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Review article: esomeprazole — enhanced bio-availability, specificity for the proton pump and inhibition of acid secretion

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SUMMARY

Esomeprazole, the *S*-isomer of omeprazole, is the first proton pump inhibitor available for clinical use as a single isomer. It demonstrates pharmacological and clinical benefits beyond those seen with the racemic omeprazole.

Esomeprazole has higher and more consistent bio-availability than omeprazole, which results in a greater area under the plasma concentration–time curve. It is the area under the plasma concentration–time curve of omeprazole and esomeprazole that determines how much of each reaches the parietal cell, and thus the control of gastric acid secretion that is achieved. Esomeprazole, like other proton pump inhibitors, has a high specificity for the acidic environment of the parietal cell, where it is accumulated, activated and covalently inhibits the proton pump. Proton pumps elsewhere in the body do not achieve the level of acidity needed for accumulation and activation.

Esomeprazole, 40 mg once daily, provides more effective control of gastric acid secretion than omeprazole, 20 or 40 mg once daily, and all other proton pump inhibitors given at their standard doses. This translates into greater clinical effect compared with omeprazole, 20 mg once daily, and lansoprazole, 30 mg once daily, in the management of reflux disease. Esomeprazole therapy is well tolerated, with a low adverse events profile, similar to that seen with omeprazole.

INTRODUCTION

The development of omeprazole, the first proton pump inhibitor, marked a major step forward in the management of acid-related diseases. Earlier therapies that reduced acid secretion, such as anticholinergics, prostaglandin analogues and H_2-receptor antagonists, acted via receptors on the basolateral membrane of the parietal cell. Thus, H_2-receptor antagonists blocked histamine-driven acid secretion, but their action was compromised (at least in part) by the presence of alternative pathways for stimulation.[1, 2] Furthermore, inter-individual variability in response to therapy with H_2-receptor antagonists, the phenomenon of acid rebound and the development of tolerance were major drawbacks to the use of these drugs.[3–6] H_2-receptor antagonists were also relatively ineffective in the treatment of reflux oesophagitis.[7, 8]

In contrast, omeprazole acted in a direct way on the gastric H^+,K^+-ATPase (otherwise known as the proton pump) in the acid secretory canaliculus of the gastric parietal cell. This enzyme is the final common step of acid secretion, on which all stimulatory pathways converge.[9] As a result of this direct action, omeprazole provided more reliable control of gastric acid secretion than the H_2-receptor antagonists,[10, 11] and thus faster symptom resolution and more predictable healing in gastro-oesophageal reflux disease and peptic ulcer

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disease.[12] Omeprazole was followed by other proton pump inhibitors, namely lansoprazole, pantoprazole and rabeprazole, all with an identical general structure, consisting of a substituted pyridylmethylsulphinyl benzimidazole.

Although omeprazole provided more effective control of acid secretion than previous therapies, it was not equally effective in all patients. A study to investigate failed healing of severe oesophagitis by omeprazole in some patients showed that this was the result of inter-patient variability in responsiveness to therapy.[13] There was therefore a need to find a therapy that provided even more effective control of acid secretion than that obtained with omeprazole, and which reduced the variation in acid inhibition between patients. After screening several hundred compounds, AstraZeneca found only four that progressed beyond pre-clinical studies and were tested in humans, and only one that exceeded omeprazole: its *S*-isomer, esomeprazole.[14] This was a surprise, as it had been confirmed in 1990 that both isomers of omeprazole had the same inhibitory effect on the proton pump in an *in vitro* gastric gland model.[15] However, at that stage, it had not been possible to prepare the single isomers in sufficient quantity for *in vivo* testing, and there appeared to be a slow racemization of the isolated isomers in aqueous solution.[15] When both of the isomers could be produced in sufficient quantity to be studied in humans, it became apparent that the *S*-isomer was approximately four times more potent than the *R*-isomer after oral administration.[16]

ESOMEPRAZOLE HAS A HIGHER BIO-AVAILABILITY THAN OMEPRAZOLE

The superior clinical efficacy of esomeprazole, compared with omeprazole and the *R*-isomer, is the result of a higher systemic bio-availability. Studies in human liver microsomes have shown that there is a significant stereoselectivity in the metabolism of the optical isomers of omeprazole to the main metabolites, omeprazole sulphone, 5-hydroxy- and 5-*O*-desmethyl omeprazole, which are all inactive.[17] The metabolism of the two isomers is mediated primarily by the two hepatic cytochrome P450 isoforms, CYP2C19 and CYP3A4, but the ratios in which they are metabolized by the two enzymes differ. Esomeprazole is metabolized to a greater extent than the *R*-isomer by CYP3A4 and, to a lesser extent, by CYP2C19. The intrinsic clearance of esomeprazole (the *S*-isomer) is approximately three times lower than that of the *R*-form. This is mainly explained by the considerably lower intrinsic clearance of esomeprazole through CYP2C19 to the 5-hydroxy metabolite, compared with the *R*-isomer (Figure 1). The first-pass metabolism of esomeprazole is therefore decreased compared with that of the *R*-isomer and omeprazole, and the total metabolic clearance of esomeprazole is lower than that of the *R*-isomer, resulting in higher plasma levels.

