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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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Extrapolating food effects on drug absorption from adults to infants

Abstract

In the present investigation, it was explored whether food effect on drug absorption in adults is similar with the food effect after administration of an infant meal with the drug product to adults. After confirming lack of pharmaceutical and pharmacokinetic interaction, a paracetamol suspension and an ibuprofen suspension were co-administered to eight healthy adults on a crossover basis in three different occasions, i.e. in the fasted state (as defined by regulatory agencies, fasted conditions), in the fed state (as defined by regulatory agencies, fed conditions) and under conditions simulating the fed state in infants (infant fed conditions). Unlike under fed conditions, under infant fed conditions early exposure was significantly lower than under fasted conditions for both paracetamol and ibuprofen. For ibuprofen, C_{max} values under infant fed conditions were also significantly higher than under fed conditions. These data suggest that, even for drugs with non-problematic absorption administered in simple dosage forms, food effects in infants may not be adequately evaluated if the protocol suggested by regulatory agencies is applied. The usefulness of the methodology employed in the present investigation for simulating the fed state in infants deserves further evaluation. Until then, food effects in infants should be considered cautiously or be evaluated in infants.

Introduction

Oral drug delivery is the route of choice for drug administration from birth to adolescence (1–3). Therefore, understanding drug and drug formulation performance in relation to the prandial conditions is essential for ensuring safety and efficacy of products to be administered to paediatric patients, especially newborns (birth – 27 days) and infants (28 days – 2 years) whose diet is specific (100 % milk in newborns) (4–6).

Understanding the impact of prandial conditions on drug/drug product performance in paediatric patients is limited by ethical concerns and the subsequent difficulty to perform such studies. Difficulties in recruitment are reflected by the limited number of food effect studies in children published to date [(25 to the best of our knowledge, (7-27)]. Importantly, most of these studies either do not focus on a specific paediatric subpopulation (9–12,20–28) or focus on school-children (13–15,17). As a result, differences in gastrointestinal physiology across paediatric subpopulations and differences in meals administered to evaluate the impact of prandial conditions increase data variability and drastically decrease their usefulness.

In recent years, there has been a growing interest in investigating whether food effect data collected in adults are useful for paediatric products (2). Based on a recent draft guidance issued by the U.S. Food and Drug Administration (FDA), when the same to-be-marketed formulation that is approved for use in adults is approved for use in a paediatric population, a separate food effect study is not necessary (6) and the same may also apply in case a paediatric formulation is very similar to the adult formulation and has been approved based on *in vitro* dissolution tests (6). To date, nine food effect studies (7 drugs) in infants and young children have been published (McCracken et al. 1978 (8) – age range 2-46 months; Ginsburg et al. 1979 (7) – age range 4-45 months). All studies were performed on a predominantly crossover basis and in all of them the tested product was an antibiotic suspension. Fasting was defined as no food or milk substance for two hours before and after drug ingestion. The

fed state was induced with milk or infant formula co-administered with the product, i.e. 4 oz of milk or infant formula administered immediately after drug administration (8) or 4 oz of milk or infant formula (Similac® or Infamil®) administered with the drug (7). The impact of food on plasma levels based on these studies is summarised and compared with the impact of food on the plasma levels of the same antibiotics in adults in **Table I**. The adult studies were performed with immediate release products, after overnight fasting (fasting state) and 0-60 min after a solid meal (fed state), on a crossover basis. Based on the data shown in **Table I**, only erythromycin ethyl-succinate seems to have similar food effect in infants and in adults. It should be noted that most of the data presented in Table I have been collected more than forty years ago.

Another concern, when food effect data on oral drug absorption in adults are to be extrapolated to paediatric populations, relates to the design of food effect studies in adults. The recent guideline on how to conduct food effect studies for newly developed paediatric formulations issued by the FDA suggests that the food effect for paediatric formulations could be evaluated in adults using foods and quantities of food that are commonly consumed with drugs in paediatric populations with a subsequent extrapolation of the results to the paediatric population (6). Although this may be a practical approach to consider, conceptually, it is different from that applied to date for the evaluation of food effects on adult pharmaceutical products. In adults, relevant studies aim at detecting the maximum effect on bioavailability by employing a high-calorie, high-fat meal, with less emphasis on its exact composition (5,6). Importantly, studies in adults are performed by administering the drug product 30 minutes after the initiation of consumption of the meal in order to maximise the potential effect, whereas in paediatric populations drug are usually administered together with meals (19).

