PHARMACOKINETICS AND DISPOSITION

M. Hassan-Alin · T. Andersson · E. Bredberg · K. Röhss

Pharmacokinetics of esomeprazole after oral and intravenous administration of single and repeated doses to healthy subjects

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Abstract Objective: To study the pharmacokinetics of esomeprazole, one of the optical isomers of omeprazole, after 20 mg or 40 mg single and repeated oral and intravenous administration to healthy subjects. The main metabolites of esomeprazole were also assessed after the 40-mg oral dose.

Methods: In two separate studies, 16 healthy male subjects and 16 healthy male and female subjects received intravenous doses of 20 mg and 40 mg esomeprazole, respectively, on the first investigation day. After a wash-out period of 5–14 days, the same doses (20 mg as a solution and 40 mg as a capsule) were given orally for 5 days and then again intravenously on day 6. Blood samples for determination of esomeprazole and its metabolites were collected 12 h or 24 h post-dose and were analysed using normal-phase liquid chromatography with ultraviolet (UV) detection. Pharmacokinetic parameters of esomeprazole and its metabolites were estimated using non-compartmental analysis. Geometric means and ratios of the geometric means together with 95% confidence intervals (CI) of the pharmacokinetic parameters were calculated using analysis of variance (ANOVA).

Results: Plasma clearance (CL) of esomeprazole decreased from 22 l/h to 16 l/h and from 17 l/h to 9 l/h following repeated dosing of 20 mg and 40 mg, respectively. Total area under the plasma concentration-time curve (AUC) increased (from 1.34 μmol × h/l to 2.55 μmol × h/l) with absolute bioavailability (F) being 50% on day 1 and 68% on day 5 after the 20-mg oral dose. AUC increased (from 4.32 μmol × h/l to 11.21 μmol × h/l) with F being 64% on day 1 and 89% on day 5 after the 40-mg oral dose. The plasma levels for esomeprazole sulphone were substantially higher on day 5 than on day 1, while those for 5-hydroxy esomeprazole were marginally higher on day 5 than on day 1 following repeated oral dosing of 40 mg esomeprazole. No side effects attributable to esomeprazole were noticed.

Conclusion: The increased AUC of esomeprazole with repeated dosing is probably due to a combination of a decreased first-pass elimination and a decreased systemic clearance.

Key words Esomeprazole · Pharmacokinetics · Single dose · Steady state

Introduction

Esomeprazole is the first proton pump inhibitor (PPI) developed as an optical isomer (S-omeprazole) for the treatment of acid-related diseases. Like other PPIs [1], the metabolism of esomeprazole is mediated by the cytochrome P450 (CYP) isoforms CYP3A4 and CYP2C19, which form two main metabolites, esomeprazole sulphone and 5-hydroxy esomeprazole, respectively [2], both pharmacologically inactive. Esomeprazole is a potent inhibitor of gastric acid secretion. The compound accumulates in the acidic compartment of the parietal cells where the molecule is transformed to its active form, the sufinamide.

One recent study in which each of the optical isomers of omeprazole, esomeprazole and R-omeprazole was incubated with human liver microsomes [2] indicated a relatively higher dependence on CYP2C19 for the metabolism of R-omeprazole than esomeprazole. The data from human liver microsomal experiments also showed that the intrinsic clearance for esomeprazole was substantially
lower than that for R-omeprazole and, consequently, lower than that for the racemate [2]. In an in vivo study in healthy subjects [3], the plasma levels of esomeprazole were higher than those of omeprazole, while those of R-omeprazole were lower. The mean AUC (area under the plasma concentration–time curve) of esomeprazole on day 7 was almost twofold higher for esomeprazole than that for omeprazole, whereas the mean AUC of R-omeprazole was approximately 50% of that for omeprazole. Furthermore, an almost twofold higher AUC with resulting higher intra-gastric pH for esomeprazole than for omeprazole was shown in patients with symptomatic gastroesophageal reflux disease (GERD) [4]. The intrinsic clearance being lower for esomeprazole than for R-omeprazole and the racemate resulting in a twofold higher AUC may therefore provide better clinical effect in the treatment of acid related diseases.

The objective of the present investigation was to study the pharmacokinetics of esomeprazole after oral and intravenous (i.v.) administration of single and repeated doses to healthy subjects.

Materials and methods

Subjects

In two separate studies, 16 healthy male subjects (study A) with a mean age of 28 years and mean weight of 76 kg and 16 healthy subjects (8 male and 8 female, study B) with a mean age of 27 years and a mean weight of 72 kg were included. The two studies were conducted in accordance with the Declaration of Helsinki and approved by the ethics committees of the University of Göteborg and the University of Uppsala and by the Swedish Medical Products Agency. Written informed consent was received from all subjects prior to participation.

