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ORIGINAL RESEARCH

Effect of Caffeine on the Bioavailability and Pharmacokinetics of an Acetylsalicylic Acid-Paracetamol Combination: Results of a Phase I Study

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ABSTRACT

Introduction: Caffeine is used as an adjuvant in analgesic combinations to enhance their efficacy. The present study aimed to determine the effect of caffeine on the pharmacokinetics of acetylsalicylic acid (ASA) and paracetamol when used as a fixed-dose ASA/paracetamol/caffeine combination.

Methods: In this single-centre, two-way, crossover phase I study, volunteers fasted overnight (≥ 12 h) and randomly received single oral doses of 250 mg ASA/200 mg paracetamol (reference) or 250 mg ASA/200 mg paracetamol/50 mg caffeine (test). Blood samples were collected before and up to 24 h after dosing. The primary end points were the area under the concentration-time curve from zero to infinity ($AUC_{0-\infty}$) and maximum plasma concentration (C_{max}) for ASA, salicylic acid (SA) and paracetamol from the two combinations. The main secondary end points were $AUC_{0-\infty}$ and C_{max} of caffeine and time to reach C_{max} (t_{max}) of all drugs.

Results: Eighteen healthy male volunteers (32.5 ± 10.5 years) participated in the study. The geometric means of C_{max} for ASA, SA and paracetamol were similar in the test (3.71, 15.8 and 2.42 μg/ml, respectively) and reference groups (3.89, 15.8, 2.42 μg/ml, respectively). The geometric mean of $AUC_{0-\infty}$ for ASA, SA and paracetamol from the test combination was 2.86, 60.5 and 7.68 μg h/ml, respectively, and that for the reference was 2.96, 59.1 and 7.77 μg h/ml, respectively. The medians of t_{max} for ASA, SA and paracetamol were similar between the two groups. The point estimates for the ratios of $AUC_{0-\infty}$ and C_{max} for test versus reference regarding ASA, SA and paracetamol were within the predefined equivalence limits. The two treatments were well tolerated.

Conclusion: Caffeine did not affect the pharmacokinetics of ASA and paracetamol when used as an adjuvant in ASA/paracetamol fixed-dose combination under fasting conditions, suggesting that caffeine enhances the analgesic efficacy of these drugs by pharmacodynamic rather than pharmacokinetic interactions.

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Keywords: Acetylsalicylic acid; Caffeine; Fixed-dose combination; Pain; Paracetamol; Pharmacokinetics

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INTRODUCTION

Analgesics such as acetylsalicylic acid (ASA), paracetamol and ibuprofen are commonly used as first-line drugs in the management of acute pain [1]. These analgesics are included in the World Health Organisation's (WHO) list of essential medicines [2] and are available over the counter (OTC) as single agents or combination drugs. Combining two analgesics is reported to be more efficacious than increasing the dose of a single agent, with reduced adverse events (AEs) [3, 4].

Caffeine is a commonly used adjuvant in analgesics. Combinations of ASA plus paracetamol plus caffeine or of ibuprofen plus caffeine have been reported to show faster onset of analgesia and more effective pain relief compared with analgesics that do not contain caffeine [5–10]. Some studies suggest that caffeine shortens the time to analgesic effect of these first-line drugs by affecting their pharmacokinetics. Two studies to determine the effect of caffeine on the pharmacokinetics and bioavailability of ASA reported that caffeine significantly increased the maximum plasma concentration (C_{max}), rate of appearance and area under the plasma concentration-time curve (AUC) of ASA in 12 healthy male volunteers each [11, 12]. Similar results were reported in another study of caffeine in combination with paracetamol [13], while in another study, caffeine did not affect time to maximum plasma concentration (t_{max}), although C_{max} and AUC were slightly increased [8]. On the other hand, preclinical data have shown that caffeine augments the analgesic effects of analgesic compounds and reduces their plasma concentrations [14].