The aim of the present study was to explore whether food effect on drug absorption in adults is similar with the food effect after administration of an infant meal with the drug product to adults. Specifically, comparative bioavailability studies of two drugs were performed under three different prandial and dosing conditions, i.e.

- fasted state conditions as defined by regulatory agencies (fasted conditions)
- fed state conditions as defined by regulatory agencies (fed conditions), and
- simulated infant fed state conditions (infant fed conditions)

Paracetamol (high solubility, weak acid, pka 9.5) and ibuprofen (low solubility, weak acid, pka 4.5) (41–43) were selected as model drugs based on their luminal stability and high intestinal permeability. After confirming the lack of pharmaceutical interaction and pharmacokinetic interaction, based on available literature data (44,45), the drugs were co-administered using commercially available paediatric suspensions, i.e. variations of dosing should impact primarily gastric emptying (paracetamol) or gastric emptying and, perhaps, dissolution (ibuprofen).

Materials and Methods

Materials

The commercially available paediatric suspensions Panadol® (24 mg/mL, *GlaxoSmithKline Consumer Healthcare (Ireland) Ltd.*) and Nurofen® (20 mg/mL, *ReckittBenckiser Healthcare International Ltd.)* were acquired from a local pharmacy. Paracetamol (Ph. Eur.) and ibuprofen (Ph. Eur.) powders were kindly donated by Uni-Pharma SA (Athens, Greece). Acetonitrile and methanol (Merck, Darmstadt, Germany) and water (Fischer Scientific, Schwerte, Germany) were of HPLC grade. All other chemicals were of analytical grade.

As listed in the patient information leaflet, the Panadol® formulation is composed of the following excipients: malic acid, azorubine, xanthan gum, maltitol syrup, strawberry flavour L10055, sorbitol 70 % (w/v) (crystallising), sodium methyl parahydroxybenzoate, sodium ethyl parahydroxybenzoate, sodium propyl parahydroxybenzoate, sorbitol, anhydrous citric acid, purified water. According to manufacturer information, the formulation contains 133.3 mg sorbitol (incl. maltitol syrup content)/mL (46), that is, 5.6 g of sorbitol in the total volume of formulation (42 mL) administered to the volunteers. This results in a total caloric content of 11.8 kcal for the administered 42 mL Panadol® suspension.

The Nurofen® formulation is composed of the following excipients: citric acid, sodium citrate, sodium chloride, sodium saccharin, domiphen bromide, purified water, polysorbate 80, maltitol liquid, xanthan gum, strawberry flavor, glycerol. The formulation contains 445.2 mg of maltitol syrup/mL of formulation (47). According to the Ph. Eur. monograph for maltitol syrup, it is composed of 68-85% maltitol (w/v) (48), resulting in a range of 12.1 – 15.1 g maltitol for the formulation volume

administered to the volunteers (40 mL). The amount of glycerol in the formulation is 126 mg/mL of formulation (47), resulting in 5.05 g of glycerol for the formulation volume administered to the volunteers. Based on these components, the total caloric content of the 40 mL formulation administered to the volunteers ranges between 45 and 52 kcal.

Methods

Study design

This study was a single-dose, open-label, randomised, crossover, three-phase comparative oral bioavailability study with a washout period of one week. The study was performed in accordance with the ethical standards for studies in humans of the Declaration of Helsinki and its amendments (49) and the International Conference on Harmonization Guideline for Good Clinical Practice (50). The study protocol, informed consent form, and insurance contract received approval by the Executive and Ethics Committee of the Red Cross Hospital of Athens, Greece (Protocol Nr. 4145/14-02-18). The clinical study was conducted at the Gastroenterological Department of the Red Cross Hospital of Athens.

Subjects

Healthy male adults between the age of 20 and 50 years with Body-Mass-Index (BMI) within 20 % above or below the ideal BMI as determined by the Metropolitan Life Tables were recruited for this study. Ten healthy adult Caucasian males were recruited. A total of eight volunteers completed all three study phases. The participation of one volunteer was discontinued, due to inability of consuming the requested amount of one meal according to the protocol early in the morning. Another volunteer was unable to proceed with his participation after completing one of the study phases for health reasons unrelated to the present study. The mean age of the volunteers who completed the three

study phases was 28.4 years (range 21-48 years) and the mean body-mass-index was 23.6 kg/m^2 (range 20.3-27.7 kg/m^2). No adverse effects were recorded in the present study.

