Journal of Bioequivalence & Bioavailability
ISSN: 0975-0851

Aitken et al., J Bioequiv Availab 2018, 10:5
DOI: 10.4172/0975-0851.1000383

Research Article Open Access

A Single Dose, Four-Way, Open-Label Bioavailability Study of Oral Acetaminophen and Ibuprofen Combinations (Maxigesic®) under both Fasting and Fed Conditions

Phillip Aitken[1]*, Isam I Salem[2], Ioana Stanescu[1], Rebecca Playne[1] and Hartley C Atkinson[1]

[1]*AFT Pharmaceuticals Ltd, Auckland, New Zealand*
[2]*International Pharmaceutical Research Center, Amman, Jordan*

Abstract

The use of fixed-dose combination pain relief has the potential to enhance analgesic efficacy. The pharmacokinetic properties of oral medication can be altered by many factors, including food, concomitant medications, and drug formulation. During the present study the pharmacokinetic parameters of an acetaminophen and ibuprofen combination was tested in four formulations. Testing was performed in two clinical trials examining either fasting or fed dosing conditions in healthy male participants. Both trials were single center, open-label, randomized, single dose studies with a four-way crossover design to compare an oral suspension product, a sachet product, and two different tablet formulations (FDC500/150 and FDC325/97.5). Each dose contained acetaminophen 975-1000 mg and ibuprofen 292.5-300 mg. A total of 26 participants completed the fasting study, while 28 completed the fed study. The absorption limits of different formulations of acetaminophen and ibuprofen were within the 80-125% bioequivalence range in both fasting and fed conditions as measured by the area under the plasma concentration–time curve from time zero to the time of the last measurable plasma concentration ($AUC_{(0-t)}$) and the area under the curve from time zero to infinity ($AUC_{(0-\infty)}$). The maximum measured plasma concentration (C_{max}) for the two tablet formulations were bioequivalent in fed conditions for both acetaminophen and ibuprofen, while in fasting conditions ibuprofen was also bioequivalent. Food reduced the C_{max} and increased the time at which maximum measured plasma concentration occurred (t_{max}) of both acetaminophen and ibuprofen. This effect was largest in the sachet and oral suspension formulations, likely due to the drug being dissolved prior to administration, conferring more rapid absorption from the gastrointestinal tract. All treatments were well tolerated, with no treatment-emergent adverse events occurring.

Overall, differing formulations and fasting conditions can alter the pharmacokinetic parameters C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and t_{max} of acetaminophen and ibuprofen combinations although the overall absorption remains bioequivalent.

Keywords: Acetaminophen; Paracetamol; Ibuprofen; Bioequivalence; Combination; Pharmacokinetics; Food-effect

Introduction

Effective treatment of postoperative pain is essential to patient outcome and well-being. Clinically, inadequate pain relief can have profound implications including cardiovascular, respiratory and gastrointestinal adverse effects, emotional and physical suffering, sleep disturbances, delayed mobilization (promoting thromboembolism and delaying rehabilitation) and the progression to chronic pain syndromes. Economically, undertreated pain can lead to extended hospital stays or readmission [1]. Opioids are commonly used for the treatment of postoperative pain but their use is often limited by dose dependent adverse events (AEs) such as nausea and vomiting, constipation, sedation and respiratory depression [2]. Sustained opioid use can also lead to tolerance, resulting in increased dosing requirements and a subsequent increase in AEs, addiction and abuse [3]. The World Health Organization (WHO) advocates the use of multimodal analgesia for optimal pain control. Multimodal, or balanced, analgesia acts at different sites within the central and peripheral nervous systems to improve pain control while reducing opioid related AEs [4]. The first step on the WHO pain relief ladder involves the use of non-opioid analgesics, such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) [5,6]. Both acetaminophen and ibuprofen are effective analgesics that have been used for many years. Two single tablet combinations, Maxigesic®, containing acetaminophen 500 mg and ibuprofen 150 mg (FDC500/150), and Maxigesic® 325, containing acetaminophen 325 mg and ibuprofen 97.5 mg (FDC325/97.5), both have a ratio of 3.3:1 acetaminophen: ibuprofen and have been shown to be effective in the treatment of postoperative pain (third molar extraction) and superior to the same dose of either acetaminophen or ibuprofen alone [7,8]. Based on the superior analgesic efficacy of FDC500/150 and FDC325/97.5, two new pharmaceutical formulations were developed: a sachet formulation (acetaminophen 500 mg and ibuprofen 150 mg, Maxigesic® Sachets) and an oral suspension formulation (acetaminophen 160 mg and ibuprofen 48 mg/5 ml) developed for the pediatric population (Maxigesic® Oral Suspension). Efficacy studies have been performed on FDC500/150 [7] and FDC325/97.5 [8] formulations. The tablet formulations have been tested in placebo-controlled trials of moderate-severe dental pain following third molar removal with both tablets providing improved pain relief over comparable doses of either monotherapy or placebo [7,8]. A pharmacokinetic/pharmacodynamic study assessed the oral

***Corresponding author:** Phillip Aitken, AFT Pharmaceuticals Ltd, PO Box 33 203, Takapuna, Auckland, 0622, New Zealand, Tel: +64 9 488 0232; Fax: +64 9 488 0234; E-mail: phillip.aitken@aftpharm.com

Received November 14, 2018; **Accepted** November 27, 2018; **Published** December 04, 2018

Citation: Aitken P, Salem II, Stanescu I, Playne R, Atkinson HC (2018) A Single Dose, Four-Way, Open-Label Bioavailability Study of Oral Acetaminophen and Ibuprofen Combinations (Maxigesic®) under both Fasting and Fed Conditions. J Bioequiv Availab 10: 84-91. 383. doi: 10.4172/0975-0851.1000383

