Administration of an alginate based gastric reflux suppressant on the bioavailability of omeprazole


Reckitt Benckiser Healthcare (UK) Ltd., Hull, UK & Wellquest Research Pvt. Ltd Wellspring Hospital, Mumbai, India

Received March 17, 2005

Background & objectives: Omeprazole treats gastro-oesophageal reflux disease (GORD) by inhibition of acid secretion whereas alginate based reflux suppressants work by forming a low density raft of near neutral pH which floats on the stomach contents and physically impedes gastro-oesophageal reflux. There is limited pharmacokinetic information regarding possible drug interaction between these two types of products, although these may be frequently co-prescribed to improve symptom control in GORD patients. This study was designed to determine whether the administration of a 10 per cent w/v liquid alginate suspension affected the pharmacokinetic profile of omeprazole.

Methods: This was a randomized, two-treatment, two-sequence, two-period crossover study in 26 volunteers. Each treatment was dosed for 3 consecutive days with a washout period of 7 days between dosing periods. Blood samples for pharmacokinetic analysis were taken over the 24 h period following the final dose of omeprazole.

Results: Geometric means and ratios were as follows: C_{max} was 555 for omeprazole/alginate and 558 for omeprazole alone (ratio 99.55%, 90% confidence interval 82.75-119.75%; AUC_{0-t} was 2050 for omeprazole/alginate and 2094 for omeprazole alone (ratio 97.90%, 90% confidence interval 87.83-109.12%); AUC_{0-a} was 2247 for omeprazole/alginate and 2231 for omeprazole alone (ratio 100.74%, 90% confidence interval 90.05-112.70%). Mean values for T_{max}, k_{el} and T_{1/2} were also similar for the two treatment regimens.

Interpretation & conclusion: As the 90 per cent confidence intervals for the geometric mean ratios for C_{max}, AUC_{0-t}, and AUC_{0-a} are all contained within the bioequivalence interval of 80-125 per cent, it can be concluded that the administration of this liquid alginate suspension does not affect the pharmacokinetic profile of omeprazole.

Key words Alginate - gastro-oesophageal reflux - omeprazole - pharmacokinetic profile
Gaviscon® is a reflux suppressant which achieves its activity by the formation of an alginate raft which floats on top of the stomach contents and provides a physical barrier to prevent acid reflux into the oesophagus. The liquid form of Gaviscon® relies on the interaction of alginate with gastric acid to form a raft of near neutral pH, but Gaviscon tablets® form a raft by interaction of alginic acid with antacids upon chewing in the mouth. Previous studies1,2 have demonstrated that liquid Gaviscon® forms a strong alginate raft in vitro and that such rafts remain in the upper part of the stomach for 1-2 h in contrast to the behaviour of antacids or other alginate products3,4. The liquid alginate preparation used in this study, Gaviscon Advance®, also forms strong alginate rafts in vitro5 which have been shown to remain in the stomach after the meal empties6. Its mode of action does not depend on absorption into the systemic circulation and no drug interactions are known.

Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, which suppress gastric secretion by specific inhibition of the H+/K+ adenosine triphosphatase enzyme system at the secretory surface of the gastric parietal cell7. The stability of omeprazole is a function of pH and it rapidly degrades in acid medium, but has acceptable stability in alkaline conditions. Absorption is rapid, with peak plasma levels of omeprazole occurring within 0.5 to 3.5 h. Peak plasma concentrations of omeprazole and area under the plasma concentration versus time curve (AUC) are approximately proportional to doses up to 20 mg with high intra-subject variability. Absolute bioavailability (compared with intravenous administration) is about 30-40 per cent at doses of 20-40 mg, due in large part to pre-systemic metabolism. In healthy subjects the plasma half-life is 0.5 to 1 h. Protein binding8 is approximately 95 per cent.