The present phase I study compared the pharmacokinetics and bioavailability of a single oral dose of ASA/paracetamol fixed-dose combination versus ASA/paracetamol/caffeine fixed-dose combination (Thomapyrin®) to understand the effect of caffeine on the pharmacokinetics of ASA and paracetamol in pain relief.

METHODS

This single-centre, double-blind, controlled, two-way cross-over phase I study was conducted at the Human Pharmacology Centre, Boehringer Ingelheim, Biberach Riss, Germany, in October 1994. The study was designed according to the standards defined by health authorities to investigate the bioequivalence of pharmaceutical products at the time [15] and fulfils many requirements of the recent 2010 European Medical Agency guideline for investigation of bioequivalence [16].

The study protocol was reviewed and approved by the ethics committee at the study site (Freiburger Ethikkommission International), and the study was conducted in accordance with the principles of the Declaration of Helsinki and the European Commission Good Clinical Practice (EC-GCP) notes for guidance and applicable local legal regulations. All volunteers provided written informed consent before participation in the study. This trial was run in 1994, i.e., almost a decade before the European Database for Clinical Trials (EudraCT) was established, and is therefore not registered in a clinical study database.

Participants

The main study inclusion criteria were: healthy males aged 18–55 years who provided written informed consent before participation. The main exclusion criteria were: use of any drugs that may influence the pharmacokinetics of the study drugs < 10 days before or during the study; presence of gastric/duodenal ulcer disease, haemorrhagic or asthmatic disease, or glucose-6-phosphate dehydrogenase deficiency; drug abuse, alcoholism or smoking; participation in a trial with an investigational drug < 2 months before the study; and excessive physical activity < 2 weeks before study initiation.

Treatment

All study volunteers were studied on two separate occasions at the study centre after an overnight (≥ 12 h) fast. The volunteers were randomly allocated to receive a single oral fixed-dose combination of 250 mg ASA/200 mg paracetamol (reference) or 250 mg ASA/200 mg paracetamol/50 mg caffeine (test) on day 1,

which they took under direct supervision of the clinical trial staff. Volunteers continued fasting and remained in an upright position for 1 h after dosing. Blood samples were collected for the assessment of plasma concentrations of all drugs [ASA, salicylic acid (SA), paracetamol, caffeine] before administration of the drugs and at 8, 15, 23, 30, 38 and 45 min, followed by 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 h after dosing. Participants were allowed to leave the study centre 13.5 h after drug administration and then returned to the study site the next morning for an additional blood sample to be taken at 24 h post-dose.

Consumption of alcohol and caffeine-containing foods and beverages was strictly prohibited from day − 2 until study completion. All volunteers were provided with standard meals during the days they spent at the study centre. No concomitant medications were allowed during the study except in cases of AEs.

The study procedures were repeated after a 7-day washout period, when volunteers returned to the centre and received the alternative treatment.

Study End Points

The primary end points were $AUC_{0-\infty}$ and C_{max} of ASA, SA and paracetamol. The secondary end points included: $AUC_{0-\infty}$ and C_{max} of caffeine, and t_{max}, mean residence time (MRT) of the unchanged drug in the systemic circulation extrapolated to infinity, apparent terminal elimination half-life ($t_{1/2}$), total plasma clearance (CL/*f*) and apparent volume of distribution during the terminal phase (V_z/f) of all drugs.

Safety assessments included AEs, tolerability and routine laboratory tests. All volunteers were assessed before dosing and at 4, 12 and 24 h after administration of test/reference for any AEs, and they underwent physical examinations, vital sign assessment and 12-lead electrocardiogram (ECG).

Blood Sampling and Analysis

Blood samples were collected using EDTA-monovette tubes and centrifuged immediately at 3500 rpm for 10 min to obtain plasma; 1 ml of the obtained plasma sample was mixed with 1 ml of 0.2 M HCl to prevent degradation of ASA and stored in polypropylene vials for ASA/SA assay. The remaining plasma sample (1.5 ml) was frozen in polypropylene vials and used for analysis of paracetamol and caffeine.