Inclusion criteria

The health status of the subjects was confirmed by reviewing their medical history and a general physical examination prior to the study (e.g. blood test to assess electrolyte balance, kidney and liver function, blood morphologic characteristics, glucose and lipid levels, Hepatitis B surface antigen, antibodies against Hepatitis C virus, and HIV combined Ag/Ab test). The volunteers had to be able to abstain from cigarette smoking, alcohol, and over-the-counter and prescription medication(s) for 3 days prior each study phase until the end of the study phase.

Exclusion criteria

Volunteers were excluded based on the existence of a major health problem (cardiovascular, pancreatic, hepatic, thyroid etc.), existence of any condition requiring prescription drug therapy, recent history of gastrointestinal disorder symptoms regardless of the severity (e.g. heartburn, constipation etc.), swallowing difficulties, and receipt of an investigational agent (new or generic) within 30 days prior to the initiation of and throughout the study. Further exclusion criteria were the presence of antibodies indicating active acute or chronic HIV, HBV, or HCV infection in the performed blood tests. Subjects who could not abstain from use of medication that may affect the gastro-intestinal function (including antacids, PPIs, H2-receptor inhibitors, and laxatives) within 30 days of the study were excluded.

Experimental protocol

The volunteers were required to comply with the fasting period of 12 h before the start of each study day. In the morning of each phase, the subjects arrived at the hospital at 8:00 a.m. and stayed until completion of the study phase. Upon their arrival, the volunteers' health status and compliance with the study protocol was confirmed and water consumption was restricted for the time period of 1h before and 4.5 h after dosing. A standard lunch comprised of a club sandwich and French fries (ca. 1000 kcal) was offered 4.5 h after drugs administration. Blood samples (8 mL) were collected from the forearm vein via peripheral venous catheter prior to drug administration, and 10, 20, 30, 45 min, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, and 10 h after drugs administration. Upon collection blood was transferred into EDTA-containing Vacutainers™, following centrifugation and plasma separation. The plasma samples were divided into two subsamples for separate analysis of ibuprofen and paracetamol to avoid repeated freeze-thaw cycles and were stored at -20° C.

Subjects were randomised to receive a single dose of 800 mg ibuprofen (40 mL Nurofen® paediatric suspension) and a single dose of 1000 mg paracetamol (42 mL Panadol® paediatric suspension) on three different occasions under three different dosing conditions: administration with water – "fasted conditions" according to regulatory guidelines for bioavailability/bioequivalence studies (Phase I), administration with water 30 minutes after the start of a high-fat, high-caloric meal (FDA meal) consumption – "fed conditions" (Phase II) (5,51), and "infant fed conditions" simulating typical administration conditions in infants (Phase III). The selected model drugs have shown no relevant pharmacokinetic interactions when co-administered orally and/or intravenously to healthy humans (44,45).

In Phase I the formulations were administered with 168 mL of water (the total fluid volume of the administered formulations and water was 250 mL) in the following manner: 84 mL of water, 20 mL of

202 Nurofen®, and 21 mL of Panadol® over 1 minute, followed by 20 mL of Nurofen®, 21 mL Panadol®, and
203 84 mL of water over 1 minute. The formulations were administered continuously, without time gaps
204 in-between. Time zero was set just after the completion of the first minute **(Figure 1)**.

205

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

212

213 For Phase III, infant formula [Noulac® (Nounou®, Fresland Campina Hellas, Athens, Greece),
214 47 % carbohydrates, 43 % fats, and 10 % proteins], was selected as an age-representative meal in the
215 paediatric subpopulations below the age of 24 months based on its frequent use (2). Breastmilk or
216 infant formula are the exclusive feed until the age of 6 months and remain a main daily feed during
217 infancy (2). Therefore, infant formula can be considered an appropriate meal for testing food effects
218 in infants including infants that are being weaned. The volume of infant formula in the present study
219 was 800 mL (520 kcal) and was based on the recommended infant formula volume for infants, scaled
220 up by a body surface area factor for adults/infants (2). To simulate dosing conditions in infants during
221 feeding, the total volume was split into two portions and 400 mL were consumed at a constant rate
222 over 8 minutes, subsequently 20 mL of Nurofen® and 21 mL of Panadol® were administered over
223 2 minutes. Upon completion, time zero was set and drugs administration continued by 20 mL of
224 Nurofen® and 21 mL of Panadol® over 2 minutes, after which the second portion (400 mL) of infant
225 formula was consumed at a constant rate over 8 minutes. The formulations and infant formula were
226 administered continuously, 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 (Lalande et al. 1986; Vertzoni et al. 2003). 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 flowrate 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 ($AUC_{0\text{-}10h}$) 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 (FDA, 2019b). 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 absorption of paracetamol is controlled by gastric emptying (55–57), these observations indicate discontinuous gastric emptying of suspension in some volunteers both in the fasted conditions and in the 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 10th and 90th 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**). These data could be related to initial slow absorption rates and a rapid increase at later times (Figure 3C). 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**).