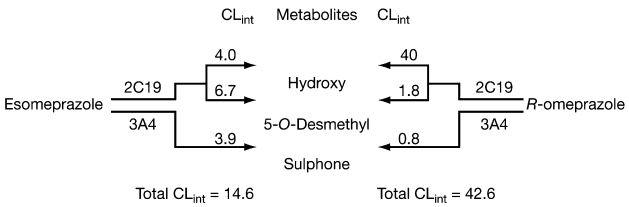

Figure 1. Metabolic scheme illustrating the intrinsic clearance values (CL_{int}) for the different metabolic pathways of esomeprazole and *R*-omeprazole from *in vitro* experiments on human liver microsomes. Values of CL_{int} are expressed as μL/mL per milligram of protein. (From Andersson *et al.*[16] with permission.)

This advantageous metabolism of esomeprazole results in a greater area under the plasma concentration–time curve (*AUC*) than that obtained for omeprazole or the *R*-isomer at the same oral dose.[18–20] Thus, in an early pharmacokinetic cross-over study of 15-mg doses of esomeprazole, the *R*-isomer and omeprazole in healthy volunteers, the mean *AUC* for esomeprazole was four times that of the *R*-isomer and almost twice that of omeprazole on day 7.[18] Similarly, esomeprazole, 20 mg once daily for 5 days, resulted in an *AUC* approximately 70% higher than that obtained with omeprazole at the same dose.[19] In patients with gastro-oesophageal reflux disease, the *AUC* value for esomeprazole, 40 mg once daily, was five times that of omeprazole, 20 mg once daily, after 5 days of treatment, and a comparison of 20-mg doses of the two drugs showed an 80% higher *AUC* with esomeprazole on day 5.[20] In addition, the variability between patients in *AUC* (as demonstrated by the standard deviation of the log *AUC* values) was less with esomeprazole 40 mg (0.47) than with esomeprazole 20 mg (0.64) or omeprazole 20 mg (0.73).[20] This greater consistency of the pharmacokinetics of esomeprazole, compared with omeprazole, was matched by a reduced inter-patient variability in the percentage of time for which the intragastric acidity exceeded pH 4.[20] Thus, the higher and more consistent bio-availability of

esomeprazole provides the rationale for its superior control of gastric acid secretion and improved clinical efficacy compared with omeprazole.

A SPECIFIC ACTION ON THE PROTON PUMP

Like omeprazole and the other proton pump inhibitors, esomeprazole is a pro-drug, which must be converted in the parietal cell to its active chemical form (for a review of the mechanism of action of omeprazole, and hence esomeprazole, see Lindberg *et al.*[21]). It is a lipophilic weak base, is inactive at neutral pH, circulates in the blood and can cross biological membranes. When acid is being secreted, the pH value within the secretory canaliculi of the gastric parietal cells is pH 1. As esomeprazole has a pK_a value of about four, it passes freely into the canaliculus and, because of the high acidity, becomes protonated. In the protonated form, it is membrane-impermeable and thus starts to accumulate as a consequence of the proton gradient between the parietal cell cytoplasm (pH 7.3) and the canaliculus (pH 1). This results in a concentration of esomeprazole in the canaliculus that theoretically could be 1000-fold greater than its level in the blood and other tissues. At pH 1, esomeprazole is rapidly converted to the sulphenamide, which is the active inhibitor of the H^+,K^+-ATPase (the proton pump). Inhibition of the proton pump is achieved through binding of the reactive sulphur atom on the sulphenamide to the thiol groups of cysteine amino acids on the luminal surface of the enzyme, forming an inactive covalent complex.[9]

The specificity of the inhibition has been confirmed experimentally using ^{14}C-radiolabelled omeprazole in the mouse.[22] One minute after intravenous administration of omeprazole, 15 μmol/kg, radiolabel was detected primarily in the stomach, liver, lungs and kidneys; after 5 min, it was located mainly in the stomach and liver; after 16 h, the radiolabel was confined to the gastric wall. Closer examination at this stage showed that virtually all of the radiolabel was located in the parietal cells, where it was confined to the tubulo-vesicles and secretory vesicles, the site of the proton pump. Biochemical analyses further identified the catalytic subunit of the proton pump as the protein that binds the drug.[23]

