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Multiple-Dose Studies can be a More Sensitive Assessment for Bioequivalence than Single-Dose Studies

The Case with Omeprazole

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Abstract

Objective: To evaluate the bioequivalence of two enteric-coated formulations of omeprazole, Losec® (reference) and Omepradex® (test). It is hypothesised that formulation differences may be accentuated following multiple-dose administration, and that testing after multiple administration may therefore provide a more sensitive assessment of bioequivalence.

Study participants and design: The study comprised two parts: an *in vitro* dissolution test and an *in vivo* bioavailability study. The latter was a randomised, two-way crossover comparative study after a single dose and after multiple doses in healthy volunteers. Forty subjects were randomly allocated to receive either test or reference product, once daily in the morning, and blood samples were taken on days 1 and 5. Standard pharmacokinetic analyses were performed, and analysis of variance (ANOVA) was used to compare the log-transformed variables in a model including terms for treatment, subject and period.

Results: Although both products meet the formal requirements specified by the United States Pharmacopoeia (USP) for enteric-coated articles, the *in vitro* dissolution experiments revealed widely differing properties for the two tested products. Less than 10% of the drug content was recovered from the Omepradex® formulation following a pre-exposure to pH 3 or 4, compared with over 90% recovered from the Losec® formulation. These findings were in agreement with the results of the *in vivo* bioavailability study, which showed that the two products differed in both their rate and extent of absorption after a single dose and following multiple doses. The products failed the bioequivalence test for area under the plasma concentration-time curve (AUC) and maximum plasma drug concentration (C_{max}) after a single dose [AUC: test/reference ratio 0.85, 90% confidence interval (0.76-0.95); C_{max}: test/reference ratio 0.85, 90% confidence interval (0.75-0.95)], and the difference between the formulations was even more pronounced after multiple doses [AUC: test/reference ratio 0.73, 90% confidence interval (0.65-0.83); C_{max}: test/reference ratio 0.71, 90% confidence interval (0.63–0.81)].

Conclusions: These data suggest that bioequivalence studies on enteric-coated proton pump inhibitors should include both single- and multiple-dose elements to be fully decisive. The two omeprazole products failed to show bioequivalence, with the observed differences being even more apparent after multiple doses, as postulated. Based on this study, the two products may not be considered either therapeutically equivalent or interchangeable.

Bioequivalence is defined as 'the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study'.[1] Bioequivalence is established by showing that the 90% confidence interval (CI) of the ratio of geometric mean response, usually the area under the plasma concentration-time curve (AUC) and the maximum plasma drug concentration (C_{max}), of the two formulations is contained within the limits of 0.8 to 1.25.[2,3] The European Committee for Propriety Medicinal Products (CPMP) recommends that bioequivalence be demonstrated after a single dose. Multiple-dose studies may also be required in the case of dose- or time-dependent pharmacokinetics or when the product has a modified-release profile.[4]

Recent FDA guidance states that single-dose studies are generally more sensitive than multiple-dose studies in assessing release of the drug substance from the drug product into the systemic circulation.[1] This statement is supported by Monte Carlo simulations demonstrating that the probability of failing the bioequivalence test dramatically decreases upon multiple-dose administration, due to the changes in CIs.[5] Consequently, multiple-dose studies are generally not recommended by the FDA for either immediate-release or modified-release products.[1] The present work examines the possibility that a multiple-dose study may be more sensitive than a single-dose study in detecting differences between formulations of a specific drug product, and hence more relevant to bioequivalence assessment.