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

342

343 To the best of our knowledge, there are no published data after administration of ibuprofen
344 suspensions under fed conditions. Data acquired for the administration of a 600 mg IR tablet suggest
345 no significant change in total exposure under fed conditions (orange juice included in the meal) (60).
346 However, total exposure ($AUC_{0\text{-}inf}$) was decreased when ibuprofen IR tablets were administered at a
347 single dose of 400 mg under fed conditions (orange juice included in the meal) or 800 mg immediately
348 after a liquid test meal (61,62). It should be noted that in the published studies investigating IR tablets,
349 deviations from the fed conditions applied in the present investigation (and recommended by
350 regulators) were evident, e.g. co-administration of orange juice (60,61) and/or drug administration to
351 intubated volunteers 15 min after initiation of liquid meal consumption (62). Moreover, in these
352 studies, decreased C_{max} and prolonged T_{max} values have been reported after ibuprofen dosing under
353 fed conditions (60–62). As for the paracetamol observations in the present study, the apparently
354 unaltered C_{max} and T_{max} values after administration under fed conditions could be caused by the
355 different gastric disposition of suspension vs. the tablet and/or the presence of small amount of
356 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 in the fasted state, 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 led 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. 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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656 **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)	1.5 (0.33 - 4) [a]	2.5 (1.0 - 5) [a]	4 (1.5 - 5) [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) [a]	1.5 (1.0 – 3) [a]	3.3 (0.33 – 5) [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

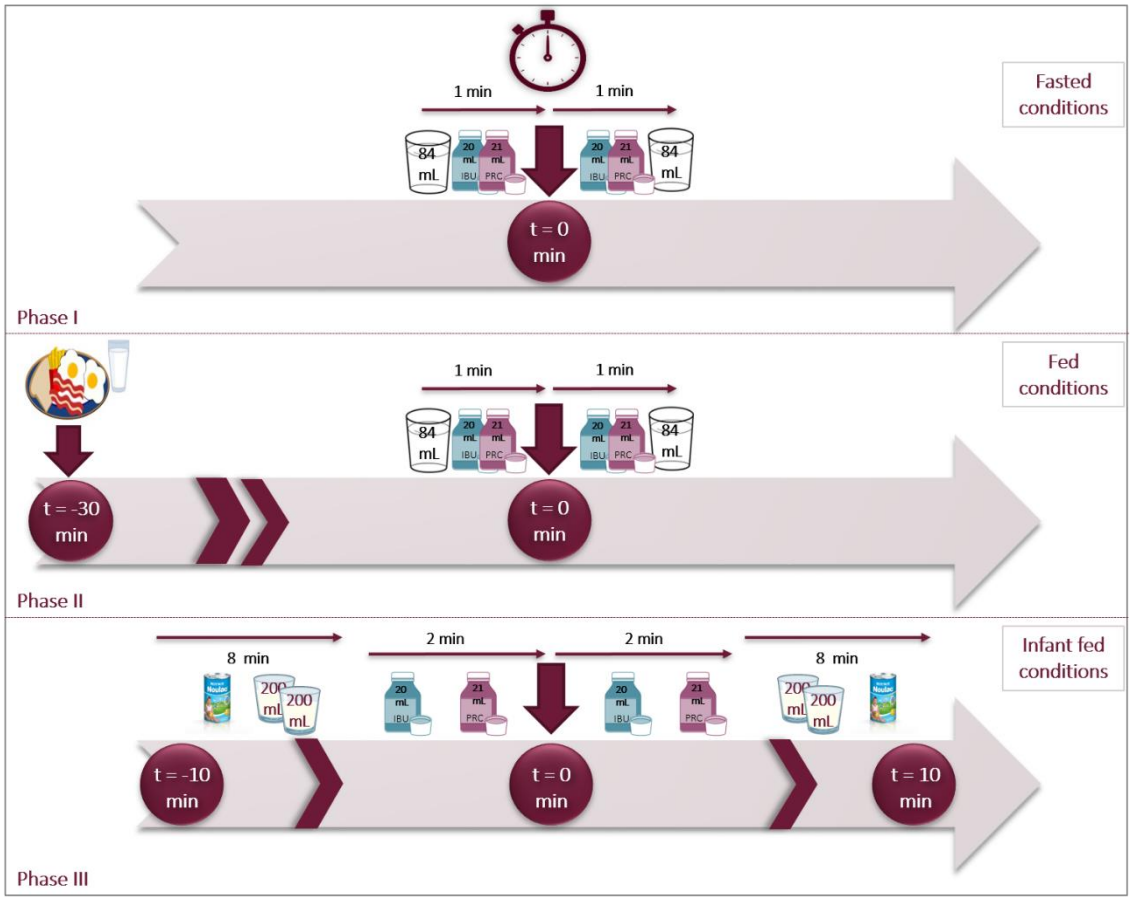
[c] significantly different from Phase II