Although the plasma half-life of proton pump inhibitors in humans is fairly short (about 60 min for omeprazole), their duration of action is much longer, and some antisecretory effect is still present 24–72 h after a dose.[24] Their specific mechanism of action leads to unique pharmacodynamics: as the proton pump inhibitor binds covalently to the proton pump, the total delivery of the drug to the active pump is more important than the concentration of the drug at a specific time point (the peak concentration).[24, 25] It is the *AUC* value of omeprazole and esomeprazole that determines how much of each proton pump inhibitor reaches the parietal cell, and is therefore a major factor in determining the control of gastric acid secretion achieved.[16, 24] Once within the parietal cell, the two enantiomers of omeprazole are equipotent inhibitors of the proton pump. However, the advantageous metabolism of esomeprazole, which results in higher *AUC* values than for omeprazole at the same dose, translates into superior control of gastric acid secretion.

SUPERIOR ACID CONTROL COMPARED WITH ALL OTHER PROTON PUMP INHIBITORS

The inhibition of pentagastrin-stimulated acid secretion by esomeprazole in healthy volunteers after 1 and 5 days of therapy has been shown to be dose-dependent, with an increased effect on repeated dosing.[19] Furthermore, the antisecretory effect can be correlated with the *AUC* value (Figure 2). The inhibition of pentagastrin-stimulated acid secretion with esomeprazole, 20 mg once daily, was 31% greater than that with omeprazole, 20 mg once daily, on the first day of therapy, and remained 13% higher after 5 days.

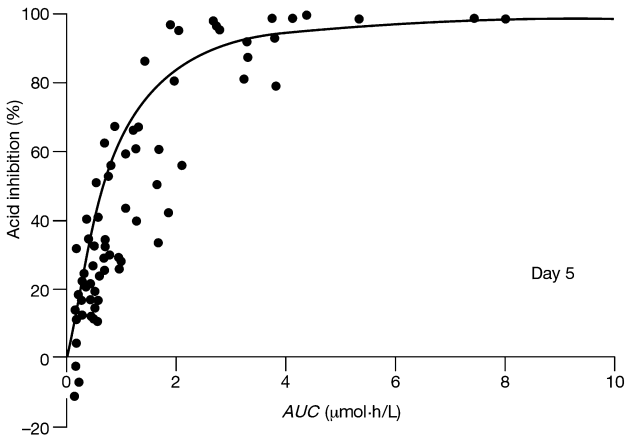

Figure 2. Percentage acid inhibition with esomeprazole is correlated with the area under the plasma concentration–time curve (*AUC*). The graph shows day 5 data, and the line represents the predicted acid inhibition (from Andersson *et al.*[19]). [Reprinted with permission from Blackwell Science (Aliment Pharmacol Ther 2001; 15: 1563–9).]

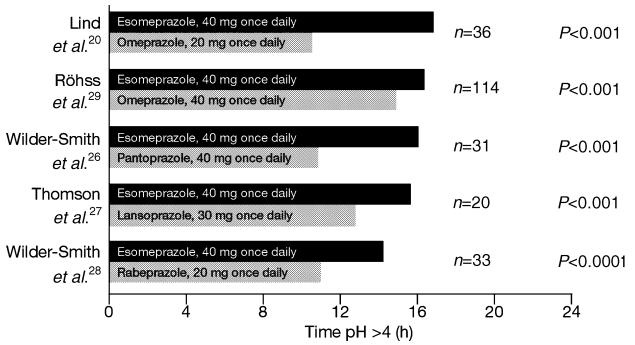

Figure 3. Esomeprazole, 40 mg once daily, controlled the intragastric pH > 4 for longer than omeprazole, 20 or 40 mg once daily, lansoprazole, 30 mg once daily, pantoprazole, 40 mg once daily, and rabeprazole, 20 mg once daily. The graphs show day 5 data.[20, 26–29]

In addition, a number of studies in healthy volunteers and patients with gastro-oesophageal reflux disease have compared the efficacy of esomeprazole and the other proton pump inhibitors in maintaining an intragastric pH > 4 (this value being chosen because it is the critical threshold of acid control for the effective management of gastro-oesophageal reflux disease).[10] Esomeprazole, 40 mg once daily, maintained an intragastric pH > 4 for significantly longer during the subsequent 24-h period than did standard doses of lansoprazole, pantoprazole and rabeprazole, and these differences became apparent from the first day of dosing (Figure 3).[26–28] Furthermore, esomeprazole, 40 mg once daily, was superior to both omeprazole, 20 mg once daily,[20] and omeprazole, 40 mg once daily (double the standard dose),[29] in this regard, and esomeprazole, 20 mg once daily, was superior to omeprazole, 20 mg once daily.[20] This provides further evidence that the higher *AUC* achieved with esomeprazole, compared with the same dose of omeprazole, results in improved inhibition of the proton pump.