All subjects underwent a full clinical examination, including past medical history, physical examination and electrocardiogram (ECG) at pre-entry. Laboratory screen for haematology and serum biochemistry was also performed prior to participation in the studies.

Study design

The two studies were conducted according to an open design and each consisted of four investigation days. In studies A and B, subjects received i.v. doses of 20 mg and 40 mg esomeprazole, respectively, on the first investigation day (first i.v.). After a wash-out period of 5-14 days, the same doses (20 mg as a solution and 40 mg as a capsule) were given orally for 5 days and then again intravenously on day 6 (second i.v.). Blood samples for determination of esomeprazole in plasma were taken up to 12 h (study A) or 24 h (study B) post-dose after the first and second i.v. doses and on day 1 and day 5 of oral dosing. Plasma samples for esomeprazole main inactive metabolites were also assessed in study B.

Alcohol intake was not allowed for 2 days prior to or during the treatment period. Drugs available on prescription had not been allowed during the last 2 weeks preceding the studies. Oral contraceptives were not allowed. On the four investigation days, the subjects arrived at the laboratory in the morning, having fasted since the previous evening, for administration of drug and for collection of repeated blood samples. On these days, standardised meals were served 4 (lunch), 7 (light meal), and 10 h (dinner) after drug administration.

Study drugs

For esomeprazole 20 mg, the oral and the i.v. study formulations were present as its corresponding sodium salt in solution, (5 mg/ml, AstraZeneca R and D Mölnidal, Sweden). The oral esomeprazole 40 mg was present as its corresponding magnesium salt as enteric-coated pellets dispensed in a hard gelatin capsule, while the i.v. 40 mg formulation was present as its sodium salt in solution, (5 mg/ml, AstraZeneca R and D Mölnidal). The concentration of esomeprazole is stated with respect to the neutral form.

For the 20-mg oral dose, 4 ml of the drug solution was diluted with distilled water to a volume of 50 ml and was given to the subject to swallow. The beaker was rinsed twice with 50 ml buffer solution (0.16 mmol/l). For the i.v. 20-mg dose, 4 ml of the solution was added to a 96-ml sodium chloride i.v. infusion to give a final concentration of 0.2 mg/ml esomeprazole. A volume of 100 ml was administered intravenously over 30 min.

The 40-mg capsule was taken orally with 200 ml water. For the i.v. 40-mg dose, 8 ml of the drug solution was added to a 192-ml sodium chloride i.v. infusion to give a final concentration of 0.2 mg/ml esomeprazole. A volume of 200 ml was administered intravenously over 30 min.

Blood sampling

On each of the four investigation days a reference blood sample was drawn from an indwelling cannula in a forearm vein followed by i.v. or oral administration of esomeprazole. The i.v. doses were infused for 0.5 h through a second indwelling cannula. Thereafter, blood samples for the assay of esomeprazole and its metabolites were taken at pre-dose and at 0.08, 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12 or 24 h post-dose, collected in heparinised tubes, centrifuged and the plasma stored frozen until analysis.

In study A (20-mg dose), the plasma samples were analysed for esomeprazole using normal-phase liquid chromatography with ultraviolet (UV) detection at AstraZeneca R and D Mölnidal [5]. In study B (40-mg dose), the plasma samples were analysed for esomeprazole and its metabolites (esomeprazole sulphine and 5-hydroxy esomeprazole) using normal-phase liquid chromatography with UV detection with some modifications. The compounds were detected in the elute using UV at 302 nm and the retention times were 3.5, 4.5, 6.0 and 5.5 min, respectively, for esomeprazole, esomeprazole sulphine, 5-hydroxy esomeprazole and the internal standard. The absolute recovery for esomeprazole and the sulphine metabolite at 25–2500 nmol/l was greater than 90% and for the hydroxy metabolite at 50–3000 nmol/l was 70%. The limit of quantification for esomeprazole and esomeprazole sulphine was 25 nmol/l with coefficient of variation (CV) less than 20% and for 5-hydroxy esomeprazole 50 nmol/l (CV < 20%). The plasma samples were analysed for the compounds at AstraZeneca R and D Mölnidal.

Pharmacokinetic and statistical analyses

Pharmacokinetic parameters of esomeprazole and its main metabolites, esomeprazole sulphine and 5-hydroxy esomeprazole, were estimated using non-compartment analysis with WinNonlin computer software. The total AUC was calculated according to the log-linear trapezoidal method and extrapolated to infinity using the last determined plasma concentration and λ, which is the elimination rate constant determined using log-linear regression analysis of the terminal slope of at least three last plasma concentration–time data. The terminal plasma elimination half-life (t½) was calculated as:

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\ln 2 / \lambda
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The absolute bioavailability (F) of esomeprazole following the oral doses was calculated as:

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F = \frac{AUC_{po, Day 1}}{AUC_{iv, 1 dose}} \cdot \frac{Dose_{po, 1 dose}}{Dose_{po, Day 1}}
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