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Relative Bioavailability of Two Enteric-Coated Formulations of Omeprazole following Repeated Doses in Healthy Volunteers

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Abstract

Objective: This study aimed to investigate the relative bioavailability and bioequivalence of two omeprazole enteric-coated formulations following repeated doses (steady state) in healthy male and female adult volunteers.

Design and Study Participants: The study formulation (Ompranyt® 20mg capsules, Bial-Industrial Farmaceutica SA, Spain) was compared with an omeprazole reference formulation (Mopral® 20mg capsules, Laboratório Astra, Spain). 24 participants were randomised using a two-way, crossover design to receive either one capsule/day of Ompranyt® or one capsule/day of Mopral® during two sequential periods of five consecutive days each. The participants were administered the drugs in the fasting state. Omeprazole concentrations in plasma samples were quantified by a validated method using a reversed-phase high performance liquid chromatography with UV detection (HPLC-UV). The validation method is described.

Setting: The study was conducted at the Human Pharmacology Unit, Department of Research & Development, Laboratorios Bial (S. Mamede do Coronado, Portugal).

Results: The arithmetic mean ± SD values of the area under the plasma concentration versus time curve from time zero to infinity ($AUC_{0-\infty}$) were 1474 ± 1417 μg/L•h for Ompranyt® and 1490 ± 1276 μg/L•h for Mopral®. The geometric means ratio (Ompranyt®/Mopral®) was 0.99, with 90% confidence intervals (CI) of 0.97-1.03. The estimated maximum plasma concentration (C_{max}) was 630.1 ± 516.7 μg/L for Ompranyt® and 736.7 ± 443.3 μg/L for Mopral®, with a geometric means ratio (Ompranyt®/Mopral®) of 0.96 (90% CI: 0.94-0.99). Bioequivalence of these two formulations was accepted based on the two one-sided ANOVA for $AUC_{0-\infty}$ as well as for C_{max}. In both cases, the 90% CI lies within the acceptance range of 0.80-1.25.

Conclusion: Bioequivalence of Ompranyt® and Mopral® was demonstrated after repeated drug administration in fasting conditions, and both products were similarly well tolerated. Therefore, both formulations are expected to be equivalent in a clinical setting.

Omeprazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, has a potent long-acting inhibitory effect on gastric acid secretion. Omeprazole is a specific inhibitor of H^+/K^+-exchanging ATPase (proton pump) in gastric parietal cells; inactivation of this enzyme system blocks the final step of acid secretion by these cells.[1] Omeprazole does notdirectly inhibit this enzyme system, but instead concentrates under the acid conditions of the parietal cell secretory canaliculi, where the drug undergoes rearrangement to its active sulphonamide metabolite; this metabolite then reacts with sulfhydryl groups of H^+/K^+-exchanging ATPase, inactivating the proton pump. Because the sulphonamide metabolite forms an irreversible covalent bond with the proton pump, acid secretion is inhibited until additional enzyme is synthesised, resulting in a prolonged duration of action.[2]

Omeprazole is largely used in the treatment of active duodenal and benign gastric ulcer, in the symptomatic relief of gastroesophageal reflux disease, as maintenance therapy following healing of erosive esophagitis to reduce its recurrence, and in the long-term treatment of pathological gastrointestinal hypersecretory conditions. Omeprazole is also used in combination with antimicrobial agents for the treatment of *Helicobacter pylori* infection and duodenal ulcer disease.[2]

Since omeprazole is acid-labile, it must be protected from intragastric acid when given orally. This is achieved by the use of encapsulated enteric-coated granules.[1] Differences in the granule coating may influence the protection against the acid and, therefore, may affect bioavailability.