On the basis of this evidence, the different proton pump inhibitors do not, as has been suggested by Kromer *et al.*, 'display similar dose–response relationships with similar potencies and efficacies on a milligram basis.'[30] The superior acid control achieved with the chosen standard dose of esomeprazole, 40 mg once daily, compared with omeprazole, 20 mg once daily, and lansoprazole, 30 mg once daily, has been shown to translate into greater clinical efficacy in patients with gastro-oesophageal reflux disease. Thus, erosive oesophagitis was healed at week 8 in significantly more patients who were treated with esomeprazole, 40 mg once daily, compared with those treated with omeprazole, 20 mg once daily.[31, 32] Indeed, in one study, the healing rate achieved at 4 weeks with esomeprazole (81.7%) was close to that achieved at 8 weeks with omeprazole (84.2%). After 8 weeks of esomeprazole therapy, 93.7% of patients were healed ($P < 0.001$ vs. omeprazole).[32] Moreover, esomeprazole, 40 mg once daily, provided the sustained resolution of heartburn more rapidly and in significantly more patients than did omeprazole, 20 mg once daily.[31, 32]

Similarly, esomeprazole, 40 mg once daily, was significantly more effective than lansoprazole, 30 mg once daily, in the healing of reflux oesophagitis at 4 and 8 weeks, and sustained resolution of heartburn occurred faster and in more patients treated with esomeprazole.[33] Esomeprazole, 20 mg once daily, has also been shown to be highly effective when given as maintenance therapy for healed oesophagitis,[34, 35] and is significantly superior to lansoprazole, 15 mg once daily, in maintaining remission across all pre-treatment grades of oesophagitis.[36]

SELECTIVITY OF ESOMEPRAZOLE

The clinical efficacy of esomeprazole reflects its advantageous metabolism compared with omeprazole, which results in improved delivery to the parietal cell. Like all proton pump inhibitors, esomeprazole has a high specificity for the acidic canalicular space of the parietal cell, where it inhibits the gastric H^+,K^+-ATPase. Although similar (but not identical) H^+,K^+-ATPases exist in the colon and kidney, the acidity in these regions does not reach the level necessary for proton pump inhibitor accumulation and transformation to the active sulphenamide. *In vivo* experiments in acid-loaded rats with induced levels of renal H^+,K^+-ATPase therefore failed to show any effect of high intravenous doses of omeprazole on the urinary excretion of potassium or hydrogen ions.[37]

There has, however, been some speculation that proton pump inhibitors may interfere with lysosomal function by reacting with vacuolar H^+-ATPases (V-ATPases). These enzymes are found in a number of locations in the body, including lysosomes, endosomes, chromaffin granules and the acidic hemivacuole of osteoclasts, and generate pH values of 4.5–6.5.[38] Indeed, Kromer *et al.* have suggested that omeprazole carries a greater potential risk than pantoprazole of

causing adverse events due to effects in moderately acidic compartments in the body.[30, 39, 40] They claim that the ratio of the serum elimination half-life to the chemical activation half-life at 'a critical pH of about 5' is important in determining the exposure of moderately acidic tissues to the activated proton pump inhibitor. No explanation is provided as to why pH $\approx$ 5 is critical, and the ratio is of questionable meaning. As explained earlier, it has been shown for omeprazole and esomeprazole that the *AUC* value is the key factor in determining how much proton pump inhibitor reaches any potential target tissue, and the degree of acidity within that tissue will determine the extent of any accumulation of the proton pump inhibitor. Many of the arguments presented by Kromer *et al.* in support of their hypothesis are flawed, and are addressed in the following paragraphs, using available data on omeprazole as representative of the proton pump inhibitor class.

The pK_a values of the proton pump inhibitors restrict accumulation of the compounds to acid spaces, such as the parietal cell. The pK_a values of esomeprazole, omeprazole, pantoprazole and lansoprazole are similar, p$K_a \approx 4$, thus allowing all of these agents to accumulate about 1000-fold in the parietal cell at pH 1.[41] Once within the parietal cell, the rate of onset of inhibition of the proton pump will be affected by the rate of activation of the proton pump inhibitor. At the pH of the lysosome, pH $\approx$ 5, no accumulation of the protonated form of esomeprazole can occur. Even rabeprazole, which is most prone to accumulate (due to its higher pK_a value of $\approx$5), will show little accumulation at all but the most acidic lysosomal pH values. Moreover, any molecules that are activated to the sulphenamide at neutral pH (a process that occurs some 600-fold more slowly than in the stomach, and 600 000-fold more slowly if one includes an accumulation factor of 1000) will be scavenged by thiols, such as cysteine and glutathione, resulting in the formation of the sulphide of the proton pump inhibitor. In the case of omeprazole, the majority of the sulphide formed is then converted back to omeprazole in the liver. Glutathione is found in high concentrations in eukaryotic cells (2–10 mmol/L),[42] and in the blood (about 1 mmol/L),[43] and plays a vital role in maintaining a reduced environment in the body.

