) and C_{max} ($p = 0.0416$) (Table 2). Food slowed down the overall extent of paracetamol absorption. Values of all of these parameters were significantly higher in the fasted state as compared to fed state. At the product level, food had a significant effect on PPS and CP for $AUC_{0-10\ h}$ and AUC_{0-inf}, only. With regard to early paracetamol exposure, food had a significant effect on AUC_{0-30} of PPS. In the fed state, AUC_{0-30} was significantly higher than that in fasted state ($p = 0.0021$, Table 3). Also speed of onset increased significantly from fasted to fed state. Time to reach plasma paracetamol concentration at minimal therapeutic level was 10 min shorter in the fed state as compared to fasted state for PPS (Table 4). In contrast, food did not have any significant effect on early paracetamol exposure from the two reference products.

Safety

Safety population included 28 subjects. A total of seven AEs were reported in the study. Out of seven subjects with AEs, one withdrew from the study due to contusion. All of the AEs observed were mild or moderate in intensity and none of them were treatment-related.

Discussion

The new PPS was bioequivalent to CP and PBI suspensions in both fasted and fed states for all three PK parameters AUC_{0-10}, AUC_{0-inf} and C_{max}. PPS had a higher rate of paracetamol concentration as measured by T_{max} given

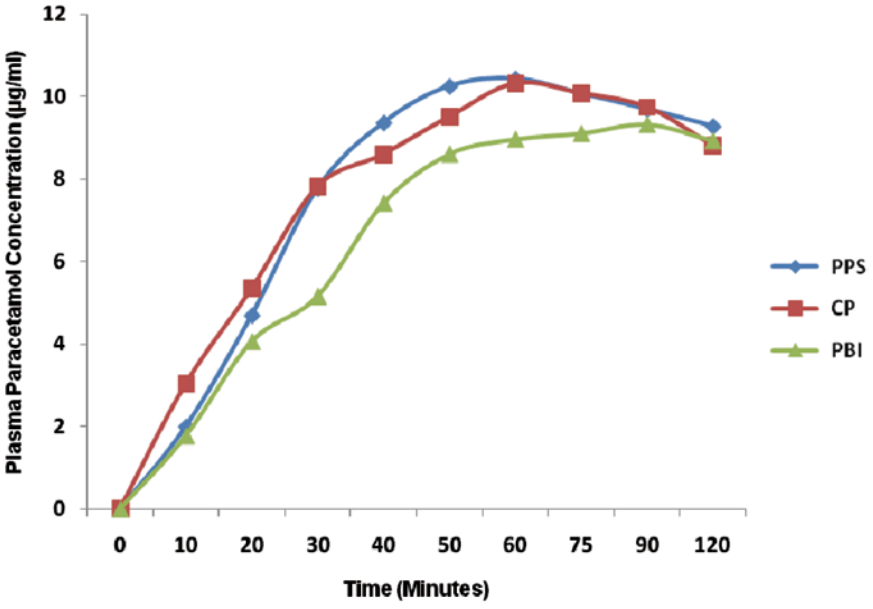

Figure 1. Mean plasma paracetamol concentration for the first two hours post-dose for new paracetamol paediatric suspension (PPS), children's panadol (CP) and panodil baby and infant (PBI) in fasted state.

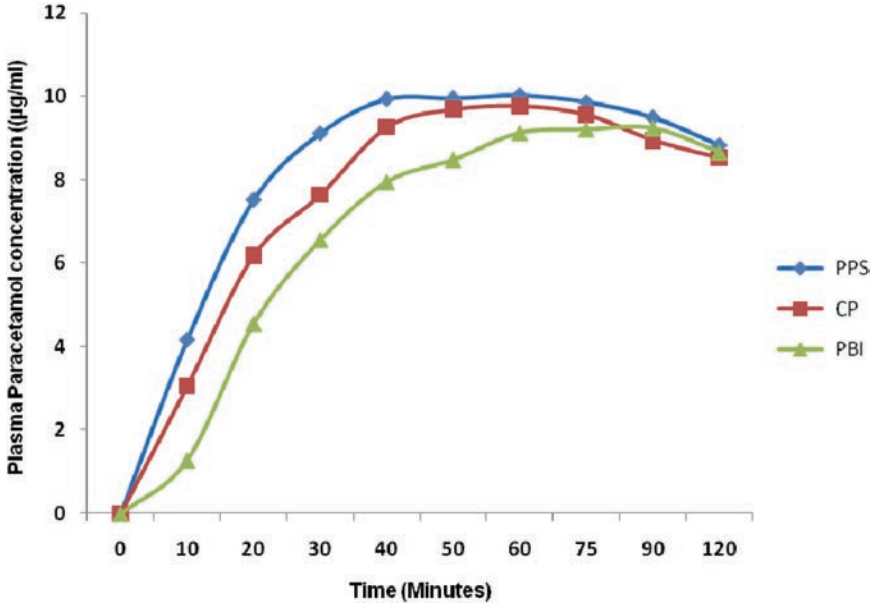

Figure 2. Mean plasma paracetamol concentration for the first two hours post-dose for new paracetamol paediatric suspension (PPS), children's panadol (CP) and panodil baby & infant (PBI) in fed state.

