On the design of food effect studies in adults for extrapolating oral drug absorption data to infants: An exploratory study highlighting the importance of infant food

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Nurofen®, and 21 mL of Panadol® over 1 minute, followed by 20 mL of Nurofen®, 21 mL Panadol®, and 84 mL of water over 1 minute. The formulations were administered sequentially, without time gaps in-between. Time zero was set just after the completion of the first minute **(Figure 1)**.

In Phase II, the formulations were administered as described for Phase I but 30 minutes after initiation of ingestion of the FDA meal [two eggs (Golden Eggs®, Athens, Greece) fried in 31.3 g of butter (Lurpak®, Danish Dairy Board, Viby, Denmark), two strips of bacon (Nikas®, Athens, Greece), two slices of toast bread (Karamolegos A.E., Koropi, Greece), 56 g of French fries (Everest, Greece) and 240 mL of whole cow's milk (Delta® 3.5% fat, Delta, Athens, Greece)] with a total caloric content of 990 kcal derived from 25 % carbohydrates, 61 % fats, and 14 % proteins.

For Phase III, infant formula [Noulac® (Nounou®, Fresland Campina Hellas, Athens, Greece), 47 % carbohydrates, 43 % fats, and 10 % proteins], was selected as an age-representative meal in the paediatric subpopulations below the age of 24 months based on its frequent use (2). Breastmilk or infant formula are the exclusive feed until the age of 6 months and remain a main daily feed during infancy (2). Therefore, infant formula can be considered an appropriate meal for testing food effects in infants including infants that are being weaned. The volume of infant formula in the present study was 800 mL (520 kcal) and was based on the recommended infant formula volume for infants, scaled up by a body surface area factor for adults/infants (2). To simulate dosing conditions in infants during feeding, the total volume was split into two portions and 400 mL were consumed at a constant rate over 8 minutes, subsequently 20 mL of Nurofen® and 21 mL of Panadol® were administered over 2 minutes. Upon completion, time zero was set and drugs administration continued by 20 mL of Nurofen® and 21 mL of Panadol® over 2 minutes, after which the second portion (400 mL) of infant formula was consumed at a constant rate over 8 minutes. The formulations and infant formula were administered sequentially, without time gaps in-between.

Both the FDA meal (Phase II) and the infant formula (Phase III) were prepared freshly on each clinical day.

Determination of drug plasma levels

Analysis of each drug was performed separately in duplicate. Sample treatment involved plasma protein precipitation and subsequent centrifugation and drug levels were measured by HPCL-UV based on previously proposed methods by Lalande *et al*., 1986 andVertzoni *et al., 2003* (52,53). The chromatographic system (SpectraSystem®) consisted of a P4000 pump, UV1000 absorbance detector, and an AS3000 autosampler. The above system was controlled by ESIchrome chromatography software package (v. 3.2, Thermo Fisher Scientific, San Jose, CA USA).

Paracetamol

For paracetamol analysis, 300 µL trifluoroacetic acid 10 % (v/v) and 150 µL plasma sample were mixed vigorously for 1 minute. The sample was centrifuged for 10 minutes at 10° C and 10 000 rpm (52). 300 µL of the clear supernatant were collected and diluted with 300 µL water and injected into the HPLC system. The separation utilised a BDS Hypersil® C18 column (250×4.0 mm, 5 µm) equipped with a preceding BDS pre-column (10×4.6 mm, 5 µm), with a mobile phase consisting of 10 mM ammonium formate of pH 6.0 and methanol (90:10 v/v). Paracetamol was eluted at an isocratic flow rate of 0.8 mL/min and detected at 424 nm. Calibration curves using the peak area of paracetamol in spiked plasma and mobile please showed no significant differences regarding their slope or intercept (t-test, 95% confidence interval). Linearity was shown over the working range 7.5 - 4 000 ng/mL, with a regression coefficient (R^2) of ≥ 0.999. The lower limit of quantification (LLOQ) was 7.5 ng/mL and only 3 out of the 336 samples exhibited drug levels below the LLOQ. Sample quantification was

performed via calibration curves constructed in spiked individual blank plasma from the corresponding volunteer.