suspension formulation in children (2-12 years) undergoing (adeno) tonsillectomy [9]. A lower dose (acetaminophen 12 mg/kg + ibuprofen 3.6 mg/kg) was compared against a higher dose (acetaminophen 15 mg/kg + ibuprofen 4.5 mg/kg). Pharmacokinetic parameters C_{max} and $AUC_{(0-t)}$ were consistent with a 25% increase in dose while remaining well tolerated by the patients. While this was not designed as an efficacy study and as such had no monotherapy or placebo comparators, other previous placebo-controlled postoperative studies of the individual components in pediatric patients show a significant reduction in the requirement of rescue analgesia [10,11]. Modelling data derived from the oral suspension study demonstrates a significant pain score reduction in children administered the combination in comparison to comparable doses of either monotherapy [12]. Previous bioequivalence studies have found that concomitant administration of acetaminophen and ibuprofen in FDC500/150 does not alter the pharmacokinetic profiles of either acetaminophen or ibuprofen in the fasted state and there was no effect of food on absorption [13]. The bioequivalence to monotherapy was confirmed in both oral tablet and intravenous (IV) formulations [13,14]. Other bioequivalence studies have found that the addition of ibuprofen can lead to an increase in the rate of absorption of acetaminophen [15,16]. The ingestion of food can alter the rate and extent of drug absorption and this has been shown to occur with both acetaminophen and ibuprofen previously [16-24]. This study aimed to determine and compare the pharmacokinetic parameters (C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, t_{max}, K_{el}, and $t_{1/2}$) of the four fixed-dose formulations of acetaminophen and ibuprofen (FDC500/150, FDC325/97.5, Sachets, Oral Suspension) in either fed or fasting conditions.

Methods

Trial design

Each admitted participant was administered single doses of the four acetaminophen + ibuprofen combination treatments in a randomized, crossover fashion. The study was an open-label, four-way crossover design with balanced sequences. Other than the difference in fasting status, each study followed the same methodology. Studies were registered on the Australian New Zealand Clinical Trials Registry (Fasting study: ACTRN12616000418471; Fed study: ACTRN12616000419460). Studies were conducted in compliance with GCP including the Declaration of Helsinki and all applicable regulatory requirements, with approval by the Institutional Review Board of the International Pharmaceutical Research Center (IPRC), Amman, Jordan and Jordanian FDA.

Participant selection

In the fasting study 60 subjects were screened, of whom 30 enrolled. In the fed study 64 subjects were screened, of whom 30 enrolled. All subjects were healthy male volunteers aged between 18 and 50 years with a body mass index (BMI) of 18.5-30.0 kg/m^2 with no significant disease as determined by medical history, physical examination and laboratory tests. Patients were excluded if they had taken prescription medications in the last 14 days or over the counter medications in the last three days, with the exception of the study medications. Written informed consent was obtained for each participant prior to commencing any screening procedures, which included recording demographic data, vital signs, physical examination and medical history assessments, hematology, biochemistry, serology, urinalysis, drugs of abuse test, alcohol screening test and concomitant medications.

Treatment and study procedures

Participants were admitted to the study site the night prior to the administration of study drugs, supervised for 10 hours for overnight fasting, and confined until the 12 h blood sample was collected. Each participant received a dose of the randomly assigned treatments as outlined below:

- Treatment A: Single-dose, Oral Suspension, 31.25 ml of acetaminophen 160 mg and ibuprofen 48 mg / 5 ml (total dose acetaminophen 1000 mg and ibuprofen 300 mg)
- Treatment B: Single-dose, Sachet, acetaminophen 1000 mg and ibuprofen 300 mg / sachet (total dose acetaminophen 1000 mg and ibuprofen 300 mg)
- Treatment C: Single-dose, two tablets of FDC500/150 (total dose acetaminophen 1000 mg and ibuprofen 300 mg)
- Treatment D: Single-dose, three tablets of FDC325/97.5 (total dose acetaminophen 975 mg and ibuprofen 292.5 mg)

All drugs were administered with 240 ml water. There was a washout period of 3 days between each consecutive study drug administration.

In the fasting study, treatments were administered following an overnight fast of at least 10 hours. Participants were fed a standardized meal at least ten hours prior to drug administration and at four and eight hours after study drug administration.

In the fed state study, subjects were admitted the night before study drug administration, supervised for at least 10 hours of overnight fasting, then were fed a standardized breakfast 30 minutes prior to study drug administration. Participants were fed a standardized meal at five and nine hours after study drug administration.

A cannula was inserted into the subject's forearm vein to collect samples before study drug administration for up to 12 hours post-dose. The same schedule was repeated in each period. Blood samples (6 ml) were collected immediately before study drug administration at 0.00 h (pre-dose) and 5, 15, 30, 45 minutes and 1.00, 1.25, 1.50, 2.00, 3.00, 6.00, 8.00, 10.00 and 12.00 h after administration of study drugs for each period. Blood samples (11 ml) were also collected during screening and at the end of each study period for hematology, biochemistry and serology testing. The total number of blood draws per participant during each study was 61. All blood samples were collected in lithium heparinized tubes. After centrifugation the resulting plasma samples were immediately stored under a nominal temperature of -70°C until analysed.

Bioanalytical methods

Plasma sample analyses were conducted using validated analytical methods developed at IPRC diagnostic laboratory as described previously [13]. Briefly, plasma concentrations of acetaminophen and ibuprofen in human plasma (Li-heparin) were determined using validated liquid chromatography and mass spectrometry procedures (LC/MS/MS). Acetaminophen plasma concentrations were analyzed using API-3000 and Quattro premier mass spectrometer in multiple reaction monitoring (MRM) mode using turbo Ion Spray with positive ionization. The Q1 was 152.12 m/s, while Q3 was 110.07 m/s. The chromatographic separation of acetaminophen employed a C18 column using a mobile phase consisting of de-ionized water, formic acid and acetonitrile. Calibration curves were linear over the working range of 50-20000 ng/mL with a regression coefficient (R2) ≥ 0.99937. The lower limit of quantification (LLOQ) was 50 ng/mL (precision 3.44%, accuracy 93.69%). For this method quality control (QC) samples were prepared at 150, 2500, 10000, and 15000 ng/ml levels. Accuracy using these QC samples ranged between 97.99% - 109.12%; while precision ranged between 1.57% - 2.16%. Long term

stability was studied for plasma samples containing acetaminophen. The drug was found stable for 309 days at -70°C. Ibuprofen plasma concentrations were analyzed using a Sciex API 3000 & API 4000 triple quadrupole mass spectrometer in MRM mode, using turbo Ion Spray with negative ionization. The Q1 was 205.25 m/s, while Q3 was 159.1 m/s. The selective analysis of ibuprofen was achieved on Symmetry C18 Column by using a mobile phase consisting of ammonium formate, methanol and acetonitrile. Calibration curves were linear over the concentration rage of 50-35000 ng/mL R2 ≥ 0.9975. The LLOQ was 50 ng/mL (precision 8.85%, accuracy 104.25%). For this method quality control (QC) samples were prepared at 150, 1250, 12500, 17500 and 27000 ng/ml. Accuracy using these QC samples ranged between 88.09% - 94.94%, while precision ranged between 0.84% - 2.21%. Long term stability of plasma samples containing ibuprofen found the drug stable for 309 days at -70°C.