Figure Captions

Figure 1 Graphical depiction of the times of meals vs. drug products administrations in the present clinical study: Phase I, fasted conditions; Phase II, fed conditions; Phase III, infant fed condtions.

Figure 2 Mean plasma paracetamol concentration-time profiles following co-administration of 1000 mg paracetamol suspension and 800 mg ibuprofen suspension to healthy male adults (n=8) under different prandial and dosing conditions: (A) fasted conditions, (B) fed conditions, (C) infant fed conditions. The shaded area represents the 10^{th} and 90^{th} percentiles estimated from the experimental data points.

Figure 3 Mean plasma ibuprofen concentration-time profiles following co-administration of 1000 mg paracetamol suspension and 800 mg ibuprofen suspension to healthy male adults (n=8) under different prandial and dosing conditions: (A) fasted conditions, (B) fed conditions, (C) infant fed conditions. The shaded area represents the 10^{th} and 90^{th} percentiles estimated from the experimental data points.



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690 Figure 1

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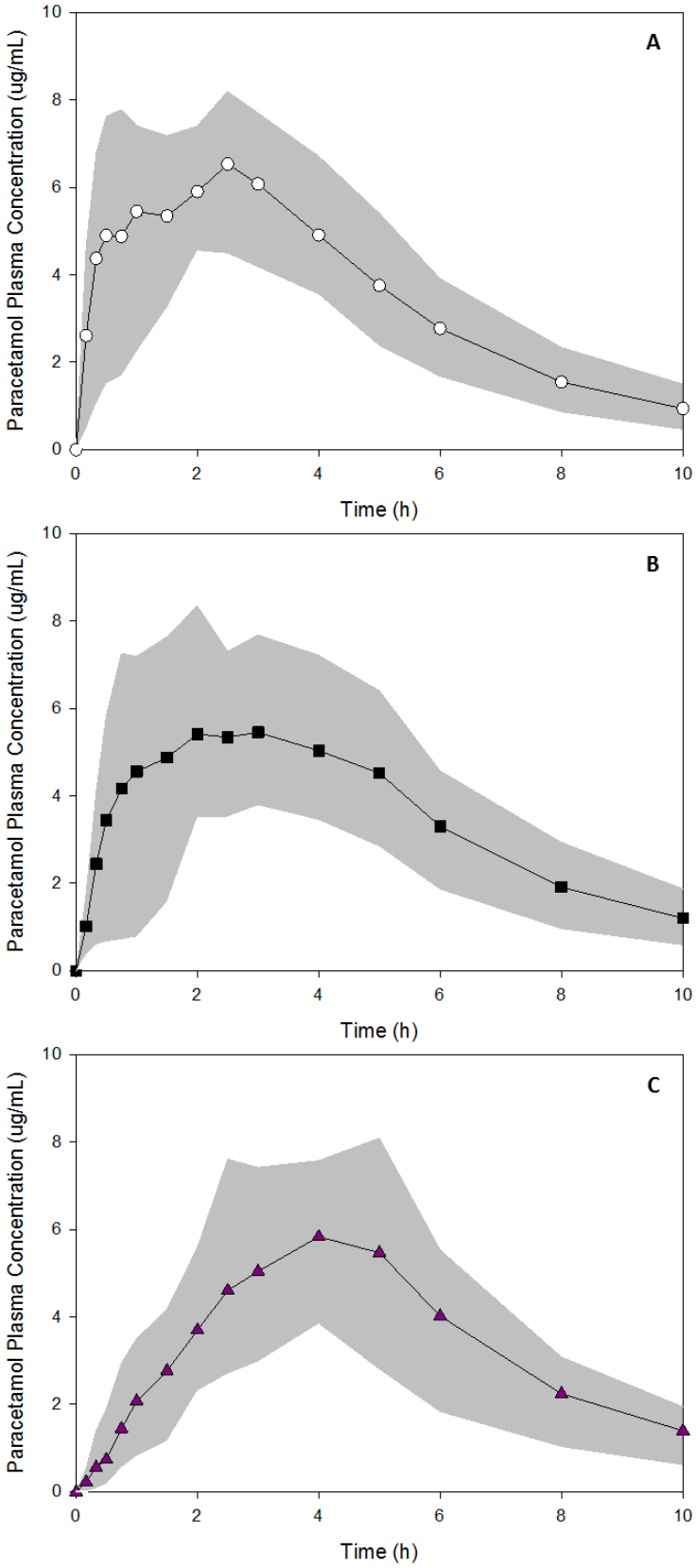