The *in vitro* experiments conducted by Kromer *et al.*, which purport to show that omeprazole displays a greater liability than pantoprazole to inhibit renal Na^+,K^+-ATPase, lysosomal acidification and the production of reactive oxygen species by neutrophils, have a number of flaws.[40] These relate to the use of non-physiological conditions and proton pump inhibitor concentrations of up to 100 μM, which are approximately 1000-fold higher than that in plasma. The peak plasma concentration of omeprazole is reported to be 2.5 μM (range, 1–5 μM) after a 40-mg dose,[44] and more than 95% is protein bound.[25] Thus, 0.1 μM is the maximum free concentration of omeprazole in the blood and, probably, in the lysosome. Furthermore, the use by Kromer *et al.* of a freeze-dried preparation of the gastric H^+,K^+-ATPase is likely to have destroyed the integrity of the canalicular membrane, making both sides of the protein equally accessible.[40] Most of the inhibition observed in this situation is likely to be due to a reaction between the activated form of the proton pump inhibitor and free sulphydryl groups on the larger, cytosolic face of the protein. This is irrelevant to the situation *in vivo*, where the enzyme is sited in the cell membrane and low-molecular-weight thiols, such as glutathione, in the cell would protect the cytosolic face. Indeed, early experiments with omeprazole showed a similar, non-specific action between omeprazole and the gastric H^+,K^+-ATPase under non-physiological conditions.[45] However, when physiological conditions were mimicked *in vitro*, a specific reaction occurred purely on the extracellular side of the membrane.

The inhibition of lysosomal acidification by omeprazole, cited by Kromer *et al.*,[40] was also observed under non-physiological conditions, in which the cytosolic face of the lysosomal V-ATPase was exposed to proton pump inhibitor in the absence of protective thiols.[46] Others have similarly reported an inhibitory effect of omeprazole at high concentrations (> 100 μM) on, for example, lysosomal V-ATPase in kidney- and bone-derived membrane vesicles.[47] However, in all of these cases, this inhibitory effect could be abolished by exogenous glutathione (which cannot pass through membranes), indicating that omeprazole was interacting with cytosolic rather than luminal SH-groups on the V-ATPase. Unlike the gastric proton pump, the lysosomal enzyme (which belongs to a structurally dissimilar family of enzymes) does not seem to have critical SH-groups at sites facing the acid space, and lysosomal acidification is therefore unlikely to be inhibited *in vivo*. When given in doses that inhibited gastric acid secretion in rats, omeprazole had no observable effect on hepatic lysosomal integrity, lysosomal enzyme activity or biliary lysosomal enzyme secretion.[48]

These data all serve to highlight the hazards involved in attempting to transfer *in vitro* findings to the *in vivo* situation and, in particular, in not taking the normal physiological conditions into account. The greater 'potential risk' of omeprazole therapy relative to pantoprazole, suggested by Kromer *et al.*, based on non-physiological *in vitro* experiments, is of questionable relevance in a clinical setting, where the safety record of these proton pump inhibitors speaks for itself.

OMEPRAZOLE AND ESOMEPRAZOLE HAVE A VERY GOOD SAFETY PROFILE

An accumulated total of more than 600 million patient treatments with omeprazole (as of 1 January 2002) have provided no cause for concern about safety (AstraZeneca, data on file). In accordance with this, esomeprazole, after 36 million patient treatments (by September 2002) so far, has a very similar safety profile to omeprazole. Documentation of the long-term safety of esomeprazole comes from two 6-month maintenance studies in reflux oesophagitis and a 12-month open-label study with esomeprazole, 40 mg once daily.[34, 35, 49] As might be expected, these showed that the adverse event profile for esomeprazole is low, similar to that of omeprazole.

Extensive clinical experience has shown omeprazole to have a good safety profile and to be well tolerated.[50–52] Indeed, the good long-term tolerability of omeprazole has been documented in patients with gastro-oesophageal reflux disease taking maintenance therapy for up to 11 years,[53] and in patients with Zollinger–Ellison syndrome who have been treated for up to 9 years with high doses of omeprazole, receiving up to 480 mg daily at times.[54, 55] Furthermore, a 5-year follow-up of a study comparing the benefits of anti-reflux surgery with omeprazole therapy found no significant difference between the two groups with regard to serum electrolytes, blood and liver status and serum values of vitamin B_{12}.[56]

A comparison of the common adverse events reported during treatment with proton pump inhibitors in general practice in England showed that they were infrequent and that there were only small absolute differences in event rates between omeprazole, lansoprazole and pantoprazole.[57] The most common adverse events were diarrhoea, nausea/vomiting, abdominal pain and headache. Compared with omeprazole, pantoprazole was associated with significantly higher rates of myalgia and headache, and lansoprazole with significantly higher rates of diarrhoea (particularly amongst older patients), depression, headache, malaise, myalgia and nausea/vomiting.