The bioavailability of omeprazole increases slightly upon repeated administration. The majority (approximately 77%) of the dose is eliminated in urine as metabolites8. In patients with chronic hepatic disease, the bioavailability is increased and the plasma half-life of the drug is increased to nearly 3 h8. In patients with chronic renal impairment, the disposition of omeprazole is very similar to that in healthy volunteers10, although there is a slight increase in bioavailability.

Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin11. There have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (e.g., cyclosporine, disulfiram, benzodiazepines). Omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts)11.

In the United Kingdom and other European countries omeprazole and Gaviscon Advance are routinely prescribed and recommended either alone or in combination for symptomatic treatment of GORD and the accompanying symptoms of acid regurgitation, heartburn and indigestion. It was therefore desirable to know whether there is any interaction between the two which may affect the pharmacokinetics of omeprazole. We carried out this study to see whether administration of liquid alginate suspension affected the pharmacokinetic profile of omeprazole in healthy male volunteers.

Material & Methods

Study design: The study was designed as a randomized, two-treatment, two-period, crossover, multiple-dose pharmacokinetic study of the omeprazole tablet (Losec, 20 mg MUPS tablet, Astra Zeneca, UK) in the presence and absence of the 10 per cent liquid alginate suspension (Gaviscon Advance, Reckitt Benckiser Healthcare, UK) and conducted at Wellquest Research Pvt. Ltd. Wellspring Hospital, Mumbai during 2001-2002 Subjects were randomly allocated to the two treatment order groups. Both treatment periods were of 3 days duration, an adequate period of time for omeprazole to reach peak plasma concentrations. Subjects received one treatment in the first period of the study, followed by a standard washout period for omeprazole of 7 days before starting the other treatment in the second period. The study was performed open label since there is no matching placebo available for the liquid alginate suspension. This lack of blinding was not considered likely to affect the study outcome since the outcome
measures were objective (plasma concentrations) and samples were assayed by analysts blind to the treatment allocation.

The study protocol was reviewed and approved by the local Independent Ethics Committee (IEC, Wellspring Hospital, Lower Parel, Mumbai). All subjects were informed about the pertinent details of the study. A written consent form, approved by the IEC, was presented orally to the volunteers and understood and signed by each volunteer prior to initiating any study procedures.

Each volunteer received, in random order – Treatment A: omeprazole magnesium 20.6 mg (equivalent to omeprazole 20 mg) tablet administered orally 15 min before breakfast for 3 days, with 240 ml drinking water. Treatment B: omeprazole magnesium 20.6 mg (equivalent to omeprazole 20 mg) tablet administered orally 15 min before breakfast, with 240 ml drinking water, plus 10 per cent liquid alginate suspension (10 ml, containing 1 g sodium alginate and 0.2 g potassium bicarbonate) administered orally 4 times daily (30 min after meals and at bedtime) for 3 days.

**Blood sampling and analysis:** Repeated blood samples were collected over the 3 study days to assess plasma omeprazole concentrations. In order to follow the final day of omeprazole closing blood samples were taken between 47.5 and 72 h. The blood samples (each 5 ml) were collected in polypropylene tubes containing 5 per cent w/v EDTA during each period. Pre dose samples were withdrawn 30 min before omeprazole administration on day 1 and day 3 and post dose samples were collected on day 3 at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, and 24.0 h after omeprazole dosing. Samples collected at each time point were centrifuged to separate plasma then stored at -50°C until analysis.

A validated high performance liquid chromatography (HPLC) (Welllquest Research Pvt Ltd, Mumbai, India) method was employed for the estimation of omeprazole in plasma samples. Plasma (500 µl) was vortexed with 100 µl of 10 µg/ml pantoprazole internal standard, extracted, by shaking, into 4 ml of dichloromethane and centrifuged; 3 ml of the dichloromethane extract was evaporated to dryness and reconstituted in 250 µl of mobile phase. A 4.6 x 150 mm column, packed with 5 µm Zorbax SB-C18, was used at 30°C with a mobile phase of 50 mM sodium dihydrogen phosphate (pH 7.2): acetonitrile (75:25) at a flow rate of 1 ml per minute. Eluted omeprazole and pantoprazole were detected by UV at 302 nm. Subject plasma samples and standard mixture were interspersed with quality control samples which consisted of plasma spiked with concentrations of between 15 and 1700 ng/ml omeprazole, extracted in the same manner as subject plasma samples. All samples were compared with a reference standard curve using omeprazole (99.5% potency) prepared at concentrations between 15 and 2000 ng/ml.