Omeprazole is a substituted benzimidazole derivative that effectively suppresses gastric acid secretion by inhibiting the H^+/K^+-ATPase (proton pump) in the parietal cells of the stomach.[6] It is widely used for the treatment of gastric or duodenal ulcers, in the relief of symptoms of gastro-oesophageal reflux disease (GORD), in the healing of erosive oesophagitis and subsequent maintenance treatment, and in the treatment of pathological gastrointestinal hypersecretory conditions. It is also used in combination with antibiotics for eradication therapy of *Helicobacter pylori*.[7]

Omeprazole has low water solubility and is chemically very unstable in acidic media. This presents a significant challenge for pharmaceutical technologists as the ideal preparation must therefore protect the active ingredient against decomposition by gastric acid, as well as assure an immediate and complete release from the dosage form as soon as it has been transported to the site of absorption in the small intestine. To this end, omeprazole is currently formulated as delayed-release capsules and tablets containing enteric-coated pellets.[7] However, variations in the quality of the enteric coating of different modified-release formulations are thought to have a substantial effect on the *in vivo* performance of the drug.[8]

The bioavailability of omeprazole has been shown to increase during days 1 to 5 of repeated drug administration,[9,10] after which time both plasma concentrations and the area under the

plasma concentration-time curve (AUC) are also greatly increased.[11] This is mainly due to reduced first-pass metabolism during repeated-dose administration.

This study was designed to investigate, in accordance with international regulatory guidelines, the bioequivalence of two omeprazole products following single- and multiple-dose administration, as it was suspected that the differences in the behaviour of the enteric coatings noted in the *in vitro* test might result in differing bioavailability profiles. Moreover, it was contemplated that any differences would be accentuated following multiple-dose administration.

Methods

Products

The test product was Omepradex® [1] (Dexcel Ltd, Or-Akiva, Israel) enteric-coated caplets containing omeprazole 20mg. The reference product was Losec® (AstraZeneca/Abic Ltd.) enteric-coated capsules containing omeprazole 20mg.

In Vitro Dissolution

The amount of omeprazole released into phosphate buffer solution (pH 6.8) after pre-exposure to simulated gastric fluid (pH 1.2) for 2 hours was assessed for six individual capsules of both test and reference product using the United States Pharmacopoeia (USP)[12] Apparatus 2 (paddle; 100 rpm) method. In further testing, the pH of the gastric fluid was modified to pH 3 and 4 by the addition of disodium hydrogen phosphate solution (0.235 mol/L). After pre-exposure, further disodium hydrogen phosphate was added to adjust the pH of the solution to pH 6.8. The amount of omeprazole released after 30 minutes was determined by reverse-phase liquid chromatography with UV detection at 302nm.

1 The use of tradenames is for product identification only and does not imply endorsement.

Design of the Bioavailability Study

The study was a randomised, two-way crossover comparative bioavailability study after a single dose (day 1) and after multiple doses (steady-state, day 5). Forty healthy volunteers received five daily doses of omeprazole (either test or reference product) in each treatment period, and there was a 9-day washout between periods. The sample size was calculated so as to provide a statistical power of 80%, based on known intra-subject variability.

Study Participants

Subjects were eligible for the study if they were non-smoking males, aged between 18 and 50 years, within 10% of ideal bodyweight, whose laboratory tests fell within 10% of the normal range, and who did not have any significant medical history or abnormalities on physical examination. Volunteers were excluded if they failed to cooperate, if they had evidence or history of significant disease or drug abuse, if they were receiving long-term medication, or if they had participated in a drug trial or donated blood within 4 weeks before the start of the study. Subjects were not phenotyped for cytochrome P450-2C19 (CYP2C19).

The study was approved by the Soroka Medical Centre Review Board (IRB) and was conducted in accordance with the Declaration of Helsinki and current regulations by the Israel Ministry of Health. All subjects gave written informed consent before entering the study.

Treatments

Volunteers were randomly allocated to one of two treatment groups by a computer-generated sequence, according to the assigned subject number. The products used during treatment were Omepradex® 20mg caplets (test product) and Losec® 20mg capsules (reference product). Both products were taken once daily in the morning, and subjects were required to fast for at least 10 hours before each dose and before blood sampling on days 1 and

5. Group assignment and the drug administration schedule were kept in a sealed envelope until the plasma samples had been analysed. All drug administrations were done by authorised personnel, thus ensuring 100% treatment compliance in all subjects. Study participants were asked to refrain from the use of all drugs, including over-the-counter medications, for at least 1 week before the first administration in each period, as well as during the entire study.