Although the identification of uncommon or idiosyncratic adverse events requires follow-up in very large numbers of patients, product surveillance programmes have not identified any serious consequences related to the use of omeprazole.

CONCLUSIONS

Esomeprazole is the first single-isomer proton pump inhibitor. It has higher bio-availability than omeprazole, and provides more pronounced inhibition of acid secretion compared with all other clinically available proton pump inhibitors. This translates into clinical superiority, as has been explicitly documented for efficacy relative to omeprazole and lansoprazole, and for predictability of response relative to omeprazole.

Omeprazole has high specificity for the parietal cell, and accumulated experience with this proton pump inhibitor has provided no cause for concern regarding its safety. As expected, esomeprazole has so far shown a similar safety profile.

REFERENCES

1 Hannan A, Chesner I, Mann S, Walt R. Can H_2-antagonists alone completely block food-stimulated acidity? Eur J Gastroenterol Hepatol 1991; 3: 533–7.
2 Merki H, Wilder-Smith C, Walt R, Halter F. The cephalic and gastric phases of gastric acid secretion during H_2-antagonist treatment. Gastroenterology 1991; 101: 599–606.
3 Klinkenberg-Knol E, Jansen J, Lamers C, Nelis F, Snel P, Meuwissen S. Use of omeprazole in the management of reflux esophagitis resistant to H_2-receptor antagonists. Scand J Gastroenterol 1989; 24(Suppl. 166): 88–93.
4 Bardhan K. Omeprazole in the management of refractory duodenal ulcer. Scand J Gastroenterol 1989; 166: 63–73.
5 Nwokolo C, Smith J, Sawyerr A, Pounder R. Rebound intragastric hyperacidity after abrupt withdrawal of histamine H_2-receptor blockade. Gut 1991; 32: 1455–60.
6 Nwokolo C, Smith J, Gavey C, Sawyerr A, Pounder R. Tolerance during 29 days of conventional dosing with cimetidine, nizatidine, famotidine or ranitidine. Aliment Pharmacol Ther 1990; 4(Suppl. 1): 29–45.
7 Blum AL. Treatment of acid-related disorders with gastric acid inhibitors: the state of the art. Digestion 1990; 47(Suppl. 1): 3–10.
8 Sandmark S, Carlsson R, Fausa O, Lundell L. Omeprazole or ranitidine in the treatment of reflux oesophagitis. Results of a