The low limit of reliable quantitation was set at 15.65 ng/ml, at which the precision was found to be 7.87 per cent and the accuracy 99.18 per cent. Intra-day precision ranged from 1.17 to 8.92 per cent and intra-day accuracy ranged from 89.8 to 104.25 per cent. Between batch/inter-day precision ranged from 3.47 to 7.87 per cent and between batch/inter-day accuracy ranged from 91.53 to 99.18 per cent.

Quality control samples spiked with known amounts of omeprazole were distributed throughout each batch of study samples and, wherever possible, samples from each subject were analysed on the same standard curve. Samples which were below the limit of quantification were set to zero for all pharmacokinetic and statistical evaluation.

**Pharmacokinetic analysis:** The following pharmacokinetic parameters for plasma omeprazole concentrations were derived for each volunteer and each dosing period from the blood samples taken from 30 min before administration of omeprazole on day 3 through to 24 h post dose, a period of 24.5 h: \( T_{\text{max}} \): Time of maximum measured plasma concentration following each treatment. If the maximum value occurred at more than one time point, \( T_{\text{max}} \) was defined as the first time point with this value. \( C_{\text{max}} \): Maximum measured plasma concentration following each treatment. AUC: The area under the plasma concentration versus time curve from the pre-dose assessment to the last measurable concentration, calculated by the linear
trapezoidal method. AUC\textsubscript{0-α}: The area under the plasma concentration versus time curve from the pre-dose assessment to infinity, calculated as the sum of AUC\textsubscript{0-t} plus the ratio of the last measurable concentration to the elimination rate constant, $K_\text{el}$. Apparent first order elimination or terminal rate constant calculated from a semi-logarithmic plot of plasma concentration versus time using linear least squares regression analysis from the last three (or more) non-zero plasma concentrations. $T_{1/2}$: Time required for the plasma drug concentration to decrease by one half.

**Statistical methods:** The reported parameters were the arithmetic means, standard deviations and the coefficient of variation (CV) for untransformed data and the geometric means and the coefficient of variation derived from the log transformed (natural) data. The geometric mean ratios for the relevant pharmacokinetic parameters were reported. The untransformed and log transformed pharmacokinetic parameters ($C_{\text{max}}$, AUC\textsubscript{0-t}, AUC\textsubscript{0-α}) were analysed using an ANOVA model with the main effects of sequence, subject nested within sequence, period and treatment. A 5 per cent level of significance was used for within subject comparison (i.e., period, treatment) and a 10 per cent level of significance for between subject comparison (i.e., sequence). Each analysis of variance included calculation of least-square means, adjusted differences between treatment means and the standard error associated with these differences. The intra-subject variability for each of the pharmacokinetic parameters reflected the residual variability after accounting for the difference between subjects, period and treatment was reported in terms of the overall coefficient of variation (% CV), from the ANOVA results using log-transformed data.

For the pharmacokinetic parameters ($C_{\text{max}}$, AUC\textsubscript{0-t}, AUC\textsubscript{0-α}) 90 per cent confidence intervals (CI) for the geometric mean ratios were calculated using the ANOVA output from the analysis of the log-transformed data. The 90 per cent confidence intervals for the geometric mean ratios were calculated by first calculating the 90 per cent confidence intervals for the differences in the arithmetic means of the log-transformed data and then taking the antilogarithms of the obtained confidence limits. The 90 per cent confidence intervals formed the basis for assessing the equivalence of the treatments. In accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) criteria for bioequivalence\textsuperscript{12}, if the point estimates of the ratios and the confidence intervals were entirely included in the range 80-125 per cent, then the treatments were claimed to be equivalent, otherwise the two treatments were assumed to be non-equivalent.