All analyses were performed using validated high-performance liquid chromatography (HPLC) methods followed by ultraviolet (UV) detection at 240 nm for ASA/SA and paracetamol and 273 nm for caffeine. All methods were revalidated before the study; interassay variability was measured and found to be negligible (see methods in supplementary material for details). Plasma concentrations were determined by the internal standard method using peak height ratios, and results were calculated using $1/y^2$ weighted least squares regression for ASA/SA and paracetamol and $1/y$ weighted least squares regression for caffeine.

ASA/SA were extracted from the acidified plasma sample using dichloromethane followed by evaporation on an ice bath to obtain samples. Chromatography was performed using a Hypersil™ ODS 5-μm analytical column, and ASA and SA were eluted isocratically and detected at 240 nm. Retention times (RTs) for ASA, SA and the internal standard (IS) were 6.0, 8.3 and 9.9 min, respectively. The method was suitable for analysis of ASA/SA in the range of 0.1–10/0.5–50 μg/ml.

For paracetamol, plasma samples were buffered to pH 7.4 and extracted with ethyl acetate, followed by evaporation of organic phase and chromatography using isocratic elution on a Nova Pak® C18 column. The RT for paracetamol and the IS were 2.8 and 4.7 min, respectively. The method was suitable for detection of paracetamol in the range of 0.5–5 μg/ml.

For caffeine analysis, proteins were precipitated from the plasma samples using perchloric acid, and the supernatant was used for chromatography using isocratic elution on a Nucleosil® C18 column. The RT for caffeine and the IS were 10.6 and 7.2 min, respectively. The method was suitable for determining caffeine in plasma samples in the range of 0.05–2.5 μg/ml.

Statistical Analysis

A sample size of 18 volunteers was considered appropriate for this study based on the results of a previous single-dose study with ASA where the intra-individual coefficients of variation were 10% for $AUC_{0-\infty}$ and 25% for C_{max} (unpublished data).

TopFit Version 2.0 was used for the determination of pharmacokinetic parameters (C_{max}, t_{max}, AUC_{0-tn}, $AUC_{0-\infty}$, $t_{1/2}$, MRT, CL/*f*, V_z/*f*) [17]. Analysis was conducted on data from volunteers who received both the treatments and completed all assessments. All pharmacokinetic parameters and ratios for test versus reference of $AUC_{0-\infty}$ and C_{max} were descriptively reported for each drug using non-compartmental methods. Descriptive statistics included: number of cases (*N*), number of cases above the lower limit of quantification (LLQ; $N >$ LLQ), geometric mean, geometric standard deviation, geometric coefficient of variation, arithmetic mean, standard deviation, coefficient of variation, minimum, lower quartile, median, upper quartile and maximum. The LLQ for all plasma concentrations was set at zero.

The Shapiro-Wilk test was used to test the normal and lognormal distribution with a 5% level of significance [18]. Bioequivalence was assumed if the central estimates for $AUC_{0-\infty}$ (test)/$AUC_{0-\infty}$ (reference) were within the predefined limits of 85% and 118% and C_{max} (test)/C_{max} (reference) were within the predefined limits of 80% and 125%. Parametric analysis was performed for logarithmically transformed data when lognormal distribution was not rejected for $AUC_{0-\infty}$ and C_{max}. Ninety percent confidence intervals (90% CIs) for the ratios of end points were calculated from CIs for the difference of least square (LS) means of the logarithmically transformed values. The (1–2α) 100% confidence limits (for $\alpha = 0.05$: 90%) were calculated using the following formula:

$$\exp\left(\mathrm{LSmean_T} - \mathrm{LSmean_R} \pm t_{(\alpha DF)} \text{square root } [2\mathrm{MSE}/N]\right) \times 100,$$

where $LSmean_T$ and $LSmean_R$ were the LS mean values of the logarithmically transformed values for test and reference formulations calculated using analysis of variance (ANOVA), which included treatment, period, sequence and volunteer within sequence as fixed effects; MSE was the mean squared error of ANOVA; *N* is the number of volunteers; *DF* is degrees of freedom of the error term.