Ibuprofen

For the analysis of ibuprofen, 200 µL plasma sample were acidified by addition of 20 µL of 5 % (v/v) trifluoroacetic acid, mixed briefly, followed by addition of 380 µL of ice-cold acetonitrile (53). The mixture was vigorously vortexed for 1 minute and subsequently centrifuged (10 minutes, 10° C, 10 000 rpm). 300 µL of the clear supernatant were collected, diluted with 300 µL mobile phase and were injected into the HPLC system. Separation was performed with a Fortis® C18 column (150×3.0 mm, 5 µm) equipped with a preceding BDS pre-column (10×4.6 mm, 5 µm). The mobile phase consisted of acetonitrile and 100 mM sodium acetate of pH 3.5 (60:40 v/v). Ibuprofen was eluted at an isocratic flowrate of 0.5 mL/min and detected at 220 nm. Calibration curves employing the peak area of ibuprofen in spiked plasma and mobile phase showed no significant differences regarding their slope or intercept (t-test, 95% confidence interval). Linearity was shown over the working range 50 - 10 000 ng/mL, with a regression coefficient (R^2) of ≥ 0.999. The LLOQ was 50 ng/mL and all 336 plasma samples exhibited drug levels above the LLOQ. Sample quantification for each volunteer was performed via calibration curves in spiked individual blank plasma from the corresponding volunteer.

Data analysis

Concentrations below the LLOQ were assigned a value of 0 µg/mL. The maximum plasma concentration (C_{max}) and the time to reach peak plasma levels (T_{max}) were read out directly from raw data. The area under the plasma concentration-time curve until the last sampling timepoint (AUC_{0-10h}) was calculated applying the linear trapezoidal rule. The area under the plasma concentration-

time curve extrapolated to infinity ($AUC_{0\text{-}inf}$) was determined with WinNonlin (Version 5.2; Certara USA, Inc., Princeton, USA). Based on a recent draft FDA guidance, for certain classes of drugs (e.g. analgesic drug products) an evaluation of the partial exposure could be required to support the determination of the relative bioavailability of the drug products (54). In this study, partial AUC values truncated at the median T_{max} of each study phase were calculated applying the linear trapezoidal rule, specifically $AUC_{0\text{-}1.5h}$, $AUC_{0\text{-}3h}$, and $AUC_{0\text{-}4h}$ for paracetamol and $AUC_{0\text{-}0.75h}$, $AUC_{0\text{-}1.5h}$, and $AUC_{0\text{-}3h}$ for ibuprofen corresponding to the median T_{max} values in Phases I, II, and III, respectively. Additionally, the partial $AUC_{0\text{-}4h}$ was calculated for ibuprofen, as the absorption phase is assumed to be completed at this timepoint.

Comparison between study phases was performed via one-way repeated measures Analysis Of Variance (ANOVA) tests with a post-hoc Tukey-test, and statistical significance level was set at $p < 0.05$ after confirming normality and equal variance for the samples under comparison using SigmaPlot (SigmaPlot 11.0, Systat Software Inc., San Jose, USA). The one-way repeated measures ANOVA was conducted for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}10h,}$ and C_{max} for both drugs, the partial $AUC_{0\text{-}1.5h}$, $AUC_{0\text{-}2.5h}$, $AUC_{0\text{-}4h}$ for paracetamol, and the partial $AUC_{0\text{-}0.75h}$, $AUC_{0\text{-}1.5h}$, $AUC_{0\text{-}3h}$, and $AUC_{0\text{-}4h}$ for ibuprofen. Friedman repeated measures ANOVA on Ranks was applied for comparison between T_{max} values in the three study phases. In all cases significance of difference was considered at 0.05 level.

Results

Paracetamol

The mean paracetamol plasma concentration-time profiles and the respective 10th and 90th percentiles are depicted in **Figure 2**. Under fasted conditions, double peaks in plasma concentration time-profiles were observed in four subjects in the absorption phase with an evident impact on the mean profile (**Figure 2A**). Similar double peak phenomenon could be observed in three subjects under fed conditions, indicating inconsistent gastric emptying even under fed conditions. Since the absorption of paracetamol is controlled by gastric emptying (55–57), these observations indicate discontinuous gastric emptying of the suspension in some volunteers both under fasted conditions and under fed conditions. The lack of the double-peak phenomenon under infant fed conditions could suggest different gastric emptying mechanism for the formulation administered with infant formula.

Paracetamol total exposure ($AUC_{0\text{-}10h}$ or $AUC_{0\text{-}inf}$) and C_{max} and T_{max} values were not significantly influenced by the prandial and dosing conditions applied in this study (**Table II**). Based on partial AUC values, early exposure under fasted conditions and fed conditions demonstrated no significant difference (**Table II**), in line with C_{max} and T_{max} data. However, under infant fed conditions, despite the lower total caloric content of infant formula (compared with the meal used to induce fed conditions), absorption of paracetamol was significantly slower than in the fasted state ($p<0.05$), regardless of the cut-off time point used for estimating the respective partial AUC (**Table II**).