**Power calculations:** In a study in 16 healthy male volunteers\textsuperscript{13}, the geometric mean area under the plasma time curve (AUC) on day 7 for subjects who had received 20mg omeprazole once daily for 7 days was 0.28 mg h/l and the geometric mean $C_{\text{max}}$ on day 7 was 0.184 mg/l. On the log scale, the mean log AUC was -1.273 (between subject S.D. 0.693) and mean log $C_{\text{max}}$ -1.693 (between subject S.D. 0.582). However, no details are available concerning the within subject variation in these parameters.

In other studies in healthy volunteers\textsuperscript{14,15}, the within subject standard deviation of the log-transformed AUC values was of the order of 25 per cent of the between subject standard deviation, while the within subject standard deviation of the log-transformed $C_{\text{max}}$ values was of the order of 50 per cent of the between subject standard deviation. Assuming that the variation in plasma profiles after once daily (o.d.) dosing for 3 days would be similar to that observed after o.d. dosing for 7 days and that the ratio of the within subject variation to between subject variation would be similar to these studies, the within subject standard deviation of log AUC and log $C_{\text{max}}$ in the current study may be expected to be approximately 0.173 and 0.291 respectively.

In order to satisfy the European Agency for the Evaluation of Medicinal Products (EMEA) criteria for bioequivalence, that the 90 per cent CI for the mean within subject ratio of the parameter (treatment/Control) is fully contained within the interval (80 to 125%) or equivalently, that the 90 per cent CI for the mean within subject difference in the log-transformed parameter [Log\textsubscript{e}(Treatment) − Log\textsubscript{e}(Control)] is fully contained within the interval (-0.2231 to +0.2231), the above assumptions suggest that to provide 80 per cent power to show equivalence of the treatments in terms of AUC a crossover design using a minimum of.
11 subjects is required if the mean log-transformed AUCs for treatment (omeprazole + alginate) and control (omeprazole without alginate) are identical, or if the mean log-transformed AUCs are not necessarily identical, but are assumed to be within 5 per cent, then at least 14 subjects are required.

To provide 80 per cent power to show equivalence of the treatments in terms of $C_{\text{max}}$, a crossover design using a minimum of 29 subjects is required if the mean log-transformed $C_{\text{max}}$ for treatment and control are identical, while if the mean log-transformed $C_{\text{max}}$ for treatment and control are not necessarily identical, but are assumed to be within 5 per cent, then a minimum of 39 subjects is required.

Using this design, a study with 24 fully evaluable subjects would therefore provide adequate power to demonstrate equivalence in terms of AUC and approximately 70 per cent power to show equivalence of the treatments in terms of $C_{\text{max}}$ if the mean log-transformed $C_{\text{max}}$ for treatment and control are identical, and approximately 62 per cent power if they are assumed to be within 5 per cent.

A sample size of 24 subjects was therefore considered appropriate for this study. To ensure that at least 24 subjects completed the study, 26 subjects were to be screened and randomized.

Results

Twenty four out of the 26 subjects enrolled in the study completed both periods of the study. All study subjects were healthy Asian males recruited from the Mumbai region of India. CYP2C19 polymorphism was not determined for this study population. Two subjects left the study following the first dosing period (one for each treatment order group) for personal reasons. Neither of these subjects reported adverse events. Two of the completed subjects reported adverse events: loose motions whilst on treatment with omeprazole plus alginate (considered possibly related to treatment) and fever whilst on treatment with omeprazole only (considered unrelated to treatment).