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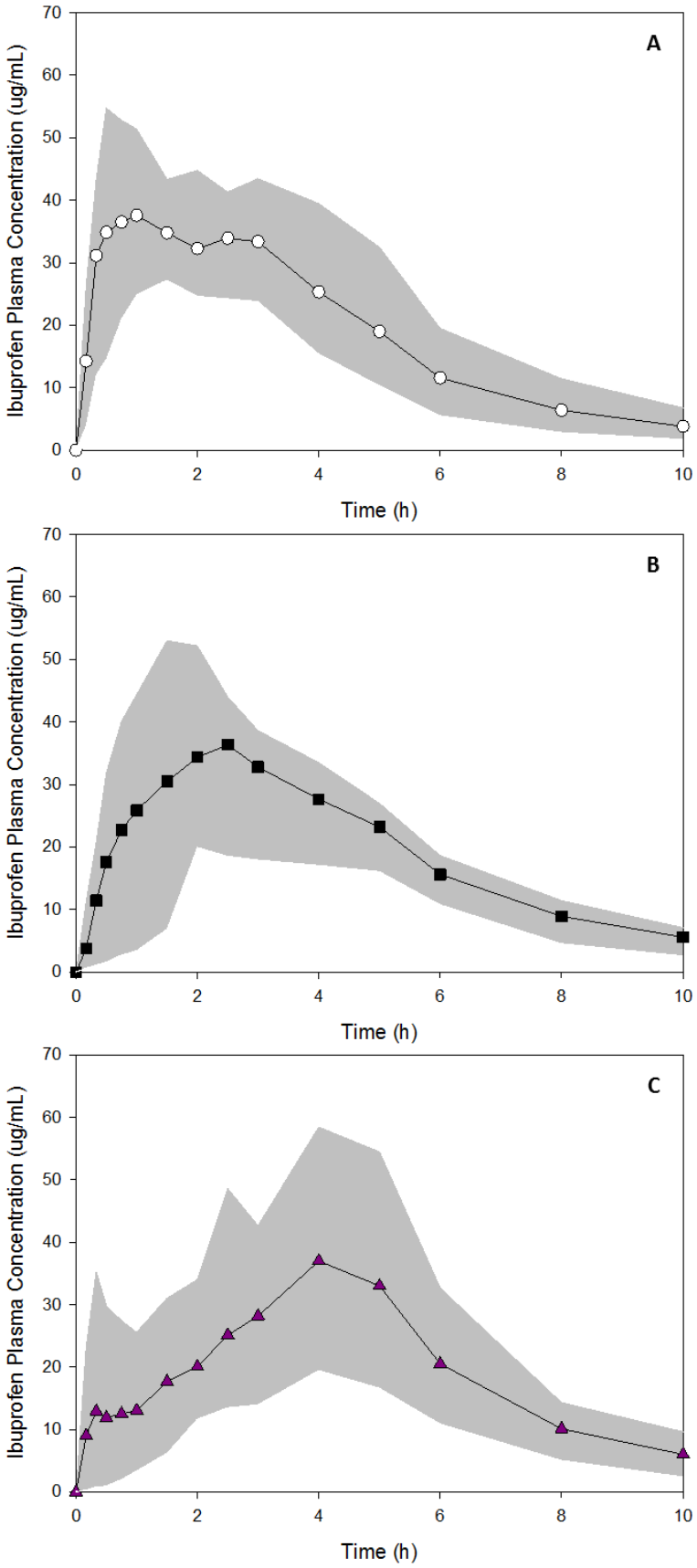
695 Figure 2



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697 Figure 3