Pharmacokinetic analysis

The pharmacokinetic parameters of acetaminophen and ibuprofen for all subjects who completed the study were estimated using standard non-compartmental methods. The maximum plasma concentration (C_{max}) and the time to peak plasma concentration (t_{max}) were taken directly from the measured data. The area under the plasma concentration-time curve ($AUC_{(0-t)}$) was calculated from measured data points from time of administration to time of last quantifiable concentration (C_{last}) by the linear trapezoidal rule. The elimination rate constant (K_{el}) was calculated by linear least-squares regression analysis using the last three (or more) non-zero plasma concentrations. The area under the plasma concentration-time curve extrapolated to infinity ($AUC_{(0-\infty)}$) was calculated according to the following formula:

$$AUC_{(0-\infty)} = AUC_{(0-t)} + C_{last} / [Ln\ (2) / t_{1/2}]$$

Where C_{last} is the last quantifiable concentration.

The ratio $AUC_{(0-t)}$ / $AUC_{(0-\infty)}$ as a percent were determined as an indicator for the adequacy of sampling time.

The elimination half-life ($t_{1/2}$) was calculated as:

$$t_{1/2} = Ln\ (2) / (-b)$$

Where *b* was obtained as the slope of the linear regression of the $\log_e$ transformed plama concentrations versus time in the terminal period of the plasma curve.

Statistical methods

Pharmacokinetic calculations and statistical analysis was performed using Kinetica™ version 5.1 SP1 software. The statistical evaluation of relative bioavailability included analysis of variance (ANOVA) in all derived pharmacokinetic parameters, calculation of formulation ratios (point estimates) and parametric confidence interval for $\log_e$ transformed C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ parameters. ANOVA tested for period, subject (sequence) and treatment effects. The mean $t_{1/2}$ was compared between treatments using ANOVA. T_{max} was compared between formulations using Wilcoxon signed rank tests. The ratios of the geometric means used to test bioequivalence were calculated from $\log_e$ transformed data for C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$. The differences between the $\log_e$ means and the 90% confidence interval of the difference (derived from the residual variance from the ANOVA model) were back-transformed to estimate the ratio of each two formulations and the confidence interval.

Safety

Evaluation of safety was based on the reported AEs, laboratory tests, electrocardiograms, physical examination and vital signs measurements.

Results

Participants

In the fasting study 60 subjects were screened, of whom 30 enrolled and 26 completed the crossover and were included in the pharmacokinetic analysis. In the fed study 64 subjects were screened, of whom 30 enrolled and 28 completed the crossover and were included in the pharmacokinetic analysis. Both studies included two alternate subjects, leading to two withdrawals as part of the protocol. Two subjects also withdrew from the fasting study for personal reasons, one after administration of the first study drug and the other after administration of the second study drug. Both studies were conducted in 2016 at IPRC, Amman, Jordan. The baseline demographic data for each study is presented in Table 1.

Pharmacokinetic results

Fasting study: The C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, t_{max}, $t_{1/2}$, K_{el} for each active product for each treatment from this study are presented in Table 2. Acetaminophen and ibuprofen related pharmacokinetic parameters (C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$) were compared between the four different treatments under fasting conditions. The plasma concentration of acetaminophen and ibuprofen over time is displayed in Figure 1. Both $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ limits fell within the 80-125% bioequivalence range for both acetaminophen and ibuprofen for all treatment comparisons (Table 3). Limits of C_{max} for acetaminophen fell outside the 80-125% bioequivalence range for all treatment comparisons except for Oral Suspension *vs.* FDC325/97.5 (A/D) comparison. Limits of C_{max} for ibuprofen fell within the 80-125% bioequivalence range for treatment comparisons Oral Suspension *vs.* FDC500/150 (A/C), FDC500/150 *vs.* FDC325/97.5 (C/D) and Oral Suspension *vs.* FDC500/150 (A/D) but not for Sachet *vs.* FDC325/97.5 (B/C), Sachet *vs.* FDC325/97.5 (B/D) and Oral Suspension *vs.* Sachet (A/B) (Table 3). Point estimates of C_{max} and $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ between tablets, FDC500/150 and FDC325/97.5 (C/D) were within the 80-125% bioequivalence range, although the upper limit of acetaminophen was >125% and there was high intrasubject variability (CV = 32.69%). Limits of $t_{1/2}$ for both acetaminophen and ibuprofen fell within the 80-125% bioequivalence range for all treatment comparisons (data not shown). Wilcoxon signed rank tests for acetaminophen t_{max} showed significant differences between the different doses of acetaminophen ($p \leq 0.01$) for Oral Suspension *vs.* FDC500/150 (A/C), Sachet *vs.* FDC325/97.5 (B/C) and Sachet *vs.* FDC325/97.5 (B/D) while for Oral Suspension *vs.* Sachet (A/B), Oral Suspension *vs.* FDC500/150 (A/D) and FDC500/150 *vs.* FDC325/97.5 (C/D) there were no significant differences ($p > 0.05$). Wilcoxon signed rank tests for ibuprofen t_{max} showed significant differences between the different doses of ibuprofen ($p \leq 0.001$) for Oral Suspension *vs.* FDC500/150 (A/C), Oral Suspension *vs.* Sachet (A/B), Sachet *vs.* FDC325/97.5 (B/C) and Sachet *vs.* FDC325/97.5 (B/D) while for Oral Suspension *vs.* FDC500/150 (A/D) and FDC500/150 *vs.* FDC325/97.5

Characteristic	Fasting Study	Fed Study
n	26	28
Age, years	34 ± 8.54	27 ± 8.28
Height, cm	175 ± 6.93	171 ± 5.03
Weight, kg	75 ± 11.29	67 ± 10.96
BMI, kg/m²	24.5 ± 3.30	22.9 ± 3.34
Smoker	19 (73%)	20 (71%)

Table 1: Demographic data. Mean ± SD, or n (%).