It has been reported that the bioavailability of omeprazole increases during the first days of repeated drug administration.[3,4] The most likely explanation is that omeprazole absorption increases with repeated administration because of a progressive suppression of acid secretion. Since omeprazole is acid-labile, less omeprazole is degraded once acid secretion is inhibited, leaving more compound available for absorption.[1]

Bial-Industrial Farmaceutica SA owns a marketing authorisation for Ompranyt®, an enteric-coated capsule formulation of omeprazole, in Spain. The present study aimed to investigate the relative bioavailability of Ompranyt® and the reference formulation (Mopral®/Losec®, Laboratório Astra, Spain), following repeated doses in 24 healthy adult volunteers. Commercially, both products are presented in 20mg capsules of omeprazole that is the usually recommended dose in the treatment of duodenal and gastric ulcers, reflux oesophagitis and *H. pylori* infection.

Participants and Methods

Study Design

This was a nonblind, single-centre, randomised, two-way crossover study in healthy adult volunteers. The study was conducted at the Human Pharmacology Unit, Department of Research & Development, Laboratórios Bial (S. Mamede do Coronado, Portugal). The bioanalytical work was performed at the Laboratory of Pharmacological Research of the same institution.

The study was conducted according to the principles of the last revision of the Declaration of Helsinki and the ICH Good Clinical Practices (CPMP/ICH/135/95). An Independent Ethics Committee revised and approved the study protocol and the information provided to the volunteers. Participants' written informed consent was obtained prior to enrolment in the study.

Each participant received Ompranyt® and Mopral® during two sequential periods of five consecutive days each; a computer-generated randomisation table defined the order of treatments for each subject. The daily dosage was 20mg, taken in the morning in a fasted condition. At the fifth day of each period, 10-hour blood samples were taken for the plasma analysis of omeprazole. No washout period was scheduled since the blood collection for analysis was performed at steady state (a similar procedure has been adopted by other investigators[5]).

Study Population

Healthy male or female volunteers, aged between 18 and 55 years, were recruited. Participants did not deviate more than 20% from the average

weight for individuals of their build and height, as described in the 1983 Metropolitan Height and Weight Tables. Previously reported pharmacokinetic studies in Asians receiving single 20mg doses of omeprazole[6] showed an approximately four-fold increase in the area under the plasma concentration versus time curve (AUC) as compared with Caucasians. Therefore, Asians were not admitted to the study.

The participants' 'healthy' condition was documented based on their medical history, a physical examination, electrocardiogram (ECG), and routine clinical laboratory tests. Individuals were excluded from participation if they had one or more of the following: (a) a history of abnormal drug reactions or drug allergies, (b) hypersensitivity or any other contraindication to omeprazole, (c) blood donation exceeding 750ml within a 12-month period before screening or any blood donation within the past 30 days, or (d) medication with any 'over-the-counter' (OTC) or prescribed drug within 1 week prior to the study. Other exclusion criteria were smoking more than 10 cigarettes per day, evidence of chronic drug abuse (including alcohol), testing positive for hepatitis B or C or for HIV, and testing positive for drugs of abuse. No medication other than study products and oral contraceptives were allowed during the study unless absolutely required for the treatment of adverse events; if and when the use of another medication did become necessary, information about the dose, frequency of administration, etc., was to be reported.

Study Formulations

The following products were used in the study: Ompranyt®, 20mg capsules, batch number 90548, manufactured by Laboratórios Bial – Portela & C[a]; and Mopral®, 20mg capsules, batch number N8 AD 3381, manufactured by Astra Production, Sweden.

Study Procedures

After providing informed written consent, volunteers were submitted to the following procedures as part of the pre-study screening: clinical history, physical examination, viral laboratory screening including HIV, hepatitis B and C serology, screening for drugs of abuse, clinical laboratory tests (haematology, biochemistry and urinalysis), 12-lead ECG, and pregnancy test in women.

The study consisted of two consecutive periods of five days each, without a washout period in between. During the two periods, participants reported to the Unit in the morning for administration of the study drug (one 20mg capsule) under the supervision of the investigation staff. At days 5 and 10, participants remained at the Human Pharmacology Unit. They had fasted since 10pm on the night before, and no food or beverages other than water and standard meals were allowed during the period of study.

Adverse events were assessed daily by direct questioning of the study participants at the time of drug administration. All adverse events were assessed regarding the type, duration, intensity, severity, outcome and relationship to treatment (causality).

