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A Pharmacokinetic Analysis of a Novel Fixed Dose Oral Combination of Paracetamol and Ibuprofen, with Emphasis on Food Effect

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Abstract

Purpose: The published literature asserts that the individual pharmacokinetic parameters of ibuprofen and paracetamol are not altered following concurrent administration in a fasted state. The present study was performed to confirm these observations for a novel fixed dose oral combination (*Maxigesic®*) containing paracetamol 500 mg and ibuprofen 150 mg/tablet. Additionally, the effect of food on the pharmacokinetic profile of the *Maxigesic®* formulation was assessed.

Methods: A single-dose, open-label, randomized, four-way crossover pharmacokinetic study was undertaken in 28 healthy volunteers. Serial plasma samples were assayed for both paracetamol and ibuprofen concentrations using validated LC-MS/MS methods. Ratios of C_{max}, $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow\infty}$ were analysed for bioequivalence as determined by 90% confidence intervals (CI) and t_{max} values were compared using the Wilcoxon matched pairs test.

Results: In the fasted state, pharmacokinetic parameters for ibuprofen and paracetamol were similar between the fixed dose combination and its mono-components. Ratios of C_{max}, $AUC_{0\rightarrow 12h}$, and $AUC_{0\rightarrow\infty}$ values fell within the 80-125% acceptable bioequivalence range and t_{max} values were not altered significantly.

In the fed state compared with the fasted state, the t_{max} from the fixed dose combination was significantly prolonged for paracetamol (53 vs 30 minutes) and slightly delayed for ibuprofen (53 vs 90 minutes). Slower absorption of paracetamol resulted in a reduced C_{max} which was outside the 80-125% bioequivalence range. Additionally, in the fed state, the extent of absorption of both paracetamol and ibuprofen from the fixed dose combination was slightly less compared with the fasted state, although the 90% CI for the $AUC_{0\rightarrow 12h}$ and $AUC0_{\rightarrow\infty}$ ratios were within the 80-125% bioequivalence range.

Conclusions: The concomitant administration of ibuprofen and paracetamol in a fixed dose combination (*Maxigesic®*) does not alter the pharmacokinetic profiles of either drug in the fasted state and there was no effect of food on the absorption from the fixed dose combination.

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

Introduction

There are many analgesic options available to physicians, but most have limitations. Paracetamol is a widely used analgesic that has been safely used for decades but it may not provide sufficient analgesia in some clinical situations necessitating dose escalation or its combination with another drug, typically an opioid.

A novel combination treatment whereby both paracetamol and ibuprofen are combined in one single tablet at a ratio of 3.3: 1 (*Maxigesic®*) has been shown to provide superior pain relief versus its individual components [1]. Both mono-components of *Maxigesic®* have a long history of use and their pharmacokinetic profiles are well characterised. Previous bioequivalence studies conducted with other fixed dose combination products containing paracetamol 650 mg and ibuprofen 400 mg [2] and paracetamol 1000 mg and ibuprofen 400 mg [3] found that the addition of ibuprofen to paracetamol resulted in an increase in the rate of absorption of the latter.

The rate and extent of absorption of a variety of drugs are affected by food ingested prior to dosing [4-9] and alterations in the pharmacokinetic and pharmacodynamic profiles may have further clinical implications [10]. Reductions in plasma concentrations of both paracetamol and ibuprofen were observed following the intake of these components after a standard meal [11-18]. A single study evaluating the food-effect of a fixed dose combination of paracetamol and ibuprofen demonstrated that, like monotherapies, the absorption of both components was delayed after the intake of food resulting in significantly decreased maximum plasma concentrations. Despite these changes, the extent of absorption as measured by $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow\infty}$, was not significantly affected [3].

We hereby report the results of a single-dose, open-label, randomized, four-way cross-over pharmacokinetic study to determine and compare the pharmacokinetic parameters of 1000 mg paracetamol and 300 mg ibuprofen, administered orally, either alone or in combination, under fasting and in combination under fed conditions.

Methods

Trial design

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This study was a Phase 1, single-centre, open-label, randomized, single-dose, four-way crossover trial in 28 healthy adult participants. After an initial screening period of 14 days, there were four study periods each separated by a washout period of 7 days. The research was conducted in accordance with GCP including the Declaration of Helsinki and all applicable regulatory requirements. The trial was registered with the Australia New Zealand Clinical Trial Registry (Registration number: ACTRN 12613001151729).