Although there are no published food effect data acquired after administration of paracetamol suspension, data after administration of 1000 mg immediate-release (IR) paracetamol tablets

indicate that fed conditions do not affect total exposure, while they decrease C_{max} and increase T_{max} values (44,58,59). The apparently unaltered C_{max} and T_{max} values after administration under fed conditions can be due to the low statistical power (0.049 for C_{max} comparison), the different gastric disposition of a suspension vs. a tablet, and/or the presence of small amount of calories in the administered suspension.

Ibuprofen

The mean ibuprofen plasma concentration-time profiles and the respective 10^{th} and 90^{th} percentiles are depicted in **Figure 3**. Double peaks were observed in the majority of individuals under fasted conditions during the absorption phase, which was reflected in the mean plasma concentration-time profile (**Figure 3A**). Under fed conditions, double peaks were observed in one subject (for the same volunteer the phenomenon was also evident for paracetamol), while the occurrence during the absorption phase was not clear under infant fed conditions. As for the paracetamol suspension, these observations indicate a discontinuous gastric emptying process of the suspension in some volunteers, primarily under fasted conditions.

Ibuprofen total exposure ($AUC_{0\text{-}10h}$ or $AUC_{0\text{-}inf}$) appeared not to be significantly influenced by the prandial and dosing conditions applied in this study (**Table III**). Differences in C_{max} and T_{max} values between fasted conditions and fed conditions or between fasted conditions and infant fed conditions were not significant. Interestingly, peak exposure (C_{max} values) for ibuprofen administration with infant formula was significantly greater than the observed under fed conditions (**Table III**). Drug dosing under fed conditions significantly reduced early exposure compared to the fasted conditions during the first 45 min after drug administration (**Figure 3B**). Early exposure was not significantly changed when estimated up to longer times. Under infant fed conditions, all partial AUC values, e.g. $AUC_{0\text{-}0.75h}$, $AUC_{0\text{-}1.5h}$, $AUC_{0\text{-}3h}$, and $AUC_{0\text{-}4h}$, were significantly lower compared to the fasted conditions

(**Table III**). This observation is in line with the initial slow absorption rates and the increased absorption rates at later times that could have led to significantly greater C_{max} values after infant formula (**Table III**).

To the best of our knowledge, there are no published data after administration of ibuprofen suspensions under fed conditions. Data acquired for the administration of a 600 mg IR tablet suggest no significant change in total exposure under fed conditions (orange juice included in the meal) (60). However, total exposure ($AUC_{0\text{-}inf}$) was decreased when ibuprofen IR tablets were administered at a single dose of 400 mg under fed conditions (orange juice included in the meal) or 800 mg immediately after a liquid test meal (61,62). It should be noted that in the published studies investigating IR tablets, deviations from the fed conditions applied in the present investigation (and recommended by regulators) were evident, e.g. co-administration of orange juice (60,61) and/or drug administration to intubated volunteers 15 min after initiation of liquid meal consumption (62). Moreover, in these studies, decreased C_{max} and prolonged T_{max} values have been reported after ibuprofen dosing under fed conditions (60–62). The apparently unaltered C_{max} and T_{max} values after administration under fed conditions could be caused by the different gastric disposition of suspension vs. the tablet and/or the presence of small amount of calories in administered suspension.

Discussion

Today, oral paediatric formulation development is usually initiated during clinical Phase II stage of the adult drug product timelines (3,63). Throughout the pharmaceutical design process for paediatric formulations paramount emphasis is placed on formulation acceptability and palatability, resulting in the common utilisation of sweeting agents in an attempt to improve the acceptance of paediatric liquid formulations for oral administration (4). The present investigation showed that after administration of paediatric suspension to adults under simulated infant fed conditions, but not under fed conditions, the absorption of paracetamol and ibuprofen is substantially slower compared with the absorption under fasted conditions.

In line with the typical excipients found in paediatric liquid formulations, sweetening agents, i.e. maltitol syrup and/or sorbitol, can be found among the excipients listed for the two paediatric suspensions investigated in the present study. Although the polyols included in these formulations exhibit lower caloric content compared to sucrose, and therefore, the total caloric content of the formulations is relatively low (ca. 60 kcal for the two formulations), a certain quantity of calories is inherently and inevitably administered under all studied prandial and dosing conditions.