On the mornings of days 5 and 10, a cannula was inserted in a forearm peripheral vein for blood sampling, the first (pre-dose) blood sample was collected, and the study drug was administered.

Blood samples of 10ml were collected for pharmacokinetic analysis at the following timepoints: pre-dose, and at 20 and 40 minutes and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8 and 10 hours post-dose. Each blood sample was collected via catheter into tubes containing heparin-lithium as an anticoagulant. The plasma was then separated by centrifugation at 3000*g* for 10 min (4°C), and two aliquots of 2ml were frozen at –80°C (Nuaire Ultralow Freezer) until analysis.

Bioanalytical Work

Plasma sample preparation was achieved by solid-phase extraction (SPE) and omeprazole levels were measured using a validated reversed-phase high performance liquid chromatography method involving UV detection (HPLC-UV), with papaverine as the internal standard. The limit of quantification was 25 μg/L.

All samples were assayed at the Laboratory of Pharmacological Research, R & D Department,

Laboratórios Bial, S. Mamede do Coronado, Portugal.

Pure omeprazole was obtained from US Pharmacopeia (Rockville, MD, USA). Papaverine (internal standard), sodium phosphate (mono- and dibasic) and ammonium hydroxide were purchased from Sigma-Aldrich (Sigma-Aldrich Chemical Co., USA), and acetonitrile from Lab-Scan Analytical Sciences (Labscan Ltd, Ireland). All solvents used for the analysis of omeprazole were of HPLC grade and Milli-Q (Millipore Corporation, Bedford, USA) water was used in all steps. The 25 mmol/L sodium phosphate buffer was adjusted to pH 8 using ammonium hydroxide, and is referred to as 'buffer' hereafter.

Sample Preparation

As in the published method of Richards et al.,[5] an SPE was used for sample preparation. After thawing the plasma sample, 1.1ml was transferred to a glass tube and 20µl of the internal standard papaverine [a 110 µg/ml solution in water/acetonitrile (ACN) 1:1, adjusted to pH 8 with ammonium hydroxyl] was added to give a final concentration of 2 µg/ml. These tubes were placed in an ASPECXL4 automated liquid handler (Gilson S.A., France) equipped with Oasis adsorption columns 30mg, Waters (Waters Corporation, USA). The columns were conditioned with 1ml ACN and 2ml buffer and, after elution of the plasma samples, washed with 1ml of each buffer and buffer/ACN (95:5). After the final elution of the analyte with 500µl ACN, the same amount of buffer was added, and 30µl of this mixture was injected onto the HPLC system.

HPLC-UV Method

Samples were analysed by means of a reversed-phase HPLC with UV detection method. This validated analytical method described by Farinha et al.[7] was modified slightly, primarily to shorten the LC run-time for each sample. This change did not affect the performance, reproducibility or selectivity, but improved the peak shape and sensitivity. A Series 1100 HPLC (Agilent Technologies, Spain) with diode array detector was employed for analysis. Separation was performed on a LiChroCART 250-4 column 5µm, Merck (Merck, Darmstadt, Germany) with buffer/ACN (75:25) as mobile phase (0.8 ml/min). The detection wavelength was 300nm, and spectra were stored in the range of 190-400nm.

Quantification

The GLP (Good Laboratory Practice) compliant HP Chemstation software from Hewlett-Packard was used for processing the sample runs. Each sample sequence contained two sets of calibration standards covering the range of 50-2000 µg/L omeprazole, and the updated calibration curves (linear regression, weighted $1/y^2$) were used for quantification of the subsequent unknown samples. The calibration standards also served as quality control samples and were analysed alongside each series of unknown samples.

Method Validation

Recovery

The recovery after sample processing (SPE) was found to be quantitative for omeprazole (105.3%, mean of 5) and 63.8% (mean of 5) for the internal standard papaverine.