Participant selection

Healthy male volunteers aged between 18 and 40 years with a Body Mass Index (BMI) of 18.5-30 kg/m^2 with no significant diseases as determined by medical history, physical examination and laboratory tests were recruited from the International Pharmaceutical Research Centre databases. Patients were excluded if they had taken prescription medications in the last 14 days or over the counter medications in the last four 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, hepatic, renal, respiratory, cardiac and gastrointestinal tests, a complete blood count and serum chemistry analysis, 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 at least 10 hours for overnight fasting, and confined until the 12-hour blood sample was collected following study drug administration. Each participant received an oral dose of the randomly assigned treatment as outlined below:

- Treatment A: Single-Dose, 2 tablets of Paracetamol 500 mg (total dose 1000 mg), fasted.
- Treatment B: Single-Dose, 2 tablets of Ibuprofen 150 mg (total dose 300 mg), fasted.
- Treatment C: Single-Dose, 2 tablets of *MAXIGESIC*® (AFT Pharmaceuticals Ltd., Auckland, NZ), (total dose paracetamol 1000 mg + ibuprofen 300 mg), fasted.
- Treatment D: Single-Dose, 2 tablets of *MAXIGESIC*®, (total dose paracetamol 1000 mg + ibuprofen 300 mg), fed.

Breakfast for the fed state (Treatment D) was provided 30 minutes prior to dosing and a standard lunch and snacks were provided for all treatment groups 4 and 8 hours after study drugs were given.

Fourteen blood samples (~6mL) were drawn at 0.00 (one pre-dose sample), 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 hours (post-dose) in each period. All blood samples were drawn from an indwelling intravenous cannula and 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

All haematology, biochemistry, urinary and serology analyses were conducted using standard methodologies within the IPRC diagnostic laboratory. Plasma concentrations of paracetamol and ibuprofen in human plasma (Li-heparin) were determined using validated Liquid Chromatography and Mass Spectrometry procedures (LC-MS/MS).

Paracetamol plasma concentrations were analysed using API-3000 and Quattro premier mass spectrometer in multiple reaction monitoring (MRM) mode using turbo Ion Spray with positive ionization. The chromatographic separation of paracetamol employed a C_{18} 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 (R^2) ≥ 0.99937. The Lower Limit of Quantification (LLOQ) was 50 ng/mL (precision 3.44%, accuracy 93.69%).

Ibuprofen plasma concentrations were analysed using a Sciex API 3000 and API 4000 triple quadrupole mass spectrometer in MRM mode, using turbo Ion Spray with negative ionization. The selective analysis of ibuprofen was achieved on Symmetry C_{18} 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 R^2 ≥ 0.9975. The LLOQ was 50 ng/mL (precision 8.85%, accuracy 104.25%).

Pharmacokinetic analysis

The pharmacokinetic parameters of paracetamol 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 raw data. The area under the plasma concentration-time curve ($AUC_{0\to t}$) was calculated from measured data points from time of administration to time of last quantifiable concentration (C_p) by the linear trapezoidal rule. The area under the plasma concentration-time curve extrapolated to infinity ($AUC_{0\to\infty}$) was calculated according to the following formula:

$$AUC_{0\to\infty} = AUC_{0\to t} + C_p/[Ln(2)/t_{1/2}]$$

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

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

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

The pharmacokinetic calculations were performed using the computer program Kinetica™ 2000.

Statistical methods

Statistical analysis was performed using the validated Kinetica™ program. The ratios of the geometric means used to test bioequivalence were calculated from loge transformed data for C_{max}, $AUC_{0\to t}$ and $AUC_{0\to\infty}$. 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 the two formulations and the confidence interval. T_{max} was compared between formulations and fast/fed states using the Wilcoxon signed rank test and the median differences and 95% CIs were determined using Hodges-Lehman estimates.

Safety

Evaluation of safety was based on the reported adverse events,

laboratory tests, electrocardiograms, physical examination and vital signs measurements.

Results

Participants

44 subjects were screened, of which 28 were enrolled and 26 completed the crossover and were included in the pharmacokinetic analysis. The baseline demographic data are presented in Table 1.

Pharmacokinetic results

In the fasted state the pharmacokinetic parameters (C_{max}, $AUC_{0\to t}$ and $AUC_{0\to\infty}$) for paracetamol and ibuprofen was similar between the fixed dose combination and mono-components. The 90% confidence intervals for the ratios of the geometric means for C_{max}, $AUC_{0\to t}$, and $AUC_{0\to\infty}$ were all within the 80% to 125% bioequivalence range (Table 2).