The presence of calories in the formulations could raise concerns whether the subjects are in fasted conditions when these formulations are administered with a glass of water and what might be the possible implications of the caloric content of the formulations on physiological processes in the gastrointestinal tract, particularly regarding the regulation of gastrointestinal motility and gastric emptying. In an investigation performed using a liquid meal containing ca. 400 kcal, the motility phase in which the test meal was introduced, e.g. during quiescence (Phase I) or during late Phase II contractions, were found to be the major determinants for the motility response following meal

ingestion and gastric emptying rate (64). Meal administration during late Phase II of the migrating motility complex (MMC) resulted in Phase III-like duodenal activity shortly after meal administration accompanied by a biphasic gastric emptying pattern observed for the gastric emptying marker paracetamol in most of the subjects, whereas meal ingestion during Phase I of the MMC lead to the typical postprandial Phase II-like motility pattern associated with a monophasic pattern of gastric emptying (64). Similar observations were reported when 60 kcal of the same liquid study meal were infused intraduodenally during Phase I or late Phase II, demonstrating that the MMC could influence postprandial responses and it is not entirely interrupted by nutrient simulation (65). In another study, Thompson and colleagues reported that the ingestion of glucose solutions (50 g in 200 mL water) during either MMC Phase I or II did not recognisably alter the appearance of the intestinal motor pattern (66). Briefly, the quiescence phase continued to persist after glucose ingestion during MMC Phase I period, while no apparent change of the duodenal irregular motor pattern or occurrence of MMC Phase III was observed after ingestion of glucose solution during Phase II motor activity (66). The authors concluded that the insignificant differences between MMC Phase III intervals of the two timings of ingestion suggested that glucose ingestion would either produce the same delay in Phase III re-appearance (despite differences in the timing of ingestion) or did not affect the appearance of Phase III contractions, implying no interference of the glucose solution with the MMC (66).

Based on the insignificant impact of the caloric load of the suspension formulations, the apparently discontinuous pattern of the gastric emptying process under fasted conditions could be related to the variable contractual activity of the gastrointestinal tract and the characteristics of the administered formulations. The double peak phenomenon could be associated with the viscosity enhancing excipients in the formulations administered, e.g. xanthan gum. It could be assumed that the insufficient ability of the suspensions to disperse in the stomach could lead to the emptying of substantial amounts only under intense contractions. Interestingly, the time interval between these double peaks, both after administration of paracetamol and ibuprofen under fasted conditions,

coincided with the reported cycle of 1.5-2.5 hours for the peristaltic, phasic contractions of the migrating motility complex (57,67). This possibility is in line with the wide use of paracetamol as a gastric emptying marker after administration of rapidly disintegrating tablets or solutions (55) and the rare observation of the double peak phenomenon in relevant previous works (68).

Under fed conditions, absorption rates did not change significantly from the ones observed under fasted conditions. This could be attributed either to the power underlying the statistical tests or the fast transfer of the drugs with the administered water into the small intestine, independently from the bulk gastric contents under fed conditions, a phenomenon known as “stomach road” or “Magenstrasse” (69,70). A pathway which may be less easily accessible for IR tablets, possibly due to the tablet disintegration step required prior to drug dissolution and mixing with the administered water that would enable the “Magenstrasse” pathway (71,72).

Perhaps the most interesting observations can be made from the comparison of infant fed vs. the fasted state data. For both suspensions, unlike to the absorption rates under fed conditions, the absorption rates under infant fed conditions were significantly slower than under fasted conditions. Compared to the inhomogeneous viscous meal used for inducing fed conditions, the homogeneous nature and low viscosity of the infant formula could facilitate mixing between the liquid drug formulation and infant formula and thus lead to the emptying of the drug from the stomach with the infant meal on a calorie-dependent basis (2). In fact, this slow absorption process led to detection of significant difference in C_{max} values for ibuprofen between fed and infant fed conditions (Table III).

Finally, from clinical perspective, the onset of pain relief and the timing of peak analgesic effects following paracetamol or ibuprofen intake profit from a faster rate of absorption. Assuming that the food type rather than age is the main determinant of gastric emptying (2,73), data from the present

study indicate a substantial delay in paracetamol or ibuprofen absorption and probably subsequent delayed induction of pharmacodynamic effects when a suspension is administered during feed with breastmilk or infant formula in infants.