Demographic and other subject characteristics: The age, height and weight of subjects enrolled in the study ranged from 18 to 28 yr, 160 to 175 cm and 49 to 71 kg, respectively. All the subjects were non-smokers (one subject reported tobacco chewing) and none drank alcohol. None of the subjects gave a history of participation in a clinical trial or a history of donation of more than 350 ml of blood in the 3 months preceding their entry into the study or had received medication within 2 wk prior to the first dose of study medication. None of the subjects had a clinically significant relevant past medical history, family history or history of allergies to animals, foods or drugs. None of the subjects enrolled in the study had any clinically significant abnormalities detected during medical examination, general and systemic examination (cardiovascular, nervous, respiratory and gastrointestinal), ECG or chest X-ray.

Pharmacokinetic results: Pharmacokinetic data analysis was carried out on the 24 completed subjects and the results are summarised in Table. Geometric means and ratio were as follows: $C_{\text{max}}$ was 555 for omeprazole/alginate and 558 for omeprazole alone (ratio 99.55%, 90% confidence interval 82.75-119.75%; $AUC_{0-t}$ was 2050 for omeprazole/alginate and 2094 for omeprazole alone (ratio 97.90%, 90% confidence interval 87.83-109.12%); $AUC_{0-\infty}$ was 2247 for omeprazole/alginate and 2231 for omeprazole alone (ratio 100.74%, 90% confidence interval 90.05-112.70%). Mean values for $T_{\text{max}}$, $K_{e1}$ and $T_{1/2}$ were also similar for the two treatment regimens. Mean omeprazole plasma concentrations over the day following the final dose of omeprazole are shown for both treatments in the Fig. The 90 per cent confidence intervals for the geometric mean ratios for $C_{\text{max}}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ are all fully contained within the interval 80-125 per cent, and thus satisfy the EMEA criteria for bioequivalence.

Discussion

The formulation of omeprazole has a profound effect on its pharmacokinetics, partly because of its acid instability. Solid dosage forms are mostly presented as enteric coated granules and although these may have a similar AUC to a buffered liquid dose the peak plasma concentration is both lower and delayed. Solid dosage form of omeprazole used in this study, MUPS tablets, has however been shown to be bioequivalent to the older, more widely used, formulation of enteric
Table. Pharmacokinetic results for the two treatments and their comparison

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng·h/ml)</th>
<th>AUC&lt;sub&gt;0-a&lt;/sub&gt; (ng·h/ml)</th>
<th>K&lt;sub&gt;el&lt;/sub&gt; (1/h)</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Omeprazole alone:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arithmetic mean (SD)</td>
<td>2.25 (338.19)</td>
<td>637.53 (3679.42)</td>
<td>3214.24 (4263.22)</td>
<td>3487.25 (4263.22)</td>
<td>0.379</td>
<td>3.656</td>
</tr>
<tr>
<td>Geometric mean (%CV)</td>
<td>- (60.52)</td>
<td>557.92 (121.09)</td>
<td>2093.80 (121.84)</td>
<td>2230.94 (121.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Omeprazole + alginate:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arithmetic mean (SD)</td>
<td>2.15 (347.42)</td>
<td>666.52 (3347.45)</td>
<td>3247.99 (3591.81)</td>
<td>3501.34 (3591.81)</td>
<td>0.312</td>
<td>3.294</td>
</tr>
<tr>
<td>Geometric mean (%CV)</td>
<td>- (79.50)</td>
<td>555.40 (145.34)</td>
<td>2049.72 (138.17)</td>
<td>2247.44 (138.17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geometric mean ratio* (%)</td>
<td>- (79.50)</td>
<td>99.55 (100.74)</td>
<td>97.90 (100.74)</td>
<td>100.74 (100.74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90% confidence Interval</td>
<td>- (82.75)</td>
<td>82.75 (90.05)</td>
<td>87.83 (90.05)</td>
<td>90.05 (90.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-subject variability (%CV)*</td>
<td>- (82.75)</td>
<td>38.61 (119.75)</td>
<td>22.16 (109.12)</td>
<td>22.92 (112.70)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*omeprazole + alginate/omeprazole alone