Characteristic	*Study Population, n=28*
Age, years	28 ± 6.51
Height, cm	172 ± 6.79
Weight, kg	76 ± 8.18
BMI, kg/m^2	25.5 ± 3.07
Smoker	26 (93)

Data presented as mean ± SD, or n (%)

Table 1: Demographic data.

In the fasted state, the median time to reach the maximum measured plasma concentration (t_{max}) was slightly faster for paracetamol and slower for ibuprofen when administered as fixed dose combination compared to monotherapy. The median t_{max} for paracetamol was 38 minutes for the monotherapy and 30 minutes for the combination, whereas the median t_{max} for ibuprofen increased from 60 to 90 minutes between the mono and combination therapy.

For the fixed dose combination in the fed state, the median t_{max} of paracetamol was extended by 23 minutes versus the fasted state. Conversely, the median t_{max} for ibuprofen was 37 minutes shorter in the fed state compared to the fasted state (Table 3, Figure 1). These differences were not statistically significant ($p>0.05$).

The changes in t_{max} corresponded with a significant change in the C_{max} for paracetamol as the 90% confidence interval for the ratios of the geometric means for C_{max} were not within the 80-125% bioequivalence range (90% CI: 76.37-104.47). The change in C_{max} for ibuprofen was smaller and within the bioequivalence range (86.56-104.18). The changes observed in the $t_{1/2}$ mirrored those of the t_{max}: the half-lives of paracetamol and ibuprofen were increased and reduced, respectively, however these changes were not statistically significant.

Despite changes in the C_{max}, comparisons of $AUC_{0\to t}$ and $AUC_{0\to\infty}$ for *Maxigesic®* in fed and fasted states demonstrated that the extent of absorption of both paracetamol and ibuprofen was not significantly affected by food intake. Although values for the fed state were generally

	Paracetamol		*Ibuprofen*	
	Maxigesic®	***Monotherapy***	***Maxigesic®***	***Monotherapy***
C_{max} (µg·mL^{-1})	13.89	14.87	21.48	22.08
Geometric mean ratio [%], (90% CI)	95.77 (81.62, 112.37)[b]		97.23 (85.28, 110.85)[b]	
AUC_{0-t} (µg·mL^{-1}·h)	38.32	36.51	80.12	78.56
Geometric mean ratio [%], (90% CI)	103.86 (100.16, 107.71)[b]		101.18 (95.72, 106.97)[b]	
AUC_{0-inf} (µg·mL^{-1}·h)	40.47	38.42	82.30	80.84
Geometric mean ratio [%], (90% CI)	104.08 (100.15, 108.15)[b]		101.07 (96.01, 106.41)[b]	
T_{max} (minutes)[a]	30	38	90	60
$T_{1/2}$ (h)	3.14	3.11	2.12	2.29

[a]median
[b]within bioequivalence limits (80%-125%)

Table 2: Comparison of the geometric mean (unless stated otherwise) pharmacokinetic parameters of paracetamol and ibuprofen after administration as monotherapy or fixed-dose combination, Maxigesic® in the fasted state.

	Paracetamol		*Ibuprofen*	
	Maxigesic® - fed	***Maxigesic® - fasted***	***Maxigesic® - fed***	***Maxigesic® - fasted***
C_{max} (µg·mL^{-1})	12.94	13.89	20.39	21.48
Geometric mean ratio fed/fasted [%], (90% CI)	89.32 (76.37 - 104.47)		94.96 (86.56 - 104.18)[b]	
AUC_{0-t} (µg·mL^{-1}·h)	38.11	38.32	70.25	80.12
Geometric mean ratio fed/fasted [%], (90% CI)	99.42 (95.89 - 103.08)[b]		88.41 (85.47 - 91.43)[b]	
AUC_{0-inf} (µg·mL^{-1}·h)	40.80	40.47	72.20	82.30
Geometric mean ratio fed/fasted [%], (90% CI)	100.78 (97.19 - 104.48)[b]		88.40 (85.80 - 91.07)[b]	
T_{max} (minutes)[a]	53	30	53	90
$T_{1/2}$ (h)	3.47	3.14	2.08	2.12

[a]median
[b]within bioequivalence limits (80%-125%)

Table 3: Comparison of the geometric mean (unless stated otherwise) pharmacokinetic parameters of paracetamol and ibuprofen after administration as Maxigesic® in fed and fasted states.