Assessments

Blood samples were obtained on days 1 and 5 of each of the two treatment periods by aseptic venepuncture, immediately before drug administration, and at the following times after administration of each product: 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10 and 12 hours. Immediately after blood collection, plasma samples were obtained by centrifugation, and the samples were deep-frozen at –75ºC until they could be analysed. Omeprazole (racemic) concentrations were determined by a specific and sensitive high-performance liquid chromatography (HPLC) method involving solvent extraction and reverse-phase chromatography. Each 0.7ml blood plasma sample was subjected to an extraction procedure. After addition of 100µl of internal standard working solution and 400mg of sodium chloride, the analyte was extracted into acetonitrile. After centrifugation, the aliquots of organic layer were evaporated and reconstituted in diluent [acetonitrile in phosphate buffer pH 7.5 (1 : 2)]. Samples were injected into HPLC after a further centrifugation at 13 000 rpm for 10 minutes.

HPLC analysis was performed using a Symmetry C18 column (5µ), with a mobile phase of 36% acetonitrile in phosphate buffer pH 7.0 and UV detection at 305nm. A single calibration curve of eight blank plasma samples, spiked with known concentrations of omeprazole, was generated for each analytical batch. The calibration range included concentrations of 10, 20, 40, 80, 100, 200, 400 and 600 µg/L.

Pharmacokinetic Analyses

The pharmacokinetic analyses were done using computer programs developed and validated by Biostudies Ltd. The single-dose (day 1) and multiple-dose (day 5) pharmacokinetics were analysed separately. The peak plasma concentration (C_{max}), time to peak (t_{max}), area under the concentration-time curve from time zero to the last quantifiable concentration (AUC_{0-t}) and that extrapolated to infinity ($AUC_{0-\infty}$), first-order elimination rate constant (k_{el}), and elimination half-life ($t_{½}$) were calculated using standard formulae.

Statistical Analyses

All statistical analyses were conducted using SAS software and in accordance with the FDA recommendations on the statistical procedures for bioequivalence studies using a standard, two-treatment crossover design.[13]

Analysis of variance (ANOVA) was used to compare the log-transformed variables C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$in a model including terms for treatment, subject and period. Consistent with the test for bioequivalence, symmetric 90% CIs for the mean treatment differences of these variables were calculated, on both day 1 and day 5, from the ANOVA model.

Results

In Vitro Dissolution

Using the normal USP procedure for enteric-coated articles (i.e. pre-exposure in simulated gastric fluid, without enzymes, at pH 1.2 over 2 hours, followed by dissolution in a medium of pH 6.8 with measurement of the amount of drug released after 30 minutes), both products fulfilled the requirements. However, after pre-exposure to gastric fluid adjusted to pH 3, the gelatine capsules of reference product dissolved, but the pellets remained intact and the solution uncoloured. After 30 minutes in the phosphate buffer solution, 96% of the total omeprazole was released (mean from six capsules). The caplets of the test product, on the other

Table I. Summary of *in vitro* dissolution data: amount of omeprazole released after 30 minutes in phosphate buffer solution, pH 6.8, after pre-exposure to acidic media of different pH over 2 hours (% of label amount)

pH of pre-exposure medium	Test (Omepradex®)		Reference (Losec®)	
	mean	range	mean	range
1.2	91	89-93	96	94-99
3.0	8.7	1.5-21	96	93-99
4.0	0.8	0.7-0.8	96	93-99