Nonparametric Wilcoxon Mann-Whitney test was performed in cases of non-normality of the logarithmically transformed $AUC_{0-\infty}$ and C_{max} values.

RESULTS

Patients

Eighteen healthy male volunteers (mean ± SD 32.5 ± 10.5 years; mean ± SD 77.5 ± 7.4 kg body weight) participated in the study. All volunteers completed the study; data from all volunteers were used for the determination of pharmacokinetic parameters and safety analysis.

Pharmacokinetics

The concentration-time curves of ASA showed that the test formulation had a slightly lower plasma ASA concentration during the first 45 min after dosing compared with the reference combination (Fig. 1a). SA and paracetamol concentration profiles were almost identical for the two treatments, with low inter- and intra-individual variations (Fig. 1b, c). The plasma concentration of caffeine from the test formulation increased during the first 45 min and decreased thereafter (Fig. 1d).

The geometric mean $AUC_{0-\infty}$ values for ASA, SA and paracetamol showed only slight differences between the reference and test combinations (Table 1). The $AUC_{0-\infty}$ for ASA after the test combination was slightly lower than after the reference agent, with a difference of 3.3%. For SA, the test combination $AUC_{0-\infty}$ values were slightly higher compared with the reference, with a difference of 2.4%. For paracetamol, the $AUC_{0-\infty}$ values for the test combination were lower than for the reference