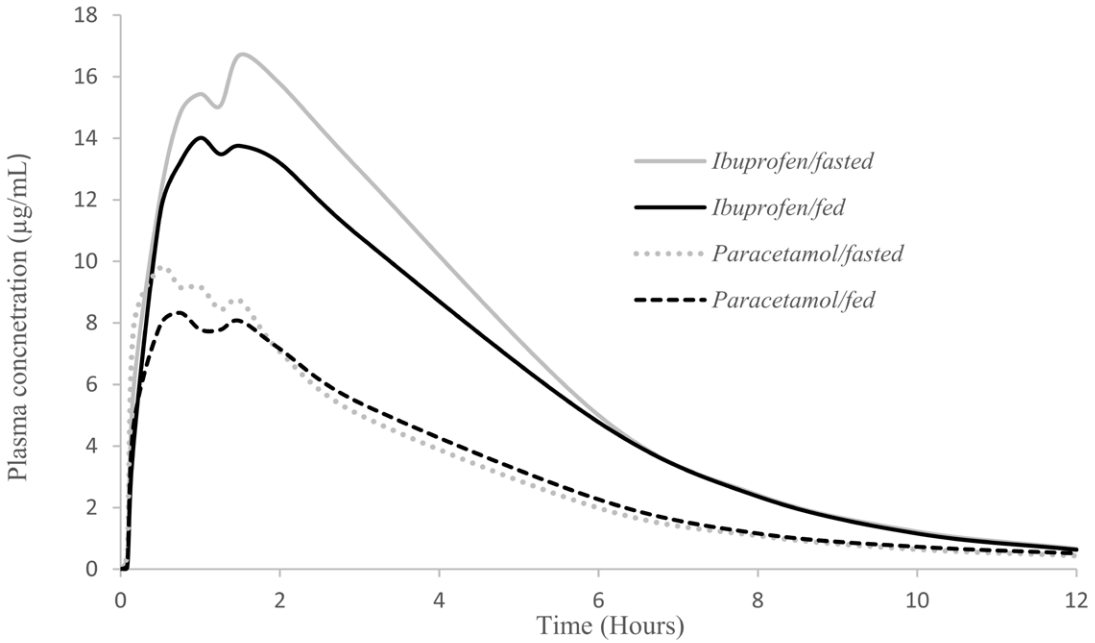

Figure 1: Mean paracetamol and ibuprofen plasma concentration versus time curves after administration of Maxigesic® in fed and fasted states.

lower than in the fasted state, the 90% confidence intervals for the ratios of the geometric mean for *Maxigesic*® were within the 80% to 125% bioequivalence range (Table 3).

Safety analysis

No adverse events occurred during the entire course of this study. The study drugs were well tolerated by all participants in the study.

Discussion

The results of this study demonstrate the lack of a pharmacokinetic interaction between paracetamol and ibuprofen when administered as a novel oral fixed dose combination (*Maxigesic*®) in the fasted state. Although there were differences observed in the rate of absorption after administration of mono and combination therapies, these differences were not significant and did not result in statistically significant alterations of C_{max}, $AUC_{0\to t}$ or $AUC_{0\to\infty}$ as the 90% CIs for the ratio of the geometric means were within the 80%-125% accepted bioequivalence range.

These results are in agreement with the literature on the pharmacokinetics of concurrent administration of ibuprofen and paracetamol [2,3]. In the fasted state there were no significant differences in the mean C_{max} and AUC of ibuprofen or paracetamol when the ingredients are administered alone or in a fixed dose combination of ibuprofen 400 mg and paracetamol 650 mg (henceforth 'FDC 400/650') [2], or a fixed dose combination of ibuprofen 400 mg and paracetamol 1000 mg (henceforth 'FDC 400/1000') [3].

In the present study, the median t_{max} of paracetamol was 8 minutes shorter for *Maxigesic*®, compared to the monotherapy in the fasted state. Similarly, the FDC 400/1000 and FDC 400/650 result in paracetamol t_{max} values that are shorter by 10 ($p<0.05$) and 6 ($p>0.05$) minutes, respectively [2,3] (Table 4).