	Fasting Study				Fed Study			
	Acetaminophen (mean ± SD)				Acetaminophen (mean ± SD)			
	A: Oral Suspension	B: Sachet	C: FDC500/150	D: FDC325/97.5	A: Oral Suspension	B: Sachet	C: FDC500/150	D: FDC325/97.5
C_{max} (ng/ml)	14825 ± 5817	17572 ± 7869	13497 ± 7123	15368 ± 5717	7488 ± 2338	6762 ± 2515	9234 ± 4776	9629 ± 5024
$AUC_{(0-t)}$ (ng.h/ml)	32276 ± 7574	35507 ± 8911	32199 ± 8356	32838 ± 7577	30645 ± 7753	31523 ± 8486	31687 ± 9151	31929 ± 9498
$AUC_{(0-\infty)}$ (ng.h/ml)	33765 ± 8455	37028 ± 9573	33832 ± 9155	34651 ± 8388	32719 ± 8481	33570 ± 8486	33726 ± 9850	33789 ± 10188
t_{max} (h)	0.38 ± 0.15	0.32 ± 0.13	0.81 ± 0.58	0.61 ± 0.59	0.96 ± 0.60	1.22 ± 0.98	1.19 ± 0.73	1.21 ± 0.77
$t_{1/2}$ (h)	2.84 ± 0.52	2.90 ± 0.70	3.04 ± 0.76	3.31 ± 0.75	3.14 ± 0.56	3.08 ± 0.77	3.00 ± 0.60	2.90 ± 0.41
K_{el} (1/h)	0.25 ± 0.04	0.25 ± 0.05	0.24 ± 0.04	0.22 ± 0.06	0.23 ± 0.05	0.24 ± 0.05	0.24 ± 0.05	0.24 ± 0.03
	Ibuprofen (mean ± SD)				Ibuprofen (mean ± SD)			
	A: Oral Suspension	B: Sachet	C: FDC500/150	D: FDC325/97.5	A: Oral Suspension	B: Sachet	C: FDC500/150	D: FDC325/97.5
C_{max} (ng/ml)	19272 ± 3897	27221 ± 4890	19279 ± 5018	20654 ± 4717	14696 ± 3318	12669 ± 2251	17665 ± 6376	17513 ± 5039
$AUC_{(0-t)}$ (ng.h/ml)	74340 ± 13874	79550 ± 15556	75842 ± 13429	76106 ± 16447	66090 ± 13135	68700 ± 12763	66679 ± 13971	64687 ± 13651
$AUC_{(0-\infty)}$ (ng.h/ml)	76531 ± 15055	81321 ± 16452	78439 ± 14464	78329 ± 17471	69257 ± 14905	71716 ± 13506	68976 ± 14738	66966 ± 14490
t_{max} (h)	1.19 ± 0.79	0.50 ± 0.35	1.79 ± 1.39	1.48 ± 1.15	1.41 ± 0.72	1.93 ± 1.62	1.70 ± 1.43	1.55 ± 0.85
$t_{1/2}$ (h)	2.21 ± 0.30	2.18 ± 0.26	2.13 ± 0.26	2.19 ± 0.33	2.25 ± 0.34	2.28 ± 0.46	2.19 ± 0.29	2.26 ± 0.50
K_{el} (1/h)	0.32 ± 0.04	0.32 ± 0.04	0.33 ± 0.04	0.32 ± 0.04	0.32 ± 0.05	0.31 ± 0.05	0.32 ± 0.04	0.32 ± 0.06

$AUC_{(0-t)}$ from time zero to the time of the last measurable plasma concentration, $AUC_{(0-\infty)}$ area under the plasma concentration–time curve from time zero to infinity, C_{max} maximum measured plasma concentration, t_{max} time at which maximum measured plasma concentration occurred, $t_{1/2}$ elimination half-life, K_{el} elimination rate constant, FDC fixed-dose combination.

Table 2: Pharmacokinetic parameters of acetaminophen and ibuprofen in oral combinations.

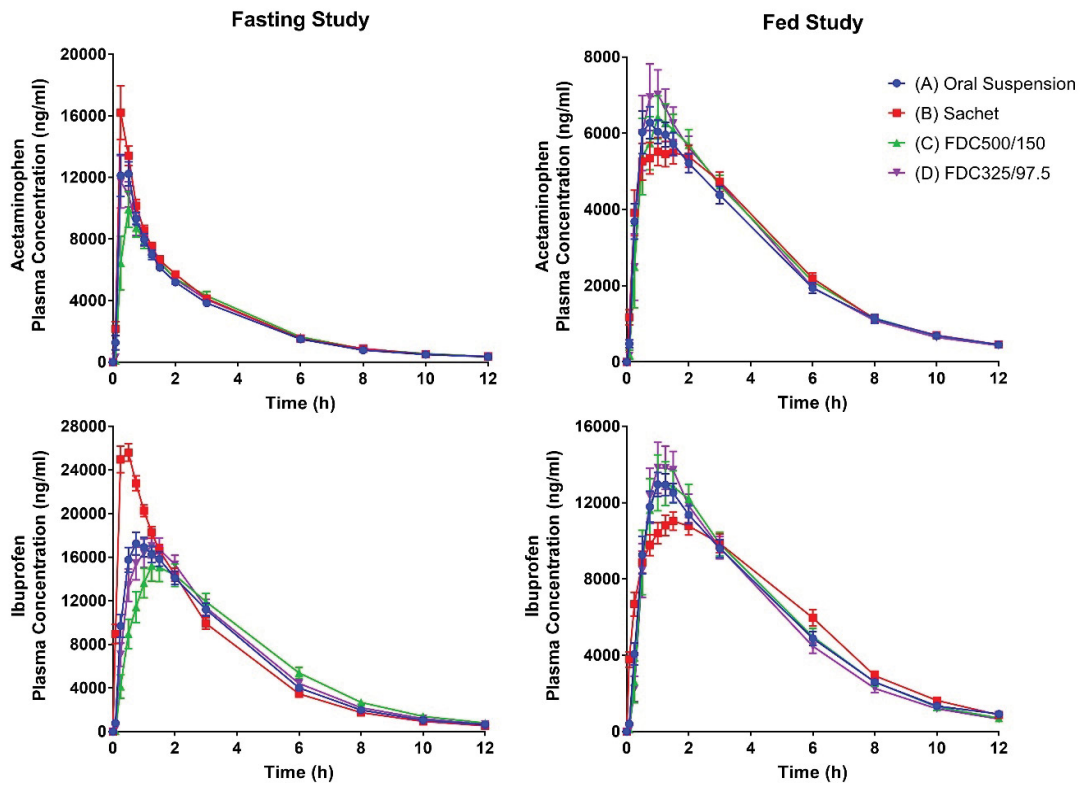

Figure 1: Plasma concentration of acetaminophen and ibuprofen over time in fasting and fed conditions (mean ± SEM). FDC, fixed dose combination.