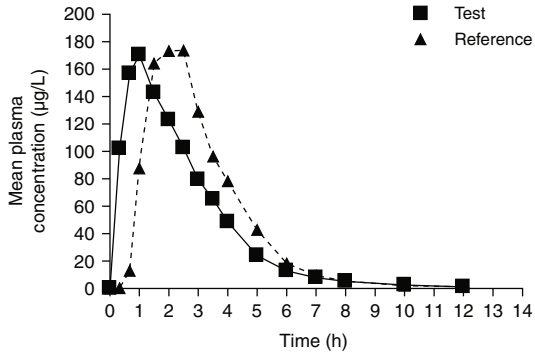

Fig. 1. Mean plasma concentration after single-dose fasted administration of test (Omepradex®) and reference (Losec®) omeprazole.

hand, disintegrated within 12 minutes of the pre-exposure, and the solution was coloured yellow/brown indicating degradation of omeprazole. After 30 minutes in the phosphate buffer solution, only 8.7% of the total amount of omeprazole was recovered (mean from six capsules), indicating that most of the omeprazole had been released into the acidic medium and had been degraded. Similar findings were made after pre-exposure to gastric fluid adjusted to pH 4, with 96% of the total omeprazole being recovered from the reference product capsules in the phosphate buffer solution compared with 0.8% from the test and reference product. These findings are summarised in table I.

Bioequivalence Study Findings

A total of 40 subjects were recruited into the study. All completed the study and were included in the pharmacokinetic analysis. No adverse reactions were observed or reported during the study.

The mean plasma concentrations of omeprazole following single-dose (day 1) administration of either the test or reference product are shown in figure 1. The mean plasma concentration-time profiles for the two products were not superimposable. Mean pharmacokinetic data are presented in table II. Although the mean profiles were similar in shape, with almost identical $AUC_{0-\infty}$ values, the test product was absorbed more quickly than the reference product. A total of 19 subjects exhibited measurable plasma concentrations of omeprazole 20 minutes after administration of the test product compared with only a single subject following administration of the reference product. The lag-time observed with the reference product is typical for enteric-coated preparations since they do not

Table II. Omeprazole single-dose (day 1) mean pharmacokinetic parameters [values are mean ± SD (range)]

	Test (Omepradex®)	Reference (Losec®)
$AUC_{0-\infty}$ (µg•h/L)	530 ± 625 (98-3883)	567 ± 540 (145-3428)
C_{max} (µg/L)	290 ± 181 (68-833)	311 ± 154 (121-745)
t_{max} (h)	1.25 ± 0.93 (0.3-3.5)	2.11 ± 0.90 (1-5)
k_{el} (h^{-1})	0.85 ± 0.33 (0.25-1.31)	0.99 ± 0.38 (0.27-1.67)

$AUC_{0-\infty}$ = area under the plasma concentration-time curve; **C_{max}** = maximum plasma concentration; **k_{el}** = first-order elimination rate constant; **t_{max}** = time to reach C_{max}.

Table III. Summary of omeprazole single-dose (day 1) pharmacokinetic data

	Test (n = 40)	Reference (n = 40)	Test/reference ratio	90% CI/p-value
Geometric mean $AUC_{0-\infty}$ (μg•h/L)	376	442	0.85	0.76-0.95
Geometric mean C_{max} (μg/L)	234	277	0.85	0.75-0.95
Median t_{max} (h) [range]	1.00 [0.3-3.5]	1.75 [1.0-5.0]		p = 0.00002

$AUC_{0-\infty}$ = area under the plasma concentration-time curve; **CI** = confidence interval; **C_{max}** = maximum plasma concentration; **t_{max}** = time to reach C_{max}.

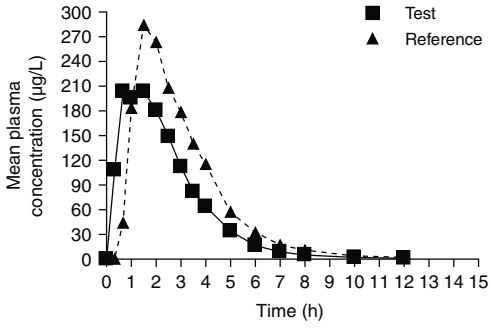

Fig. 2. Mean plasma concentration after multiple-dose fasted administration of test (Omepradex®) and reference (Losec®) omeprazole.

release the active drug ingredient during their residency in the stomach. The difference in t_{max} observed between the test and reference product was statistically significant ($p < 0.001$). The mean k_{el} differed slightly between test and reference product; however, this difference did not reach statistical significance.