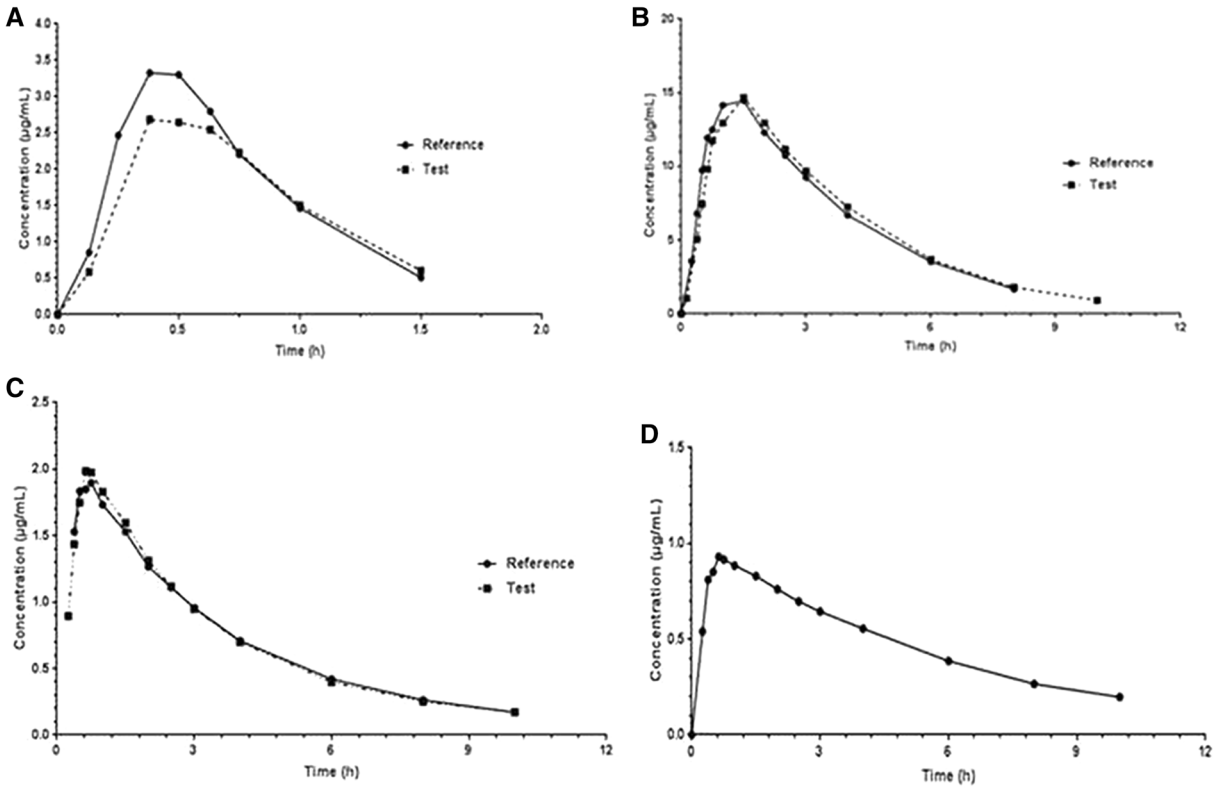

Fig. 1 Plasma concentration-time curves for **a** acetylsalicylic acid, **b** salicylic acid, **c** paracetamol and **d** caffeine during the study

combination by 1.2%. Similar differences were seen in the geometric mean C_{max} values for individual drugs. The geometric mean C_{max} of ASA was slightly lower with the test combination than the reference, whereas the geometric mean C_{max} of SA and paracetamol was identical with both the test and reference products.

The geometric and arithmetic mean MRT values for ASA were approximately 10% higher for the test compared with reference; median t_{max} for ASA in the test and reference formulations was 0.44 h. The median t_{max} values for SA were similar for the two treatments. Median t_{max} for paracetamol in the test formulation was 0.63 h compared with 0.44 h for reference. Details are given in Table 1.

The point estimates and 90% CIs for the ratios of $AUC_{0-\infty}$ and C_{max} (test:reference) were within the predefined equivalence limits for ASA, SA and paracetamol (Table 2).

Safety

Overall, the treatments were well tolerated. No AEs or clinically significant deviations in laboratory parameters or ECGs were reported during the study.

DISCUSSION

The results of this phase I study showed that the two combinations of ASA plus paracetamol with and without caffeine were bioequivalent in the extent of bioavailability of ASA and paracetamol. The label approved by the Austrian and German health authorities (where the test product is marketed) recommends a single dose of 1 (to 2) tablets, demonstrating the relevance of the investigated dose. The point estimators for $AUC_{0-\infty}$ and C_{max} ratios for ASA, SA and paracetamol, as well as the 90% CI values for $AUC_{0-\infty}$

Table 1 Pharmacokinetic parameters for caffeine, acetylsalicylic acid, salicylic acid and paracetamol ($N = 18$)

	Treatment	Geometric mean	Median	Arithmetic mean	GCV (%)
	Caffeine				
$AUC_{0-\infty}$ (µg h/ml)	Test	5.73		6.06	35.0
C_{max} (µg/ml)		1.06		1.09	25.9
AUC_{0-tn} (µg h/ml)		5.42		5.62	28.5
t_{max} (h)			0.50		
MRT (h)		6.06		6.21	23.5
$t_{1/2}$ (h)		4.29		4.50	31.7
CL/f (ml/min)		145.0		153.0	35.0
V_z/f (l)		54.0		55.0	20.5
	Acetylsalicylic acid				
$AUC_{0-\infty}$ (µg h/ml)	Reference	2.96		3.00	16.0
	Test	2.86		2.92	20.3
C_{max} (µg/ml)	Reference	3.89		4.07	32.6
	Test	3.71		3.86	30.0
t_{max} (h)	Reference		0.44		
	Test		0.44		
MRT (h)	Reference	0.74		0.75	19.2
	Test	0.81		0.83	27.5
$t_{1/2}$ (h)	Reference	0.31		0.32	13.5
	Test	0.31		0.31	12.6
CL/f (ml/min)	Reference	1406		1422	16.0
	Test	1457		1484	20.3
V_z/f (l)	Reference	38.0		39.0	23.7
	Test	38.9		39.6	18.8
	Salicylic acid				
$AUC_{0-\infty}$ (µg h/ml)	Reference	59.1		59.7	14.8
	Test	60.5		61.1	14.3
C_{max} (µg/ml)	Reference	15.8		15.9	12.0
	Test	15.8		15.9	13.6
t_{max} (h)	Reference		1.00		
	Test		1.25		