double-blind, randomized Scandinavian multicenter study. Scand J Gastroenterol 1988; 23: 625–32.
9 Sachs G. Proton pump inhibitors and acid-related disease. Pharmacotherapy 1997; 17: 22–37.
10 Bell NJV, Burget D, Howden CW, Wilkinson J, Hunt RH. Appropriate acid suppression for the management of gastro-oesophageal reflux disease. Digestion 1992; 51(Suppl. 1): 59–67.
11 Howden C, Burget D, Hunt R. Appropriate acid suppression for optimal healing of duodenal ulcer and gastro-oesophageal reflux disease. Scand J Gastroenterol 1993; 29(Suppl. 201): 79–82.
12 Langtry H, Wilde M. Omeprazole. A review of its use in Helicobacter pylori infection, gastro-oesophageal reflux disease and peptic ulcers induced by non-steroidal anti-inflammatory drugs. Drugs 1998; 56: 447–86.
13 Holloway R, Dent J, Narielvala F, Mackinnon A. Relation between oesophageal acid exposure and healing of oesophagitis with omeprazole in patients with severe reflux oesophagitis. Gut 1996; 38: 649–54.
14 Carlsson E, Lindberg P, von Unge S. Two of a kind. Chem Br 2002; 38: 42–5.
15 Erlandsson P, Isaaksson R, Lorentzon P, Lindberg P. Resolution of the enantiomers of omeprazole and some of its analogues by liquid crystal chromatography on a tris-phenylcarbamoylcellulose-based stationary phase. The effect of the enantiomers of omeprazole on gastric glands. J Chromatogr 1990; 532: 305–19.
16 Andersson T, Hassan-Alin M, Hasselgren G, Rohss K, Weidolf L. Pharmacokinetic studies with esomeprazole, the (S)-isomer of omeprazole. Clin Pharmacokinet 2001; 40: 411–26.
17 Äbelö A, Andersson T, Antonsson M, Naudot A, Skånberg I, Weidolf L. Stereoselective metabolism of omeprazole by human cytochrome P450 enzymes. Drug Metab Dispos 2000; 28: 966–72.
18 Andersson T, Bredberg E, Sunzel M, Antonsson M, Weidolf L. Pharmacokinetics (PK) and effect on pentagastrin stimulated peak acid output (PAO) of omeprazole (O) and its 2 optical isomers, S-omeprazole/esomeprazole (E) and R-omeprazole (R-O). Gastroenterology 2000; 118: A1210(Abstract).
19 Andersson T, Röhss K, Bredberg E, Hassan-Alin M. Pharmacokinetics and pharmacodynamics of esomeprazole. Aliment Pharmacol Ther 2001; 15: 1563–9.
20 Lind T, Rydberg L, Kylebäck A, *et al.* Esomeprazole provides improved acid control vs omeprazole in patients with symptoms of gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2000; 14: 861–7.
21 Lindberg P, Brändstrom A, Wallmark B, *et al.* Omeprazole: the first proton pump inhibitor. Med Res Rev 1990; 10: 1–54.
22 Helander HF, Ramsay C-H, Regårdh C-G. Localization of omeprazole and metabolites in the mouse. Scand J Gastroenterol 1985; 20(Suppl. 108): 95–104.
23 Fryklund J, Gedda K, Wallmark B. Specific labelling of gastric H^+,K^+-ATPase by omeprazole. Biochem Pharmacol 1988; 37: 2543–9.
24 Lind T, Cederberg C, Ekenved G, Haglund U, Olbe L. Effect of omeprazole — a gastric proton pump inhibitor — on pentagastrin stimulated acid secretion in man. Gut 1983; 24: 270–6.
25 Regårdh C-G, Gabrielsson M, Hoffman K-L, Löfberg I, Skånberg I. Pharmacokinetics and metabolism of omeprazole in animals and man — an overview. Scand J Gastroenterol 1985; 20(Suppl. 108): 79–94.
26 Wilder-Smith C, Röhss K, Lundin C, Rydholm H. Esomeprazole (E) 40 mg provides more effective acid control than pantoprazole (P) 40 mg. Gastroenterology 2000; 118: A22–3.
27 Thomson A, Claar-Nilsson C, Hasselgren G, Niazi M, Röhss K, Nyman L. Esomeprazole 40 mg provides more effective acid control than lansoprazole 30 mg during single and repeated administration. Gut 2000; 47(Suppl. 3): A63 (Abstract).
28 Wilder-Smith C, Claar-Nilsson C, Hasselgren G, Röhss K. Esomeprazole 40 mg provides faster and more effective acid control than rabeprazole 20 mg in patients with symptoms of GORD. J Gastroenterol Hepatol 2002; 17(Suppl.): A612 (Abstract).
29 Röhss K, Hasselgren G, Hedenström H. Effect of esomeprazole 40 mg vs omeprazole 40 mg on 24-hour intragastric pH in patients with symptoms of gastroesophageal reflux disease. Dig Dis Sci 2002; 47: 954–8.
30 Kromer W, Horbach S, Luhmann R. Relative efficacies of gastric proton pump inhibitors: their clinical and pharmacological basis. Pharmacology 1999; 59: 57–77.
31 Kahrilas P, Falk G, Johnson D, *et al.* Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux esophagitis patients: a randomised controlled trial. Aliment Pharmacol Ther 2000; 14: 1249–58.
32 Richter J, Kahrilas J, Johanson J, *et al.* Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. Am J Gastroenterol 2001; 96: 656–65.
33 Castell D, Kahrilas P, Richter J, *et al.* Esomeprazole 40 mg compared with lansoprazole 30 mg on the treatment of erosive esophagitis. Am J Gastroenterol 2002; 97: 575–83.
34 Vakil N, Shaker R, Johnson D, *et al.* The new proton pump inhibitor esomeprazole is effective as a maintenance therapy in GERD patients with healed erosive esophagitis. A 6-month, randomized, double-blind, placebo-controlled study of efficacy and safety. Aliment Pharmacol Ther 2001; 15: 926–35.
35 Johnson D, Benjamin S, Vakil N, *et al.* Esomeprazole once daily for 6 months is effective therapy for maintaining healed erosive esophagitis and for controlling gastroesophageal reflux disease symptoms: a randomized, double-blind, placebo-controlled study of efficacy and safety. Am J Gastroenterol 2001; 96: 27–34.
36 Lauritsen K, Junghard O, Eklund S. Esomeprazole 20 mg compared with lansoprazole 15 mg for maintenance therapy in patients with healed reflux esophagitis. J Gastroenterol Hepatol 2002; 17(Suppl.): A1007 (and associated poster).
37 Nilsson A, Torvén A, Sohtell M. Lack of effect of omeprazole on kidney function in hypokalemic rats expressing increased mRNA levels for a renal H,K-ATPase. Gastroenterology 1995; 108(Suppl.): A179(Abstract).