the fact that maximum plasma concentration for this product was bioequivalent to the two reference products. PPS reached maximum plasma paracetamol concentration faster than the other two products. T_{max} of PPS was significantly shorter than that of PBI in both fasted (20 min) and fed state (30 min). PPS demonstrated this trend when compared to CP. Median T_{max} of PPS was 9 and 4 min shorter than median T_{max} of CP in fasted and fed states (Table 1), although these differences were not significant. The extent of paracetamol absorption from PPS in terms of AUC_{0-10} and AUC_{0-inf} was similar to that of two marketed products. However, greater early AUCs (AUC_{0-30} and AUC_{0-60}) observed for PPS indicate a greater earlier absorption rate for this product as compared to the other two marketed products, given that the longer AUCs were bioequivalent. The new PPS is absorbed significantly faster than the two marked paracetamol products, especially in the fed state where PPS demonstrated significantly higher $AUC_{0-30\ min}$ and $AUC_{0-60\ min}$ compared to CP and PBI. The higher rate of early paracetamol exposure from PPS is likely to be of clinical importance as it is related to a faster time to reach minimal effective concentration level (a marker of onset of clinical effect). In the fed state, PPS reached the threshold of plasma paracetamol concentration of 4 µg/mL significantly faster than both CP and PBI.

In contrast to previous paracetamol formulations, PPS shows improved rate of early exposure in the presence of food. For most pediatric suspensions as for paracetamol formulations in general, food has an inverse effect in the rate and extent of paracetamol absorption[27–29]. In this study food decreased the extent of paracetamol absorption. Overall, AUC_{0-10}, AUC_{0-inf} and C_{max} were significantly greater in the fasted state as compared to the fed state. However, food positively affected speed of early paracetamol absorption by PPS during the first hour after dose. PPS in the fed state had higher early exposure as compared to fasted state for AUC_{0-30} and AUC_{0-60}. Also, the onset of therapeutic effect as measured by time to reach plasma paracetamol concentration 4 µg/mL was positively affected by food. In the feed state, PPS reached this therapeutic threshold 10 min earlier than in the fasted state. These findings are particularly important for administration of the new paracetamol suspension to manage fever in children since food enhanced early exposure and speed of onset.

This study had a limitation in assessing full-food effect. Instead of a complete 'fed' state with dosing 30 min after starting meal consumption, we used a feeding state where dosing was applied 2.5 h after the start of meal consumption. Also, instead of a high-fat, high-calorie meal we used a light-fat, low-calorie meal. Both timing and the kind of food used do not represent a clear 'fed' state to assess the complete food effect. However, this feeding state was chosen primarily for a better differentiation of products as compared to complete 'fed' state. Several of our studies[11,17,18,19] especially with fast releasing paracetamol products have shown that with this structure of feeding state the differentiation is better than in the fed state (0.5 h after starting of the meal). Also, by using this feeding state, we were trying to mimic the common actual use of products[29,30], when children with fever usually don't consume high-fat food, or take medication immediately after a heavy meal.

The higher early rate of paracetamol absorption and the faster onset of MEC level found for PPS as compared to the existing marketed paracetamol suspension products could have a positive clinical effect on the onset of antipyretic/analgesic action. In a previous study, a faster

onset of analgesic action following greater early exposure of paracetamol tablets as compared to standard paracetamol tablets has been reported[31]. Other studies[29,32] have concluded that only rapid absorption of paracetamol produces sufficiently high plasma levels to induce an effective passage of the drug to the central nervous system and cause a significant analgesic effect. Rapid absorption improves rate of fever reduction, and provides clinical benefits to reduce fever- and pain-associated discomfort[6,32,33]. Therefore, it is likely that the faster rate of paracetamol absorption from new PPS will bring the clinical benefit of a faster onset of antipyretic action.

This study was conducted in adults although children were the target population. The large volume of blood required and frequent withdrawals for a relatively long period of time made this six-way crossovers study not feasible in children[30]. However, relative results we found in this study for adults are also valid for children, assuming a linear relationship of paracetamol concentration and PK responses. For drugs with linear pharmacokinetics in adults, single-dose studies, often allow adequate pharmacokinetic assessment in the pediatric population[34]. For these cases, doses should be based on mg/kg of body weight or mg/m^2 of body surface area, extrapolated from adult doses. In our study, we applied the extrapolation based on body weight. Previous studies have confirmed the linear relationship of paracetamol PK responses with dose[35,36] and therefore, PK results found in this single-dose study can be extrapolated to the pediatric population.

Compared to the existing products, the new PPS has the potential of enhancing efficacy by improving the speed of early paracetamol absorption. The enhanced effect in the presence of light food makes this new formulation particularly advantageous over the existing marketed products for children.

Conflict of interest

Dr. Smith is an employee of MDS and was contracted and financially reimbursed by GlaxoSmithKline Consumer Healthcare, USA in respect of the work undertaken in this research. Dr. Collaku is an employee of GlaxoSmithKline Consumer Healthcare, USA. His current position within the company is Principal Biostatistician. Dr. Heaslip is an employee of MDS and was contracted and financially reimbursed by GlaxoSmithKline Consumer Healthcare, USA in respect of the work undertaken in this research. Dr. Yue is an employee of GlaxoSmithKline Consumer Healthcare, USA. His current position within the company is Principal Clinical Research Scientist. Dr. Starkey is an employee of GlaxoSmithKline Consumer Healthcare, USA. Her current position within the company is Medical Director. Dr. Clarke is an employee of GlaxoSmithKline Consumer Healthcare, USA. His current position within the company is Vice President of Panadol Future Team Research and Development. Dr. Kronfeld is an employee of GlaxoSmithKline Consumer Healthcare, USA. His current position within the company is Medical Director.

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