For details of parameters please see Material & Methods section

Fig. Comparative linear plots of mean plasma omeprazole concentrations versus time for Treatment A (omeprazole only) and Treatment B (omeprazole plus alginate).
coated pellets in hard gelatine capsules\textsuperscript{17} after one and 6 days dosing. This means that the main pharmacokinetic parameters obtained for omeprazole in this study (AUC, $C_{\text{max}}$, $t_{\text{max}}$, $t_{1/2}$, $K_{el}$) can be compared with those of other studies with the capsule dosage form as well as the few available studies with the MUPS tablet form. It is obvious that the pharmacokinetic results fall into two groups, based upon the ethnic origin (Caucasian or Asian) of the subjects. This is known to be related to the major enzyme involved in omeprazole metabolism, CYP2C19, which is deficient in some individuals, resulting in plasma concentrations and AUCs four or five times larger than in those with this cytochrome P450 isoform. This deficiency also results in a plasma elimination half life of three times longer in such poor metabolisers\textsuperscript{11}. It is known that the genetic variant in which CYP2C19 is deficient is much more common in Asians than in Caucasians, although this has normally been reported for Japanese, Chinese and Koreans\textsuperscript{18}. The pharmacokinetic parameters reported in this study are directly comparable with those obtained in a previous study known to be carried out in Indian subjects\textsuperscript{19} and also with those of an earlier Australian study\textsuperscript{20}. These contrast with several European/US studies carried out with enteric coated granules in capsules\textsuperscript{15,21,22} in which the repeat dose AUC was between a quarter and a fifth of the present study AUC. These studies report a $t_{\text{max}}$ between 1.25 and 1.6 h, substantially lower than the 2.2 h of the current study.

The only bioavailability studies previously reported for omeprazole MUPS tablets\textsuperscript{23,24} have been carried out in Europe and show the typical pharmacokinetic parameters for Caucasian subjects.

There is conflicting evidence on the effect of antacids on omeprazole bioavailability from enteric coated granules. Two European studies\textsuperscript{16,25} found no effect of concomitant liquid antacids containing aluminium and magnesium hydroxides on single dose omeprazole, whereas a Japanese study\textsuperscript{26} found a marked decrease in AUC from omeprazole enteric coated tablets given concomitantly with Maalox granules but not with Maalox suspension. There was no bioavailability difference found in the present study when Gaviscon Advance was administered with omeprazole MUPS tablets but this may be because Gaviscon Advance has only a very weak acid neutralizing capacity and does not contain either of the above aluminium or magnesium hydroxide antacids. Gaviscon Advance may perhaps be considered to be more similar to food, since it is given after the meal and forms floating gelatinous mass which is retained in the stomach. The effect of food on the bioavailability of omeprazole from enteric coated granules in capsules is to delay absorption of the drug but without affecting overall availability\textsuperscript{16}. In the present study, the omeprazole was administered 15 min before a breakfast and the Gaviscon Advance 30 min after the breakfast. The results showed that the administration of Gaviscon Advance had no effect on the plasma level curve and that it therefore did not add to the effect of the meal on omeprazole absorption from MUPS tablets.

As the 90 per cent confidence intervals for $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{\text{ave}}$ are all contained within the bioequivalence interval of 80-125 per cent, it can be concluded that the co-administration of this liquid alginate suspension, which has a physical mode of action and does not depend on absorption into the systemic circulation, has no effect on the multiple dose pharmacokinetics of omeprazole after a 3 day dosing period.

### Acknowledgment

The authors acknowledge the financial support from Reckitt Benckiser Healthcare (UK) Limited and thank John Sykes for his expert statistical analysis.

### References


Reprint requests: Dr P.W. Dettmar, Reckitt Benckiser Healthcare (UK) Ltd., Dansom Lane, Hull, HU8 7DS, UK e-mail: peter.dettmar@technostics.com