Calibration Range and LOD/LOQ

The calibration range was found to be linear from 50-2000 µg/L and linear regression of the calibration curve (weighting factor $1/y^2$) resulted in correlation factors of $R > 0.995$ in all cases. The limit of quantification (LOQ), at a signal-to-noise ratio (S/N) of >10, was 25 µg/L and the limit of detection (LOD) [S/N > 3] was determined to be approximately 9 µg/L.

Selectivity

The chromatographic method used for analysis allows a selective determination of both omeprazole and papaverine. With retention times of approximately 3.6 minutes (omeprazole) and approximately 5.4 minutes (papaverine), these compounds are very efficiently separated from any other signal.

The peak purity was assessed by using the purity algorithm of the HP Chemstation software. A minimum of 7 spectra (240-400nm) were compared at equidistant time-points over the area of the

peak and the peak declared pure if the threshold of 99% agreement was exceeded. For processed human plasma samples the purities were found to be >99.93% for both compounds, which corresponds with the purities found for standard solutions in water/ACN. Furthermore, an overlay of the compound spectra in plasma and buffer solution revealed a perfect match.

Precision and Accuracy

Intra-Assay

The precision of the analytical method was evaluated using three different concentrations (n = 5) over the calibration range (50, 500 and 1500 μg/L). For the lowest concentration, the precision (coefficient of variation of the mean, CV%) was 6.7%, with an accuracy (mean determined concentration as a percentage of the nominal concentration) of 99.8%. For the concentrations of 500 and 1500 μg/L, these values were 10.9 and 6.5% (precision) and 98.5 and 105.3% (accuracy), respectively.

Interassay

The mean interassay precision of the analytical procedure was calculated from the results of the calibration standards at concentrations of 50, 100, 500 and 2000 μg/L, and was between 3.0 and 8.3% (n = 14). The accuracy was found to be between 96.8 and 108.8%, with higher accuracy at the lower concentrations.

Ruggedness and Reproducibility

The exchange of the HPLC column (same manufacturer, stationary phase and batch) as well as moderate changes of the ACN content, buffer concentration or pH of the mobile phase did not have a significant effect on the performance and selectivity of the chromatographic separation. Likewise, small changes in column temperature, flow rate and the type of sample matrix (plasma, buffer, water) did not significantly influence the separation and quantification performance.

Pharmacokinetic Parameters

All pharmacokinetic parameters were determined using non-compartmental models. The plasma concentration versus time curves were plotted for each participant. Peak concentrations (C_{max}) and the time to peak (t_{max}) were read directly from the observed data. The AUC was calculated by using the trapezoidal rule until the last datapoint and extrapolated to infinity using the approximation of the last data-point ($AUC_{0-\infty} = AUC_{0-10} + AUC_{10-\infty}$). As the plasma concentrations were measured after the last dose of each period, all parameters estimated were considered to be steady-state parameters. All pharmacokinetic parameters were calculated by conventional methods.

Statistical Considerations

Sample Size

Taking into account the reported intra- and interparticipant variability of the omeprazole plasma levels,[1,5,7-10] for detecting differences of 20% between both preparations with a power of 80% and a significance level (α) of 0.05, a sample size of 24 subjects was required.

Statistical Analysis of Pharmacokinetic Data

According to the European Agency for the Evaluation of Medicinal Products (EMEA), the statistical method for testing bioequivalence should be based upon the 90% confidence interval (CI) for the ratio of the population means (test/reference) for the parameters under consideration. This method is equivalent to the corresponding two 1-sided test procedure with the null hypothesis of bioinequivalence at the 5% significance level.[11]

The pharmacokinetic parameters are presented as arithmetic mean ± SD, mean ± SEM, and geometric mean with 90% CI. The AUC values were calculated by the trapezoidal rule and C_{max} and t_{max} parameters were derived from the individual raw data. The ANOVA model was used for comparing AUC and C_{max}. Treatment comparisons were based on 90% CIs. As established by current applicable European guidelines,[11] equivalence was defined as 80 to 125% for AUC values, and equivalence was accepted if the 90% CI was totally contained within 0.8 to 1.25. For defining statistical difference, $\alpha = 0.05$ was used. The PK Solutions 2.0 software (Summit Research Services, Ashland, USA) was used for data analyses.