The geometric mean $AUC_{0-\infty}$ values for test and reference product were 376 and 442 μg•h/L, respectively. The geometric mean ratio of $AUC_{0-\infty}$ test/reference was 0.85. The width of the 90% CI (0.76-0.95) was not within the bioequivalence acceptance limits for the extent of absorption. The geometric mean C_{max} values for test and reference product were 234 and 277 μg/L, respectively. The geometric mean ratio of C_{max} test/reference was 0.85, and the width of the 90% CI (0.75-0.95) was again outside the acceptance limits for bioequivalence. These results are summarised in table III.

The mean plasma concentrations of omeprazole following multiple-dose administration (day 5) of either the test or reference product are shown in figure 2. Once again, the mean plasma concentration-time profiles for the two products were not superimposable, and the observed differences were more pronounced than after single-dose administration. Mean pharmacokinetic data are presented in table IV. The test product exhibited a shorter t_{max} than the reference product, with 29 subjects exhibiting measurable plasma concentrations of omeprazole 20 minutes after administration of test product, compared with three subjects who received the reference product. The difference in t_{max} between test and reference products was statistically significant ($p < 0.001$). The mean k_{el} was similar in the test and reference product.

The geometric mean $AUC_{0-\infty}$ values for test and reference products were 502 and 684 μg•h/L, re-

Table IV. Omeprazole multiple-dose (day 5) mean pharmacokinetic parameters [values are mean ± SD (range)]

	Test (Omepradex®)	Reference (Losec®)
$AUC_{0-\infty}$ (μg•h/L)	688 ± 514 (53-2317)	865 ± 629 (203-2853)
C_{max} (μg/L)	325 ± 172 (42-770)	421 ± 182 (139-912)
t_{max} (h)	1.13 ± 0.69 (0.33-3.00)	1.82 ± 0.84 (0.67-4.00)
k_{el} (h^{-1})	0.82 ± 0.30 (0.27-1.49)	0.89 ± 0.33 (0.28-1.97)

$AUC_{0-\infty}$ = area under the plasma concentration-time curve; **C_{max}** = maximum plasma concentration; **k_{el}** = first-order elimination rate constant; **t_{max}** = time to reach C_{max}.

Table V. Summary of omeprazole steady-state (day 5) pharmacokinetic data

	Test (n = 40)	Reference (n = 40)	Test/reference ratio	90% CI/p-value
Geometric mean $AUC_{0-\infty}$ (μg•h/L)	502	684	0.73	0.65-0.83
Geometric mean C_{max} (μg/L)	268	378	0.71	0.63-0.81
Median t_{max} (h) [range]	1.0 [0.3-3.0]	1.5 [0.7-4.0]		p = 0.00007

$AUC_{0-\infty}$ = area under the plasma concentration-time curve; **CI** = confidence interval; **C_{max}** = maximum plasma concentration; **t_{max}** = time to reach C_{max}.

spectively. The geometric mean test/reference ratio was 0.73, and the width of the 90% CI (0.65-0.83) was not within the bioequivalence acceptance limits for the extent of absorption. The geometric mean C_{max} values for test and reference product were 268 and 378 μg/L, respectively. The geometric mean test/reference ratio was 0.71, and the width of the 90% CI (0.63-0.81) was not within the acceptance limits for bioequivalence. These results are summarised in table V.

After both a single dose and multiple doses, the interindividual variability in the pharmacokinetic parameters was high, as indicated by the wide range for each of the parameters, and was evident after administration of both the test and the reference products. Omeprazole exhibits non-linear pharmacokinetics (saturable first-pass metabolism and genetic differences in metabolic pathway and rate of metabolism) and is associated with high interindividual variability in AUC and C_{max}. A high variability in t_{max} is also expected for multiple-unit enteric-coated formulations owing to differences in gastric emptying rate.