Table 1 continued

	Treatment	Geometric mean	Median	Arithmetic mean	GCV (%)
MRT (h)	Reference	3.52		3.54	12.4
	Test	3.69		3.72	13.6
$t_{1/2}$ (h)	Reference	1.94		1.95	10.7
	Test	2.01		2.02	10.9
CL/*f* (ml/min)	Reference	70.5		71.3	14.8
	Test	68.8		69.5	14.3
V_z/f (l)	Reference	11.9		12.0	17.3
	Test	12.0		12.1	17.7
	Paracetamol				
$AUC_{0-\infty}$ (µg h/ml)	Reference	7.77		8.02	25.4
	Test	7.68		7.88	22.7
C_{max} (µg/ml)	Reference	2.42		2.49	24.6
	Test	2.42		2.53	31.2
AUC_{0-tn} (µg h/ml)	Reference	7.71		7.95	24.9
	Test	7.62		7.81	22.2
t_{max} (h)	Reference		0.44		
	Test		0.63		
MRT (h)	Reference				
	Test	4.31		4.37	17.8
$t_{1/2}$ (h)	Reference	3.21		3.27	20.6
	Test	3.40		3.45	18.1
CL/*f* (ml/min)	Reference	429		441	25.4
	Test	434		444	22.7
V_z/f (l)	Reference	119		122	22.6
	Test	128		131	23.8

$AUC_{0-\infty}$ area under the concentration-time curve from zero to infinity, AUC_{0-tn} area under the concentration-time curve from time 0 to the last measurable concentration, *CL/f* total plasma clearance, C_{max} maximum observed plasma concentration, *GCV* geometric coefficient of variation, *MRT* mean residence time, t_{max} time to reach maximum plasma concentration, $t_{1/2}$ apparent terminal elimination half-life, V_z/f apparent volume of distribution during the terminal phase

and C_{max} test versus reference ratios, were all within the predefined limits for bioequivalence.

Paracetamol and NSAIDs are among the most widely used treatments for mild-to-moderate pain and are recommended as first-line therapy in the WHO pain ladder [2]. However, when used alone, they may be sub-optimally effective in many patients who require

Table 2 Point estimates and 90% confidence intervals (test versus reference) for $AUC_{0-\infty}$ and C_{max} ratios of acetylsalicylic acid, salicylic acid and paracetamol

	Point estimate	90% CI
Acetylsalicylic acid		
$AUC_{0-\infty}$ (μg h/ml)[a]	96.5	92.6, 100.4
C_{max} (μg/ml)	95.4	81.8, 111.2
Salicylic acid		
$AUC_{0-\infty}$ (μg h/ml)[a]	102.4	99.7, 105.2
C_{max} (μg/ml)	99.7	97.3, 102.2
Paracetamol		
$AUC_{0-\infty}$ (μg h/ml)[b]	101.3	95.7, 105.3
C_{max} (μg/ml)	100.0	90.0, 111.1

$AUC_{0-\infty}$ area under the concentration-time curve from zero to infinity, *C_{max}* maximum observed plasma concentration, *CI* confidence interval

[a] Parametric

[b] Non-parametric

faster and stronger pain relief. This has led to the development of new formulations and/or combinations to enhance the rapidity and strength of analgesia with these agents. Addition of caffeine to analgesic combinations at a dose of ≥ 100 mg enhances pain relief [7]. A combination of 1000 mg paracetamol plus 130 mg caffeine has been reported to provide relative benefit for pain relief in various states of acute pain compared with paracetamol alone [19]. Similarly, caffeine is also reported to enhance the analgesic efficacy of ibuprofen when taken in combination [20]. The present study showed that addition of caffeine to a paracetamol/ASA combination does not affect the pharmacokinetics of the formulation, indicating that higher efficacy of caffeine-containing pain relief formulations may be due to pharmacodynamic rather than pharmacokinetic effects of caffeine.