(C/D) there were no significant differences ($p>0.05$). There was no difference between treatments in K_{el} for either acetaminophen or ibuprofen. For the $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of acetaminophen, there were statistically significant differences between the different treatments of acetaminophen ($p<0.05$) for formulation, subject (seq) and sequence effects but not for period effect. For C_{max} of acetaminophen, there were statistically significant differences between the different treatments of acetaminophen ($p<0.05$) for subject (seq) and formulation effects but not for period and sequence effects (Table 4). The mean C_{max} of the sachet formulation was significantly higher when compared to other formulations for both acetaminophen (12.5-23.2%) and ibuprofen (24.1-29.2%) (Table 2). For the $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of ibuprofen,

there were statistically significant differences between the different treatments of ibuprofen ($p<0.05$) for period, subject (seq) and sequence effects but not for formulation effect. For C_{max} of ibuprofen, there were statistically significant differences between the different treatments of ibuprofen ($p<0.05$) for formulation effect but not for period, subject (seq) and sequence effects (Table 4).

Fed study: The C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, t_{max}, $t_{1/2}$, K_{el} for each active product for each treatment from this study are presented in Table 2. Acetaminophen and ibuprofen related pharmacokinetic parameters (C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$) were compared between the four different treatments under fed conditions and it was found that both $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ limits fell within the 80-125% bioequivalence range for both acetaminophen and ibuprofen for all individual comparisons (Table 5). Limits of C_{max} for both acetaminophen and ibuprofen were within 80-125% bioequivalence range for the FDC500/150 *vs.* FDC325/97.5 (C/D) comparison but not for the other treatment comparisons (Table 5). Limits of $t_{1/2}$ for both acetaminophen and ibuprofen fell within the 80-125% bioequivalence range for all treatment comparisons (data not shown). Wilcoxon signed rank tests for t_{max} of both acetaminophen and ibuprofen showed no significant differences between the different doses of acetaminophen ($p>0.05$) for all treatment comparisons. There was no difference between treatments in K_{el} for either acetaminophen or ibuprofen. For $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of acetaminophen, there were statistically significant differences between the different treatments of acetaminophen ($p<0.05$) for subject (seq) and sequence effects but not for period and formulation effects. For C_{max} of acetaminophen, there were statistically significant differences between the different treatments of acetaminophen ($p<0.05$) for subject (seq), formulation and sequence effects but not for period effect (Table 4). For $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of ibuprofen, there were statistically significant differences between the different treatments of ibuprofen ($p<0.05$) for period, subject (seq), sequence and formulation effects. For C_{max} of ibuprofen, there were statistically significant differences between the different treatments of ibuprofen ($p<0.05$) for formulation and sequence effects but not for period and subject (seq) effects (Table 4). A rough estimate of the effect of food on the pharmacokinetics of each of the products used in this study can be drawn by comparing the data between the fed and fasted studies. The C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ for each active product for each treatment from this study are presented in Table 2. Table 6 displays the ratio of the pharmacokinetic parameters obtained from fed state and the fasting studyOverall, food does not appear to have a substantial impact on the extent of absorption of acetaminophen and ibuprofen ($AUC_{(0-t)}$ and $AUC_{(0-\infty)}$) nor the peak concentration (C_{max}) of ibuprofen from FDC500/150 and FDC325/97.5 (ratio >80%). However, the C_{max} of acetaminophen from each product and the C_{max} of ibuprofen from Oral Suspension and Sachets is reduced to a greater extent by food. This is particularly true for both active products from Sachets (ratios <50%). An extension in t_{max} that was approximately inversely proportional to the reduction in C_{max} was observed for both ingredients in all products when administered with food.

Safety analysis

No AEs related to the study drugs occurred during the entire course of these studies. A single subject had toothache, unrelated to the study drug, during the FDC325/97.5 phase in the fasting study. There were no withdrawals due to AEs in either study. The study drugs were well tolerated by all participants in both studies.

	Acetaminophen				Ibuprofen			
	Point Estimate %	Lower Limit %	Upper Limit %	Intrasubject CV% (Logarithmic)	Point Estimate %	Lower Limit %	Upper Limit %	Intrasubject CV% (Logarithmic)
A/C								
C_{max}	115.03	98.9	133.79	32.69	101.2 [a]	91.04	112.5	22.91
$AUC_{(0-t)}$	100.92 [a]	97.82	104.11	6.74	97.82 [a]	92.95	102.94	11.05
$AUC_{(0-\infty)}$	100.38 [a]	97.27	103.59	6.8	97.32 [a]	92.76	102.1	10.38
B/C								
C_{max}	133.67	114.92	155.47	32.69	144.08	129.61	160.17	22.91
$AUC_{(0-t)}$	110.39 [a]	107.01	113.89	6.74	104.43 [a]	99.23	109.9	11.05
$AUC_{(0-\infty)}$	109.64 [a]	106.25	113.14	6.8	103.22 [a]	98.39	108.29	10.38
C/D								
C_{max}	118.84	102.18	138.23	32.69	107.49 [a]	96.69	119.49	22.91
$AUC_{(0-t)}$	102.49 [a]	99.35	105.73	6.74	99.43 [a]	94.48	104.64	11.05
$AUC_{(0-\infty)}$	102.92 [a]	99.74	106.21	6.8	98.99 [a]	94.35	103.85	10.38
A/D								
C_{max}	96.79 [a]	83.21	112.57	32.69	94.15 [a]	84.69	104.67	22.91
$AUC_{(0-t)}$	98.46 [a]	95.44	101.58	6.74	98.38 [a]	93.49	103.53	11.05
$AUC_{(0-\infty)}$	97.53 [a]	94.51	100.64	6.8	98.31 [a]	93.71	103.14	10.38
B/D								
C_{max}	112.47	96.7	130.82	32.69	134.05	120.58	149.02	22.91
$AUC_{(0-t)}$	107.71 [a]	104.41	111.12	6.74	105.03 [a]	99.8	110.53	11.05
$AUC_{(0-\infty)}$	106.53 [a]	103.23	109.93	6.8	104.28 [a]	99.4	109.4	10.38
A/B								
C_{max}	86.05	73.99	100.09	32.69	70.24	63.18	78.08	22.91
$AUC_{(0-t)}$	91.41 [a]	88.61	94.31	6.74	93.67 [a]	89.01	98.58	11.05
$AUC_{(0-\infty)}$	91.55 [a]	88.72	94.48	6.8	94.28 [a]	89.86	98.91	10.38

$AUC_{(0-t)}$ from time zero to the time of the last measurable plasma concentration, $AUC_{(0-\infty)}$ area under the plasma concentration–time curve from time zero to infinity, C_{max} maximum measured plasma concentration. Treatment A = Oral Suspension, B = Sachet, C = FDC500/150, D = FDC325/97.5.