Discussion

International regulatory authorities require that generic versions of any drug product are bioequivalent to the innovator product. Differences in the quality of the enteric coating of modified-release formulations may have a substantial effect on the *in vivo* performance of the drug.[8] Bloor et al.,[14] for example, noticed the failure of a neutralised hydroxypropyl methylcellulose (HPMC) phthalate enteric coating on prednisolone tablets manifested in a much earlier onset of drug absorption *in vivo*, compared with tablets coated by cellulose acetate phthalate. Prednisolone tablets coated by neutralised HPMC phthalate were also unstable at pH levels >3. The Omepradex® caplet coating includes HPMC acetate succinate (Omepradex® physician's insert). Dexcel Ltd, the manufacturer of Omepradex®, issued a patent application describing the coating of benzimidazole derivatives (such as omeprazole) by means of a neutralised layer, such as HPMC acetate succinate.[15] This neutralised enteric coating could be expected to exhibit the same deficiencies noted by Bloor et al.[14]

Results from the dissolution study indicate that the test and reference product differ considerably in their resistance to acidic media, and cannot therefore be considered to have equivalent *in vitro* dissolution profiles. After pre-exposure of the reference product to media with pH 1 to 4 over 2 hours, the enteric-coating was intact, since 96% of the total omeprazole was recovered after 30 minutes in the subsequent *in vitro* dissolution test in buffer solution, pH 6.8. The resistance of the test product to gastric fluid adjusted to pH 3 to 4 was, on the other hand, very poor, with the majority of the omeprazole being released into the acidic media and degraded, leaving less than 10% of the omeprazole to be released in the buffer medium.

The observation that t_{max} differed considerably between the two products, after both a single dose and multiple doses, suggests differences in the quality of the enteric coating. The reference product exhibited the normal behaviour of multiple-unit enteric-coated dosage forms, as demonstrated by the lag-time between administration and absorption of omeprazole into the systemic circulation. The test product, on the other hand, was released almost immediately following administration, with the majority of patients showing ob-

servable plasma omeprazole concentrations soon after administration. This would suggest that the quality of the enteric-coating is inferior to that of the reference product, further supporting the conclusions of the dissolution study.

The rate and extent of absorption of the test and reference products were found to differ considerably. These differences were more pronounced after multiple doses and may give rise to potential concerns regarding the efficacy of the test compound in clinical use. The results are somewhat at odds with the FDA assertion that single-dose investigations are generally more sensitive in assessing bioequivalence. In the case of enteric-coated drug products of acid-labile proton pump inhibitors, which alter the gastrointestinal environment in which they are constructed to function during continuous treatment, multiple-dose studies may be more discriminating. In this study, after a single dose, the 90% CIs for the mean ratios of $AUC_{0-\infty}$ and C_{max} were slightly outside the acceptance range, while the geometric mean ratios were within the range. After multiple doses, both the ratios and the respective 90% CIs of $AUC_{0-\infty}$ and C_{max} were far outside the acceptance limits for bioequivalence.

Conclusions

In this study, Losec® and Omepradex® were not bioequivalent, and on the basis of these findings cannot be considered as either therapeutically equivalent or interchangeable. The data also indicated that bioequivalence studies on enteric-coated proton pump inhibitor drug products should include both single-dose and multiple-dose elements to be fully decisive. The change in the gastrointestinal environment, caused by multiple doses of proton pump inhibitors, may affect the enteric-coating and *in vivo* dissolution of the formulations differently, such that formulations that may exhibit bioequivalence in a single-dose study may fail to show bioequivalence following multiple doses. Since the clinical use of proton pump inhibitors involves multiple doses, it is crucial to ensure bioequivalence following multiple-dose administration, and thus minimise concerns over differences in therapeutic efficacy.

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