Table I. Pharmacokinetic parameters according to treatment (arithmetic mean ± SD)

	Mopral® (reference)	Ompranyt®
$AUC_{0-\infty}$ (μg/L•h)	1490 ± 1276	1474 ± 1417
C_{max} (μg/L)	736.7 ± 443.3	630.1 ± 516.7
$t_{1/2}$ (h)	1.81 ± 1.15	1.72 ± 0.75
K_e (h^{-1})	0.4785 ± 0.19	0.4707 ± 0.18
t_{max} (h)	1.49 ± 0.63	2.25 ± 1.32*

$AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time zero to infinity; **C_{max}** = peak plasma concentration; **K_e** = rate constant for the appearance of unchanged drug in the urine; **SD** = standard deviation; **$t_{1/2}$** = elimination half-life; **t_{max}** = time to reach peak plasma concentration.
p > 0.05, * p = 0.0118 (Wilcoxon signed rank test).

Results

Study Population

Among the 24 individuals enrolled, 15 (62.5%) were male and nine (37.5%) were female. All participants were Caucasian. Mean age (± SD) was 25.6 ± 7.6 years (range 18-43 years). Weight and height ranged from 52 to 85kg (mean ± SD: 67.2 ± 10.7) and 147 to 187cm (mean ± SD: 170.3 ± 9.7), respectively. All enrolled subjects completed the study; no premature withdrawals occurred.

Pharmacokinetics

Omeprazole Plasma Concentrations

The main pharmacokinetic parameters are summarised in tables I and II. The mean omeprazole plasma concentration versus time profiles are shown in figure 1.

The arithmetic mean ± SD values of $AUC_{0-\infty}$ were 1474 ± 1417 μg/L•h for Ompranyt® and 1490 ± 1276 μg/L•h for Mopral®. The geometric means ratio (Ompranyt®/Mopral®) was 0.99, with a 90% CI of 0.97-1.03.

The estimated C_{max} was 630.1 ± 516.7 μg/L for Ompranyt® and 736.7 ± 443.3 μg/L for Mopral®. The geometric means ratio (Ompranyt®/Mopral®) was 0.96, with a 90% CI of 0.94-0.99.

Bioequivalence Evaluation

Bioequivalence of the two formulations was accepted based on the two one-sided ANOVA for $AUC_{0-\infty}$ as well as for C_{max}. In both cases, the 90% CI lies within the acceptance range of 0.80-1.25.

Adverse Events

A total of 33 adverse events (AEs) were reported in 19 volunteers (13 with Mopral® and 12 with Ompranyt®; six volunteers reported AEs with both products). From the total of 33 AEs, 21 events were considered by the investigator to possibly be treatment related, 12 with Mopral® (in nine individuals) and nine with Ompranyt® (in eight individuals) [table III]. These adverse reactions were primarily transient in duration, of mild to moderate intensity, and resolved without any sequelae or need for additional drug treatment.

Discussion

This study was intended to test the bioequivalence of Ompranyt® in relation to the reference drug Mopral. To exert an optimal therapeutic effect, an active substance should be delivered to its site of action in an effective concentration for the desired period. To allow prediction of the therapeutic effect, the performance of the pharmaceutical formulation containing the active substance should be reproducible. Assuming that in the same individual an essentially similar plasma concentration-time course will result in essentially similar concentrations at the site of action and, thus, having an essentially similar effect, pharmacokinetic

Table II. AUC and C_{max} parameters (geometric mean)

	Mopral® (reference)	Coefficient of variation (%)	Ompranyt®	Coefficient of variation (%)	Geometric means ratio (Ompranyt®/Mopral®)	90% CI (lower, upper)
$AUC_{0-\infty}$ (μg/L•h)	3.026876794	11.23	2.989833024	12.37	0.988	0.973-1.026
C_{max} (μg/L)	2.775599863	10.11	2.664836507	12.13	0.960	0.935-0.992

$AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time zero to infinity; **C_{max}** = peak plasma concentration.

data instead of therapeutic results may be used to establish bioequivalence.[11]

In practice, bioequivalence is generally demonstrated by randomised, crossover studies performed in healthy male and female subjects aged between 18 and 55 years, the study design applied in this study. In general, single-dose studies will suffice, but in the case of omeprazole the bioavailability is time dependent, and a steady-state study is required.