Concluding remarks

The present exploratory study in healthy adults suggests that even for drugs with non-problematic absorption (no intestinal permeability limitations, highly soluble in the small intestine, no documented intraluminal interactions with food components) administered in simple dosage forms (aqueous suspensions), food effects on drug absorption in infants may not be adequately evaluated by data collected as suggested by regulatory agencies for adult drug products. Evaluation of the importance of differences observed in the present investigation when extrapolating to infants is currently underway. It would be highly interesting to evaluate the extent to which differences between fasted conditions and infant fed conditions in adults reflect differences between fasted state conditions and fed state conditions in infants. Until then, for any drug product, food effects in infants should be considered cautiously or be evaluated in infants.

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List of Figures

Figure 1

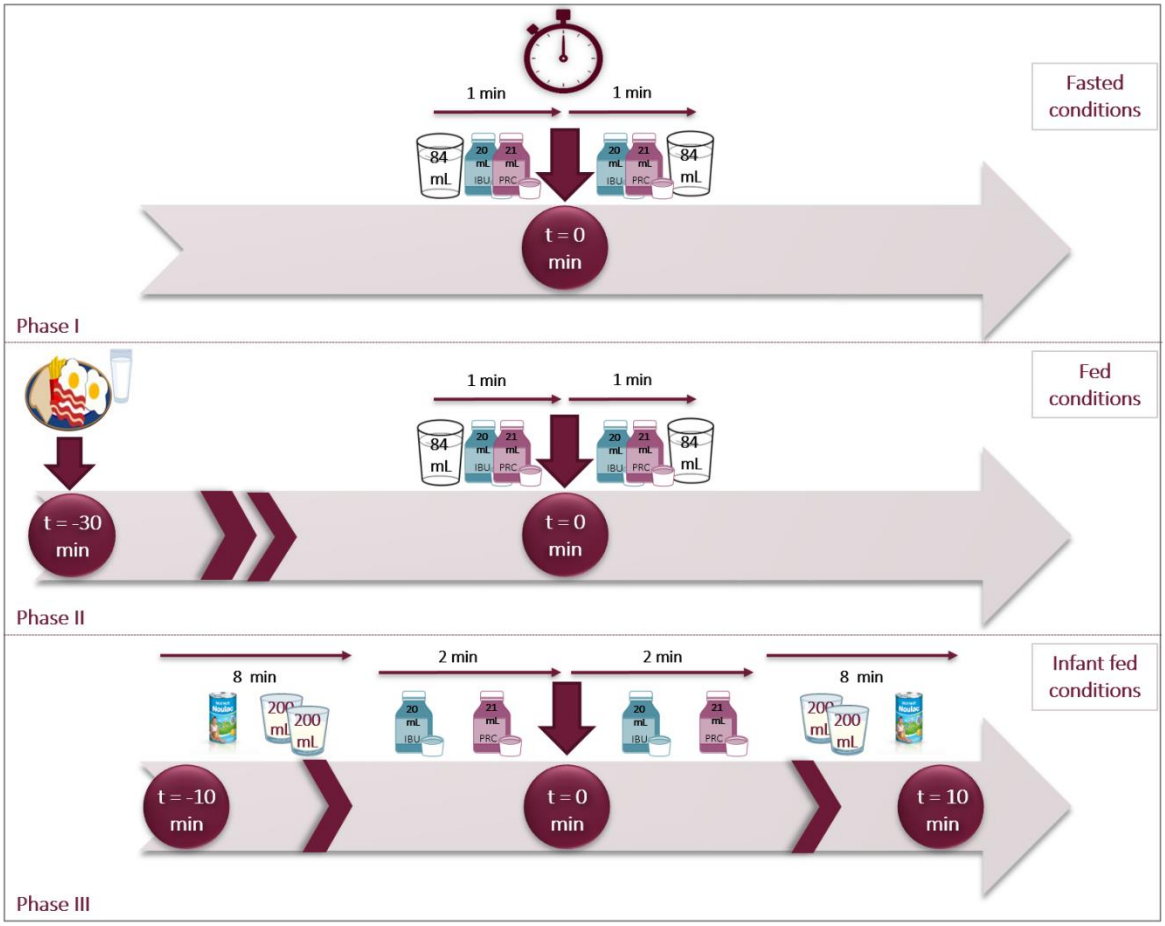
Fasted conditions
1 min
1 min
84 mL
20 mL IBU
21 mL PRC
20 mL IBU
21 mL PRC
84 mL
t = 0 min
Phase I
Fed conditions
1 min
1 min
84 mL
20 mL IBU
21 mL PRC
20 mL IBU
21 mL PRC
84 mL
t = -30 min
t = 0 min
Phase II
Infant fed conditions
8 min
2 min
2 min
8 min
200 mL
200 mL
20 mL IBU
21 mL PRC
20 mL IBU
21 mL PRC
200 mL
200 mL
t = -10 min
t = 0 min
t = 10 min
Phase III