While there is a large body of literature demonstrating the pharmacokinetics of paracetamol and ibuprofen monotherapies, the literature concerning fixed dose combinations of such ingredients is comparatively scant. A single food effect study was identified concerning the FDC 400/1000 [3] (the food effect has not been evaluated for the FDC 400/650). The 90% CIs of $AUC_{0\to t}$ and $AUC_{0\to\infty}$ between fed and fasted states for both ibuprofen and paracetamol in the FDC 400/1000 are within the accepted 80-125% bioequivalence range. However, the 90% CIs for both paracetamol and ibuprofen C_{max} show a lack of bioequivalence for both ingredients (53.4% - 69.5%, 70.3%-83.1%, respectively). The present study demonstrated that the $AUC_{0\to t}$ and $AUC_{0\to\infty}$ of both ingredients in *Maxigesic*® are not altered in the fed state. These data suggest that a smaller dose of ibuprofen (300 mg in *Maxigesic*® vs. 400 mg in the FDC 400/1000) results in a smaller attenuation of absorption of both ingredients in the fed state compared to the fasted state.

Administration of the FDC 400/1000 after a meal results in a significant increase in median paracetamol t_{max} of 60 minutes ($p<0.001$, 95% CI: 30-80) to 90 minutes, and non-significant extension of median ibuprofen t_{max} of 45 minutes ($p>0.05$, 95% CI: 0-45) to 120 minutes and unlike the present study, the two ingredients in this combination do not reach maximal concentration at the same time (Table 4). As expected, the lower dose of ibuprofen in *Maxigesic*® (300 mg) resulted in a shorter t_{max} in the fed state than the FDC 400/1000 (53 and 120 minutes in the fed state, respectively), however, despite the dose of paracetamol being the same, the t_{max} of paracetamol was 53 minutes for *Maxigesic*® and 90 minutes for the FDC 400/1000. Comparatively, the food effect is less pronounced in *Maxigesic*® and the active ingredients reach maximal plasma concentration earlier than in a fixed dose combination of ibuprofen 400 mg and paracetamol 1000 mg (FDC 400/1000), and at the same time in the fed state (53 minutes). The shorter and coordinated time to C_{max} for both ingredients in *Maxigesic*® may be clinically relevant, resulting in a greater analgesic effect with an earlier time of onset. Furthermore, *Maxigesic*® at normal daily dosages

T_{max} *(minutes)*	*n*	*Paracetamol*		*Ibuprofen*	
		Combination - fasted	***Monotherapy -fasted***	***Combination - fasted***	***Monotherapy -fasted***
FDC 300/1000 (*Maxigesic®*)	26	30	38	90	60
Median difference (95% CI)		-6.4 (-22, 15)		22.5 (-22, 60)	
FDC400/650[a] (mean [SD])	20	48 (24)	54 (30)	84 (42)	84 (42)
FDC 400/1000	25	30	40	75	75
Median difference (95% CI)		-15 (-30, 0)		7.5 (-15, 37.5)	
		Combination - fed	Combination - fasted	Combination - fed	Combination - fasted
FDC 300/1000 (*Maxigesic®*)	26	53	30	53	90
Median difference (95% CI)		22.5 (0, 60)		-22.5 (-45, 0)	
FDC 400/1000	25	90	30	120	75
Median difference (95% CI)		55 (30, 80)		25 (0, 45)	

[a]no fast-fed comparison has been published for FDC 400/650

Table 4: Tmax for ibuprofen and paracetamol after single dose administration of fixed dose combinations: 300/1000 (Maxigesic®), 400/650 and 400/1000.

provides a lower cumulative dose of ibuprofen than the FDC 400/1000 and thereby offers a potentially lower risk of class-related adverse events such as nausea and gastrointestinal ulceration.

Conclusion

The concomitant administration of ibuprofen and paracetamol in a fixed dose combination (*Maxigesic®*) does not alter the pharmacokinetic profiles of either drug in the fasted state and there was no effect of food on the absorption from the fixed dose combination. These results are largely in accord with the literature on the pharmacokinetics of monotherapy or combination doses of ibuprofen and paracetamol.

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Author Contributions

H Atkinson supervised the project and was involved in the design of the study, development of the protocol, interpretation of the data and writing of the manuscript. I Stanescu was involved in the study design, protocol development, and writing of the manuscript. C Beasley contributed to the statistical data interpretation and assisted in drafting the manuscript. I Salem performed the plasma drug assays, data analysis and interpretation and reviewed the manuscript. C Frampton critically reviewed the manuscript.

Conflicts of Interest

H Atkinson is a shareholder and Managing Director of AFT Pharmaceuticals, and I Stanescu and C Beasley are Employees of AFT Pharmaceuticals Ltd. I Salem is an employee of IPRC. C Frampton provides consultancy services to AFT Pharmaceuticals Ltd.

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