[a] Within the bioequivalence range of 80-125%

Table 3: Fasting study 90% confidence intervals of parametric means. Comparisons between treatment groups A, B, C and D.

	Fasting Study				Fed Study			
	Acetaminophen				Acetaminophen			
	Period	Subject (Seq)	Drug	Sequence	Period	Subject (Seq)	Drug	Sequence
C_{max}	0.443	≤0.001	0.021	0.423	0.986	0.003	0.01	0.037
$AUC_{(0-t)}$	0.468	≤0.001	≤0.001	≤0.001	0.342	≤0.001	0.415	≤0.001
$AUC_{(0-\infty)}$	0.345	≤0.001	≤0.001	≤0.001	0.23	≤0.001	0.542	≤0.001
	Ibuprofen				Ibuprofen			
C_{max}	0.332	0.05	≤0.001	0.485	0.905	0.053	≤0.001	0.02
$AUC_{(0-t)}$	0.04	≤0.001	0.183	≤0.001	0.042	≤0.001	0.004	≤0.001
$AUC_{(0-\infty)}$	0.032	≤0.001	0.227	0.002	0.016	≤0.001	≤0.001	≤0.001

$AUC_{(0-t)}$ from time zero to the time of the last measurable plasma concentration, $AUC_{(0-\infty)}$ area under the plasma concentration–time curve from time zero to infinity, C_{max} maximum measured plasma concentration, (Seq) sequence.

Table 4: P-values obtained from ANOVA of pharmacokinetic variables following single dose administration of treatments A, B, C and D.

	Acetaminophen				Ibuprofen			
	Point Estimate %	Lower Limit %	Upper Limit %	Intrasubject CV% (Logarithmic)	Point Estimate %	Lower Limit %	Upper Limit %	Intrasubject CV% (Logarithmic)
A/C								
C_{max}	86.27	73.64	101.07	35.59	86.54	77.19	97.02	25.7
$AUC_{(0-t)}$	97.33 [a]	94.14	100.64	7.5	99.41 [a]	96.59	102.32	6.48
$AUC_{(0-\infty)}$	97.60 [a]	94.52	100.77	7.2	100.47 [a]	97.52	103.52	6.72
B/C								
C_{max}	77.25	65.93	90.5	35.59	75.31	67.18	84.44	25.7
$AUC_{(0-t)}$	99.80 [a]	96.52	103.19	7.5	103.64 [a]	100.69	106.67	6.48
$AUC_{(0-\infty)}$	99.85 [a]	96.7	103.1	7.2	104.62 [a]	101.54	107.79	6.72
C/D								
C_{max}	103.65 [a]	88.47	121.43	35.59	101.41 [a]	90.45	113.69	25.7
$AUC_{(0-t)}$	100.33 [a]	97.04	103.74	7.5	97.12 [a]	94.36	99.97	6.48
$AUC_{(0-\infty)}$	99.77 [a]	96.63	103.02	7.2	97.17 [a]	94.31	100.12	6.72
A/D								
C_{max}	83.24	71.05	97.52	35.59	85.34	76.12	95.67	25.7
$AUC_{(0-t)}$	97.01 [a]	93.83	100.3	7.5	102.36 [a]	99.45	105.35	6.48
$AUC_{(0-\infty)}$	97.82 [a]	94.74	101.01	7.2	103.40 [a]	100.36	106.54	6.72
B/D								
C_{max}	74.53	63.61	87.32	35.59	74.27	66.25	83.26	25.7
$AUC_{(0-t)}$	99.47 [a]	96.21	102.85	7.5	106.71 [a]	103.68	109.83	6.48
$AUC_{(0-\infty)}$	100.08 [a]	96.93	103.33	7.2	107.67 [a]	104.5	110.94	6.72
A/B								
C_{max}	111.68	95.33	130.84	35.59	114.9	102.49	128.82	25.7
$AUC_{(0-t)}$	97.53 [a]	94.33	100.84	7.5	95.92 [a]	93.2	98.73	6.48
$AUC_{(0-\infty)}$	97.75 [a]	94.67	100.93	7.2	96.04 [a]	93.21	98.95	6.72

$AUC_{(0-t)}$ from time zero to the time of the last measurable plasma concentration, $AUC_{(0-\infty)}$ area under the plasma concentration–time curve from time zero to infinity, C_{max} maximum measured plasma concentration. Treatment A = Oral Suspension, B = Sachet, C = FDC500/150, D = FDC325/97.5.
[a] Within the bioequivalence range of 80-125%

Table 5: Fed study 90% confidence intervals of parametric means. Comparisons between treatment groups A, B, C and D.

	Oral Suspension	Sachet	FDC500/150	FDC325/97.5
Acetaminophen				
C_{max}	51%	38%	68%	63%
$AUC_{(0-t)}$	95%	89%	98%	97%
$AUC_{(0-\infty)}$	97%	91%	100%	98%
t_{max}	253%	381%	147%	198%
Ibuprofen				
C_{max}	76%	47%	92%	85%
$AUC_{(0-t)}$	89%	86%	88%	85%
$AUC_{(0-\infty)}$	90%	88%	88%	85%
t_{max}	118%	386%	95%	105%

$AUC_{(0-t)}$ from time zero to the time of the last measurable plasma concentration, $AUC_{(0-\infty)}$ area under the plasma concentration–time curve from time zero to infinity, C_{max} maximum measured plasma concentration, t_{max} time at which maximum measured plasma concentration occurred, FDC fixed dose combination.

Table 6: Ratio of Fed/Fasting Study pharmacokinetic parameters.