Figure 2

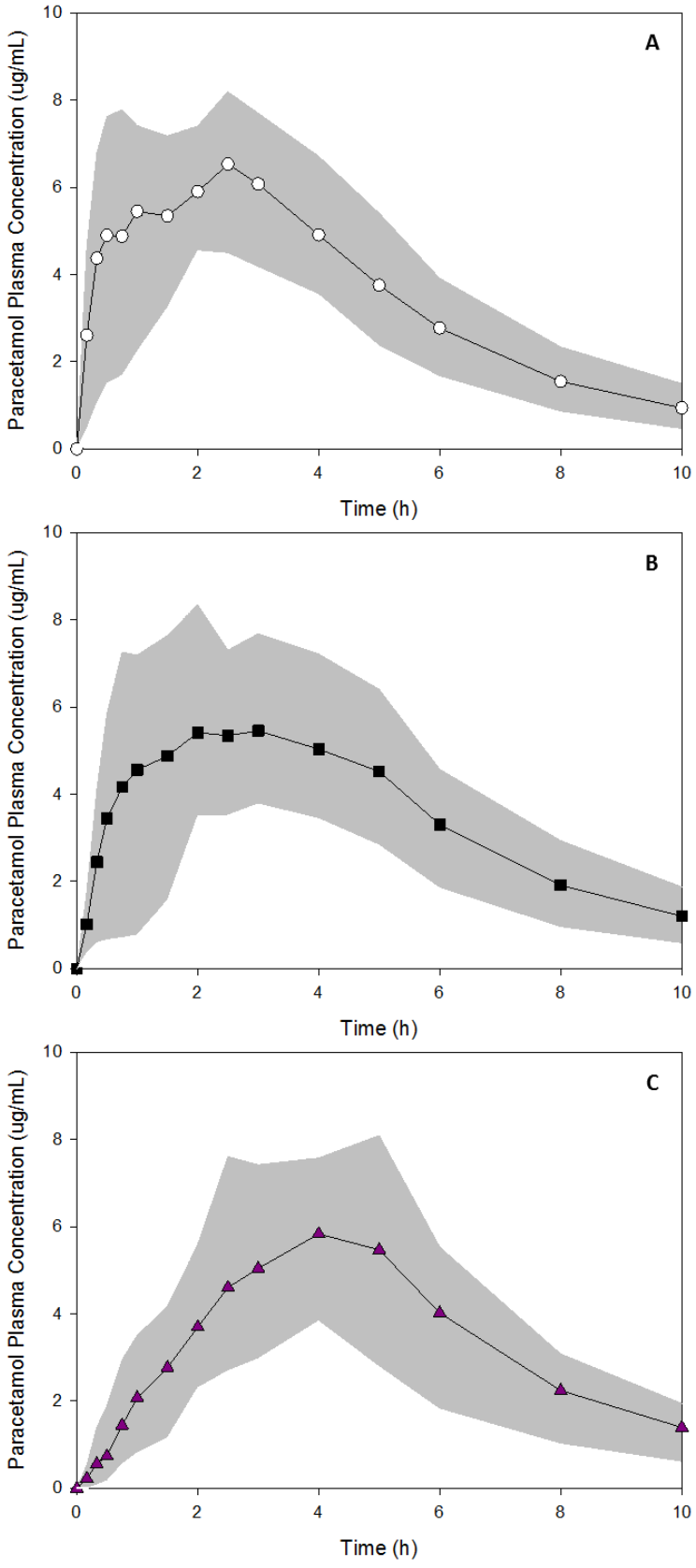

Figure 3

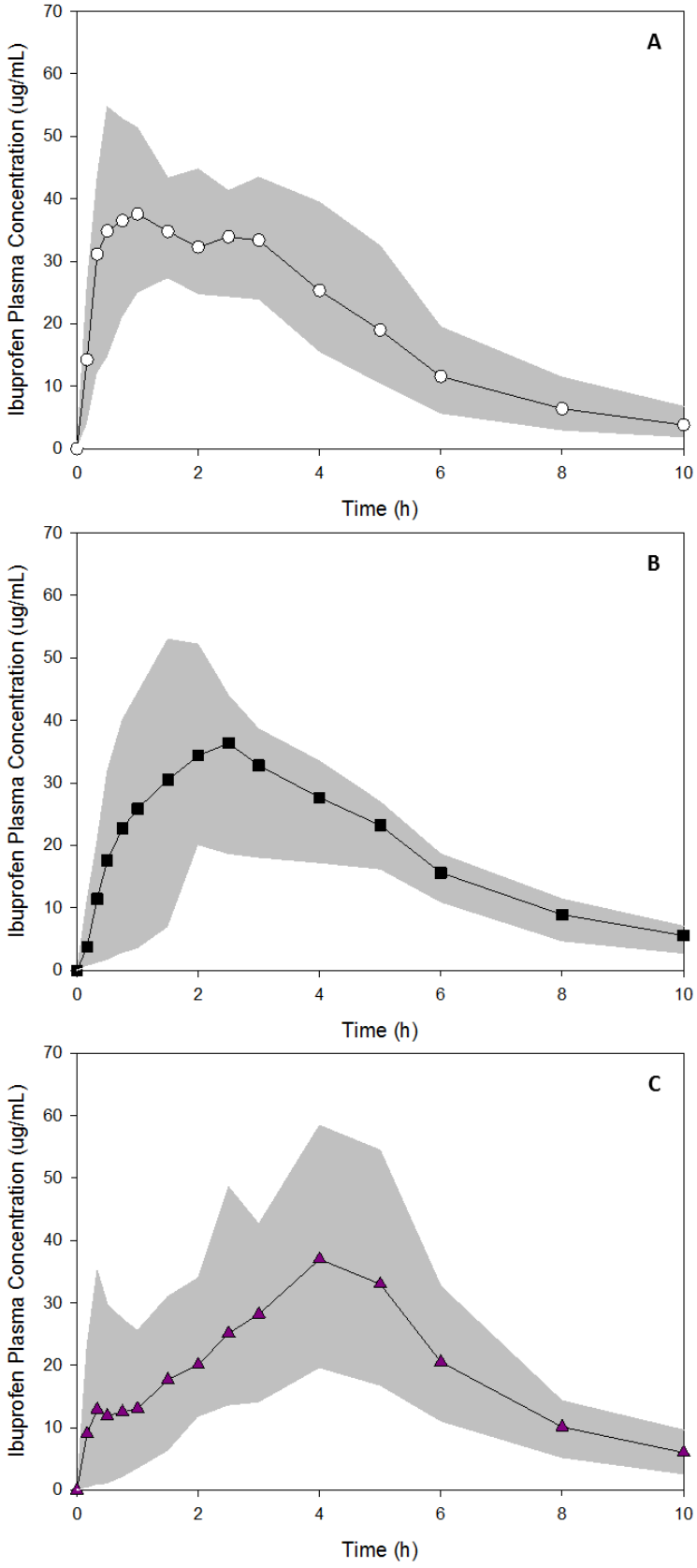
A
B
C
Ibuprofen Plasma Concentration (ug/mL)
Time (h)
0
10
20
30
40
50
60
70
0
2
4
6
8
10

Table I Published food effect data for seven antibiotic suspensions.