In studies to determine average bioequivalence, the acceptance ranges for the main pharmacokinetic characteristics are the AUC ratio and C_{max} ratio, according to the general acceptance criteria for bioequivalence studies.[11] For the AUC ratio, the 90% CI should lie within an acceptance range of 0.80 and 1.25. In the present study, the mean AUC ratio was approximately 0.99 (90% CI: 0.97-1.03) and the mean C_{max} ratio was 0.96 (90% CI: 0.94-0.99).

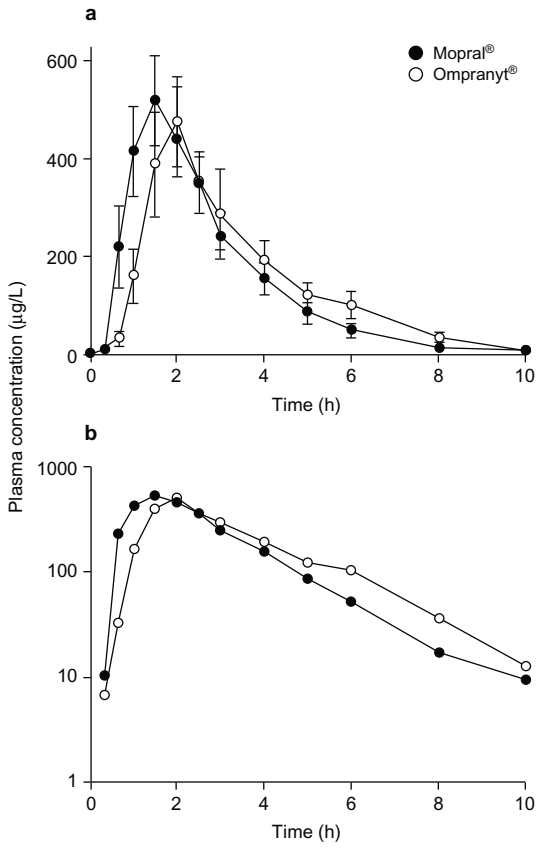

Fig. 1. Omeprazole plasma concentration versus time profiles (mean ± SEM) of the two study products. (**a**) linear scale ($p > 0.05$); and (**b**) semilog scale.

Table III. Summary of adverse reactions

Adverse event[a]	Mopral® (n = 9)	Ompranyt® (n = 8)
Abdominal pain or discomfort	5	2
Headache	3	4
Flatulence	2	1
Diarrhoea	1	1
Fatigue	1	0
Nausea	0	1

a Some participants reported more than one adverse reaction.

With regard to t_{max}, a statistical difference between the two products was observed (table I). After Ompranyt® treatment, C_{max} was detected 0.76 hours later than after Mopral® treatment. However, because of the characteristics of the mechanism of action of omeprazole and the fact that omeprazole formulations are controlled-release, this difference can not be considered to be clinically relevant. As clearly stated by the EMEA, '*statistical evaluation of t_{max} only makes sense if there is a clinically relevant claim for rapid release or action or signs related to adverse effects*'.[11]

As found in other studies with omeprazole formulations,[1,5,7-9] a high intra- and interparticipant variability was also observed in this study.

The two products were similarly well tolerated; the verified adverse events were mainly mild in intensity and of short duration. None of the reported adverse events required medical treatment or caused withdrawal of the individual from the study.

Conclusion

Bioequivalence of the Ompranyt® formulation in relation to the reference formulation Mopral® was demonstrated in this study, and the two treatments were similarly well tolerated. There are no

expected differences between these two formulations when used in a clinical setting.

Acknowledgements

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