38 Futai M, Oka T, Sun-Wada G-H, Moriyama Y, Kanazawa H, Wada Y. Luminal acidification of diverse organelles by V-ATPase in animal cells. J Exp Biol 2000; 203: 107–16.
39 Kromer W. Relative efficacies of gastric proton pump inhibitors on a milligram basis: desired and undesired SH reactions. Impact of chirality. Scand J Gastroenterol 2001; 234(Suppl.): 3–9.
40 Kromer W, Kruger U, Huber R, Hartmann M, Steinjans V. Differences in pH-dependent activation rates of substituted benzimidazoles and biological *in vitro* correlates. Pharmacology 1998; 56: 57–70.
41 Sachs G. Improving on PPI-based therapy of GORD. Eur J Gastroenterol Hepatol 2001; 13(Suppl. 1): S35–41.
42 Uhlig S, Wendel A. The physiological consequences of glutathione variations. Life Sci 1992; 51: 1083–94.
43 Rossi R, Milzani A, Dalle-Donne I, *et al.* Blood glutathione disulfide: in vivo factor or in vitro artifact? Clin Chem 2002; 48: 742–53.
44 Andersson T, Cederberg C, Heggelund A, Lindberg P. The pharmacokinetics of single and repeated once-daily doses of 10, 20 and 40 mg omeprazole as enteric-coated granules. Drug Invest 1991; 3: 45–52.
45 Keeling D, Fallowfield C, Underwood A. The specificity of omeprazole as an (H^++K^+)-ATPase inhibitor depends upon the means of its activation. Biochem Pharmacol 1987; 36: 339–44.
46 Simon W, Keeling D, Laing S, Fallowfield C, Taylor A. BY 1023/SK&F 96022: biochemistry of a novel (H^+ + K^+)-ATPase inhibitor. Biochem Pharmacol 1990; 39: 1799–806.
47 Mattsson J, Väänänen K, Wallmark B, Lorentzon P. Omeprazole and bafilomycin, two proton pump inhibitors: differentiation of their effects on gastric, kidney and bone H^+-translocating ATPases. Biochim Biophys Acta 1991; 1065: 261–8.
48 Grinpukel S, Sewell R, Yeomans N, Mihaly G, Smallwood R. Lack of effect of omeprazole, a potent inhibitor of gastric (H^+ + K^+) ATPase, on hepatic lysosomal integrity and enzyme activity. J Pharm Pharmacol 1986; 38: 158–60.
49 Maton P, Vakil B, Hwang C, Skammer W, Hamelin B, Lundborg P. The safety and efficacy of long-term esomeprazole therapy in patients with healed erosive esophagitis. Drug Saf 2001; 24: 625–35.
50 Creutzfeldt W. Risk–benefit assessment of omeprazole in the treatment of gastrointestinal disorders. Drug Saf 1994; 10: 66–82.
51 Joelson S, Joelson I-B, Lundborg P, Wala A, Wallander M-A. Safety experience from long-term treatment with omeprazole. Digestion 1992; 51(Suppl. 1): 93–101.
52 Sölvell L. The clinical safety of omeprazole. Digestion 1990; 47(Suppl. 1): 59–63.
53 Klinkenberg-Knol E, Nelis F, Dent J, *et al.* Long-term omeprazole treatment in resistant gastroesophageal reflux disease: efficacy, safety and influence on gastric mucosa. Gastroenterology 2000; 118: 661–9.
54 Lloyd-Davies K, Rutgersson K, Sölvell L. Omeprazole in the treatment of Zollinger–Ellison syndrome: a 4-year international study. Aliment Pharmacol Ther 1988; 2: 13–32.
55 Metz D, Strader D, Orbuch M, Koviack P, Feigenbaum K, Jensen R. Use of omeprazole in Zollinger–Ellison syndrome: a prospective 9-year study of efficacy and safety. Aliment Pharmacol Ther 1993; 7: 597–610.
56 Lundell L, Miettinen P, Myrvold H, *et al.* Continued (5 year) follow up of a randomized clinical study comparing antireflux surgery and omeprazole in gastroesophageal reflux disease. J Am Coll Surg 2001; 192: 172–81.
57 Martin R, Dunn N, Freemantle S, Shakir S. The rates of common adverse events reported during treatment with proton pump inhibitors used in general practice in England: cohort studies. Br J Clin Pharmacol 2000; 50: 366–72.