Discussion

The results of these studies show a significant effect of formulation on the pharmacokinetic parameters C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and t_{max} in fixed combination acetaminophen and ibuprofen under fasted and fed conditions. Though period, subject (seq), drug and sequence effects were observed following analysis of C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$, accumulation of the drugs is unlikely due to the single dose study design, with a washout period of three days, which covers more than ten half-lives of acetaminophen and ibuprofen. An adequate study design was chosen, with balanced sequences and healthy volunteers, while a significant subject (seq) effect may have occurred as each subject is assigned to only one sequence. A sequence effect would indicate a treatment by period effect. This can happen due to differences in environmental conditions between the periods affecting the formulations differently. Although this was controlled for as acetaminophen and ibuprofen are

not endogenous substances, concentrations of acetaminophen and ibuprofen in the following periods were undetectable in all volunteers and there were no differences in the management, analysis and storage of samples in each of the periods or in climatic conditions, dietary and physical activity of volunteers between study periods. Close inspection of the data reveals that there was some imbalance in the distribution of pharmacokinetic parameters in participants in each sequence group. This is likely attributable to statistical reasons, especially the small number of participants in each sequence group.

The pharmacokinetic parameters $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ limits fell within the 80-125% bioequivalence range for both acetaminophen and ibuprofen in both fasting and fed conditions for all formulation comparisons. This reinforces the evidence of a similar extent of absorption between all four formulations: Oral Suspension, Sachets, FDC500/150 and FDC325/97.5. However, the limits of C_{max} fell outside the 80-125% bioequivalence range for the majority of comparisons. The effect of food on bioavailability is generally greatest when the drug product is administered shortly after a meal is ingested [25,26]. In general, meals that are high in total calories and fat content are more likely to affect the gastrointestinal physiology and thereby result in a larger effect on the bioavailability of a drug substance or drug product [25-27]. Food typically increases the t_{max} and reduces the C_{max} in paracetamol and ibuprofen [28]. Administration of the combination tablet formulations following a meal resulted in an increase in t_{max} and decrease in C_{max} of acetaminophen compared to fasting conditions. However, food did not have a substantial impact on the overall extent of absorption of acetaminophen and ibuprofen, as measured by $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$. The food effect has been illustrated previously in tablet formulations of FDC500/150, with the C_{max} of acetaminophen and ibuprofen decreased in the fed state [13]. Another fixed-dose combination, FDC500/200, also has a food effect with a decreased C_{max} and increased t_{max} illustrated previously in tablet formulations of FDC500/150, with the Cmax of acetaminophen and ibuprofen decreased in the fed state [13]. Another fixed-dose combination, FDC500/200, also has a food effect with a decreased Cmax and increased tmax for both acetaminophen and ibuprofen in the fed state compared to the fasting state [16]. These studies only examined the effect of food on tablet formulations, which has the smallest food effect of any formulation in the present experiment. The liquid Sachet formulation had faster absorption (t_{max}) with a higher maximum plasma concentration (C_{max}) than the two tablet formulations for both active products. This effect was not observed when the products were taken on a full stomach. The food effect, with faster absorption seen under fasting conditions, was also present to a lesser extent in the Oral Suspension product. The increased food effect seen in the Sachet and Oral Suspension products is likely due to the fact that they are administered as solutions, therefore skipping the disintegration and dissolution steps required by the tablet formulations and providing an increased rate of absorption in the fasting state [28,29]. In practice, each of the fixed-dose combination formulations should be administered following food to provide consistent dosing and reduce the risk of NSAID related gastrointestinal AEs [30].

The C_{max} limits for the comparison between both tablets fell within the 80-125% bioequivalence range for ibuprofen in both fasting and fed conditions, and for acetaminophen in the fed condition. This shows that both tablet formulations are bioequivalent under normal fed conditions, but that under fasting conditions there was an increase in the C_{max} of acetaminophen in the lower dose formulation. While this effect is possibly due to statistical reasons, the increased C_{max} of the lower dose may actually be due to the decreased size of the individual tablets compared to FDC500/150 leading to an increased surface area and more rapid absorption. This is supported by the t_{max} measurements which were non-significantly faster in the fasting condition for FDC325/97.5 compared to FDC500/150 (acetaminophen tmax = 0.61 *vs.* 0.81 h, p = 0.059). Previously, both FDC500/150 and FDC325/97.5 have been shown to provide a significant increase in pain relief in a model of moderate to severe dental pain in contrast to comparable doses of the individual components or placebo [7,8]. As each formulation in the present experiment provides bioequivalent $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of each individual component, the overall pain-relieving efficacy is expected to be similar for each formulation. This is despite C_{max} being not within the bioequivalence range for all formulation comparisons.

Conclusion

The overall extent of absorption of four different formulations of a combined combination product containing acetaminophen and ibuprofen are within the bioequivalent limits in both fasting and fed conditions as measured by $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$. The C_{max} of two different tablet formulations (FDC500/150 and FDC325/97.5) were bioequivalent in fed conditions for both acetaminophen and ibuprofen, while in fasting conditions ibuprofen was also bioequivalent. Food reduces the C_{max} and increases t_{max} of both acetaminophen and ibuprofen. This effect is largest in the Sachet and Oral Suspension formulations. Overall, differing formulations and fasting conditions can alter the pharmacokinetics of acetaminophen and ibuprofen combinations although overall extent of absorption remains bioequivalent. This study indicates that administration of the novel Sachet and Oral Suspension formulations of combination acetaminophen and ibuprofen may confer an equivalent pain-relieving effect to the existing tablet formulations.

Acknowledgement

We thank the staff at IPRC for the administration of the study protocol, data collection and analysis. We are grateful to the volunteers who participated in this study. This study was funded by AFT Pharmaceuticals Ltd, Auckland, NZ.

Conflicts of Interest

H Atkinson is a shareholder and Managing Director of AFT Pharmaceuticals, I Stanescu is a shareholder and employee of AFT Pharmaceuticals Ltd, P Aitken and R Playne are employees of AFT Pharmaceuticals Ltd. I Salem is an employee of IPRC.