Drug	Food effects in infants and pre-school children								Food effects in adults		
	Food effects	C_{max} [a] (μg/mL)		AUC_{0-6h} [a] (μg/mL·h)		T_{max} [a] (h)		Reference	Food effects	Effect on C_{max}, AUC, and T_{max}	Reference
		Fasted	Fed	Fasted	Fed	Fasted	Fed				
Ampicillin	Unlikely	6.4	6.1	18	25	1.0	2.0	(8)	Negative	C_{max} and AUC_{0-t} significantly lower; T_{max} prolonged on average	(29)
		5.0	4.1	12	12	1.0	1.0	(7)		C_{max} lower on average; AUC_{0-t} significantly lower T_{max} significantly delayed	(30)
Penicillin G	Likely negative	0.98	0.61	1.7	1.0	0.5	0.5	(8)	Unclear	C_{max} 22% lower on average; AUC_{0-t} unchanged (“long-acting” tablet); T_{max} prolonged on average	(31)
Penicillin V	Likely negative	2.1	1.1	3.0	1.9	0.5	0.5	(8)	Unclear	AUC_{0-2h} significantly lower	(32)
										C_{max} 20% and AUC_{0-t} 35% higher on average; T_{max} prolonged on average	(31)
										C_{max} significantly lower; T_{max} prolonged on average urine recovery 10% lower	(33)
Amoxicillin	Unlikely	5.4	3.2	16	14	1.0	1.5	(7) [b]	Likely negative	C_{max} and AUC_{0-t} unchanged T_{max} significantly delayed	(30)
		8.9	7.9	24	24	1.0	1.0	(7) [c]		C_{max} and AUC_{0-t} significantly lower; T_{max} prolonged on average	(29)
										C_{max} and AUC_{0-t} significantly lower; T_{max} not significantly prolonged	(34)
Cephalexin	Likely negative	23.4	9.0	40.0	23.0	0.5	1.0	(8)	Unlikely	C_{max} unchanged; AUC_{0-t} unchanged; T_{max} unchanged/slightly prolonged	(35–38)
										C_{max} 40% lower on average; AUC_{0-t} 10% lower on average; T_{max} prolonged on average	(39)
Erythromycin Estolate	Unlikely	4.7	4.8	45	40	2.0	2.0	(8)	Positive	C_{max} and AUC_{0-t} significantly increased; T_{max} significantly delayed	(40)
Erythromycin Ethyl-succinate	Likely positive	0.82	1.4	2.4	4.8	1.0	1.0	(8)	Likely positive	Serum levels to 12 hr post-dosing increased on average	(33)

[a] C_{max}, AUC_{0-6} (μg/mL·h), and T_{max} values from the mean plasma profiles were published in studies in infants

[b] Amoxicillin dose 15 mg/kg; [c] Amoxicillin dose 25 mg/kg

Table II Mean ± SD values of pharmacokinetic parameters for paracetamol in each phase of the clinical study.

Parameter	Phase I Fasted conditions	Phase II Fed conditions	Phase III Infant fed conditions
$AUC_{0\text{-}inf}$ (µg/mL×h)	39.4 ± 9.7	40.4 ± 11.0	39.2 ± 10.1
$AUC_{0\text{-}10h}$ (µg/mL×h)	35.8 ± 7.9	35.5 ± 8.9	34.0 ± 8.0
C_{max} (µg/mL)	7.85 ± 1.54	6.96 ± 2.42	7.24 ± 1.32
T_{max} (h)	1.50 (0.33 - 4.00) [a]	2.50 (1.00 - 5.00) [a]	4.00 (1.50 - 5.00) [a]
$AUC_{0\text{-}1.5h}$ (µg/mL×h)	6.78 ± 3.14	5.27 ± 2.99	2.12 ± 1.37 [b]
$AUC_{0\text{-}2.5h}$ (µg/mL×h)	12.7 ± 4.4	10.5 ± 4.8	5.81 ± 2.72 [b]
$AUC_{0\text{-}4h}$ (µg/mL×h)	21.4 ± 5.2	18.5 ± 5.9	13.7 ± 4.3 [b]

[a] median value (range)

[b] significantly different from Phase I

Table III Mean ± SD values of pharmacokinetic parameters for ibuprofen in each phase of the clinical study.

Parameter	Phase I Fasted conditions	Phase II Fed conditions	Phase III Infant fed conditions
$AUC_{0\text{-}inf}$ (µg/mL×h)	205 ± 60	203 ± 47	213 ± 54
$AUC_{0\text{-}10h}$ (µg/mL×h)	192 ± 50	185 ± 40	194 ± 44
C_{max} (µg/mL)	45.0 ± 7.4	41.3 ± 10.6	49.6 ± 9.0 [c]
T_{max} (h)	0.75 (0.33 – 4.00) [a]	1.50 (1.00 – 3.00) [a]	3.30 (0.33 – 5.00) [a]
$AUC_{0\text{-}0.75h}$ (µg/mL×h)	19.4 ± 8.2	10.8 ± 6.5 [b]	7.7 ± 9.0 [b]
$AUC_{0\text{-}1.5h}$ (µg/mL×h)	46.7 ± 15.6	32.6 ± 19.6	18.6 ± 17.4 [b]
$AUC_{0\text{-}3h}$ (µg/mL×h)	96.9 ± 21.0	80.5 ± 34.4	52.6 ± 29.2 [b]
$AUC_{0\text{-}4h}$ (µg/mL×h)	126 ± 25	109 ± 36	85.2 ± 29.4 [b]

[a] median value (range)

[b] significantly different from Phase I

[c] significantly different from Phase II