Several studies have explored the pain relief mechanisms of caffeine. Caffeine is thought to relieve pain by blocking central and peripheral adenosine receptors and inhibiting cyclooxygenase activity at some sites [21–25]. However, the exact mechanism by which caffeine enhances pain relief in combination with other analgesics is not completely understood.

The pharmacokinetics of analgesic/caffeine combinations may be influenced by fasting or fed conditions. Two single-dose, randomised, crossover studies comparing the pharmacokinetics of ibuprofen (as acid) with or without caffeine in healthy volunteers reported that the C_{max} and t_{max} values of ibuprofen from the two formulations remained the same under fasting conditions (31.0 μg/ml and 1.88 h, respectively) [26]. However, presence of food decreased the t_{max} (1.25 versus 1.63 h) and increased the C_{max} (26.3 versus 23.4 μg/ml) of ibuprofen from the ibuprofen/caffeine combination compared with ibuprofen alone (as lysinate) [26]. Although the pharmacokinetics of ASA/paracetamol combination were not affected by caffeine in the present study, it should be noted that this study was conducted under 12-h fasting conditions, and the dose of caffeine used in the ASA/paracetamol combination was 50 mg. Analgesics are usually taken with food, and under these conditions caffeine might increase the C_{max} and reduce the t_{max} of the analgesic.

Interestingly, the t_{max} values for ASA and paracetamol from the two formulations in this study were comparable to the t_{max} for fast-releasing oral ibuprofen formulations [27]. This suggests that fast-releasing ibuprofen formulations may have no pharmacokinetic advantages compared with the fixed dose combination of ASA/paracetamol (with or without caffeine).

The two analgesic combinations of ASA plus paracetamol with and without caffeine were well tolerated during the present study. No AEs or clinically relevant changes in laboratory values, vital signs or ECG were reported with single oral administration of ASA/paracetamol or ASA/paracetamol/caffeine.

Although this study is not recent, the results are highly reliable as the study was conducted in a standardised and quality-controlled environment, and it fulfils many of the current requirements and criteria for investigating bioequivalence of pharmaceutical products. Therefore, this study can provide additional information on the effect of caffeine on the pharmacokinetic properties of ASA/paracetamol

in particular and on analgesic compounds in general.

CONCLUSION

This phase I study showed that addition of caffeine to an ASA/paracetamol pain relief combination does not affect the pharmacokinetics of these drugs under fasting conditions. Both paracetamol and ASA from combinations with or without caffeine were bioequivalent, suggesting that caffeine enhances the analgesic efficacy of these drugs by pharmacodynamic rather than pharmacokinetic interactions. Further studies with this combination under fed conditions may be useful to determine the effect of food on the pharmacokinetics of ASA and paracetamol.

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Authorship Contributions. Thomas Weiser and Harald Weigmann contributed substantially to conception of the study and interpretation of data. Thomas Weiser and Harald Weigmann were also involved in drafting the manuscript and were accountable for all aspects of the study to ensure that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved. Finally, Thomas Weiser and Harald Weigmann approved the final version of the manuscript before submission for publication.

Disclosures. Thomas Weiser is an employee of Sanofi Aventis, Germany. Harald Weigmann is an employee of Sanofi Aventis, Germany.

Compliance with Ethics Guidelines. The study protocol was reviewed and approved by the ethics committee at the study site (Freiburger Ethikkommission International), and the study was conducted in accordance with the principles of the Declaration of Helsinki and the European Commission Good Clinical Practice (EC-GCP) notes for guidance and applicable local legal regulations. All volunteers provided written informed consent before participation in the study.

Data Availability. Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan and data set specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data-sharing criteria, eligible studies and process for requesting access can be found at: https://www.clinicalstudydatarequest.com.

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