References

1. Apfelbaum JL, Chen C, Mehta SS, Gan TJ (2003) Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged: Anesth Analg 97: 534-540.
2. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, et al. (2008) Opioid complications and side effects. Pain Physician 11: S105-S120.
3. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, et al. (2015) Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain 156: 569-576.
4. Elvir-Lazo OL, White PF (2010) The role of multimodal analgesia in pain management after ambulatory surgery. Curr Opin Anesthesiol 23: 697-703.
5. Wong C, Lau E, Palozzi L, Campbell F (2012) Pain management in children: part 1 — pain assessment tools and a brief review of nonpharmacological and pharmacological treatment options. Can Pharm J Rev Pharm Can 145: 222-225.
6. Tobias JD (2014) Acute pain management in infants and children—part 1: pain pathways, pain assessment, and outpatient pain management. Pediatr Ann 43: e163-e168.
7. Merry AF, Gibbs RD, Edwards J, Ting GS, Frampton C, et al. (2010) Combined acetaminophen and ibuprofen for pain relief after oral surgery in adults: a randomized controlled trial. Br J Anaesth 104: 80-88.
8. Daniels SE, Atkinson HC, Stanescu I, Frampton C (2018) Analgesic efficacy of an acetaminophen/ibuprofen fixed-dose combination in moderate to severe

postoperative dental pain: a randomized, double-blind, parallel-group, placebo-controlled trial. Clin Ther 40: 1765-1776.e5.

9. Playne R, Anderson BJ, Frampton C, Stanescu I, Atkinson HC, et al. (2018) Analgesic effectiveness, pharmacokinetics, and safety of a paracetamol/ibuprofen fixed-dose combination in children undergoing adenotonsillectomy: A randomized, single-blind, parallel group trial. Pediatr Anesth.

10. Viitanen H, Tuominen N, Vääräniemi H, Nikanne E, Annila P, et al. (2003) Analgesic efficacy of rectal acetaminophen and ibuprofen alone or in combination for paediatric day-case adenoidectomy. Br J Anaesth 91: 363-367.

11. Pickering AE, Bridge HS, Nolan J, Stoddart PA (2002) Double-blind, placebo-controlled analgesic study of ibuprofen or rofecoxib in combination with paracetamol for tonsillectomy in children. Br J Anaesth 88: 72-77.

12. Hannam JA, Anderson BJ, Potts A (2018) Acetaminophen, ibuprofen, and tramadol analgesic interactions after adenotonsillectomy. Pediatr Anesth 28: 841-851.

13. Atkinson HC, Stanescu I, Beasley CP, Salem II, Frampton C, et al. (2015) A pharmacokinetic analysis of a novel fixed dose oral combination of paracetamol and ibuprofen, with emphasis on food effect. J Bioequivalence Bioavailab 7: 150-154.

14. Atkinson HC, Stanescu I, Frampton C, Salem II, Beasley CPH, et al. (2015) Pharmacokinetics and bioavailability of a fixed-dose combination of ibuprofen and paracetamol after intravenous and oral administration. Clin Drug Investig 35: 625-632.

15. Wright CE, Antal EJ, Gillespie WR, Albert KS (1983) Ibuprofen and acetaminophen kinetics when taken concurrently. Clin Pharmacol Ther 34: 707-710.

16. Tanner T, Aspley S, Munn A, Thomas T (2010) The pharmacokinetic profile of a novel fixed-dose combination tablet of ibuprofen and paracetamol. BMC Clin Pharmacol 10.

17. Armstrong J, Challenor VF, Macklin BS, Renwick AG, Waller DG, et al. (1997) The influence of two types of meal on the pharmacokinetics of a modified-release formulation of nifedipine (Adalat Retard). Eur J Clin Pharmacol 53: 141-143.

18. Smith S, Collaku A, Heaslip L, Yue Y, Starkey YY, et al. (2012) 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. Drug Dev Ind Pharm 38: 372-379.

19. Stillings M, Havlik I, Chetty M, Clinton C, Schall R, et al. (2000) Comparison of the pharmacokinetic profiles of soluble aspirin and solid paracetamol tablets in fed and fasted volunteers. Curr Med Res Opin 16: 115-124.

20. Divoll M, Greenblatt DJ, Ameer B, Abernethy DR (1982) Effect of food on acetaminophen absorption in young and elderly subjects. J Clin Pharmacol 22: 571-576.

21. Kapil R, Nolting A, Roy P, Fiske W, Benedek I, et al. (2004) Pharmacokinetic properties of combination oxycodone plus racemic ibuprofen: two randomized, open-label, crossover studies in healthy adult volunteers. Clin Ther 26: 2015-2025.

22. Borin MT, Khare S, Beihn RM, Jay M (1990) The effect of food on gastrointestinal (GI) transit of sustained-release ibuprofen tablets as evaluated by gamma scintigraphy. Pharm Res 7: 304-307.

23. Pargal A, Kelkar MG, Nayak PJ (1996) The effect of food on the bioavailability of ibuprofen and flurbiprofen from sustained release formulations. Biopharm Drug Dispos 17: 511-519.

24. Siemon D, de Vries JX, Stötzer F, Walter-Sack I, Dietl R, et al. (1997) Fasting and postprandial disposition of R(-)- and S(+)-ibuprofen following oral administration of racemic drug in healthy individuals. Eur J Med Res 2: 215-219.

25. Welling PG (1996) Effects of food on drug absorption. Annu Rev Nutr 16: 383-415.

26. Custodio JM, Wu CY, Benet LZ (2008) Predicting drug disposition, absorption/elimination/transporter interplay and the role of food on drug absorption. Adv Drug Deliv Rev 60: 717-733.

27. Charman WN, Porter CJH, Mithani S, Dressman JB (1997) Physicochemical and physiological mechanisms for the effects of food on drug absorption: the role of lipids and pH. J Pharm Sci 86: 269-282.

28. Moore RA, Derry S, Wiffen PJ, Straube S (2015) Effects of food on pharmacokinetics of immediate release oral formulations of aspirin, dipyrone, paracetamol and NSAIDs - a systematic review: Food and pharmacokinetics of analgesics. Br J Clin Pharmacol 80: 381-388.

29. Daniel-Mwambete K, Torrado S, Cuesta-Bandera C, Ponce-Gordo F, Torrado J, et al. (2004) The effect of solubilization on the oral bioavailability of three benzimidazole carbamate drugs. Int J Pharm 272: 29-36.

30. Castellsague J, Riera-Guardia N, Calingaert B, Varas-Lorenzo C, Fourrier-Reglat A, et al. (2012) Individual NSAIDs and upper gastrointestinal complications: a systematic review and meta-analysis of observational studies (the SOS project). Drug Saf 35: 1127-1146.