REVIEW ARTICLE

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Proton Pump Inhibitors

Pharmacology And Rationale For Use In Gastrointestinal Disorders

Paul Richardson, Christopher J. Hawkey and *William A. Stack*

Division of Gastroenterology, University Hospital, Queens Medical Centre, Nottingham, England

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Abstract

Proton pump inhibitors (PPIs) are drugs which irreversibly inhibit proton pump (H^+/K^+ ATPase) function and are the most potent gastric acid–suppressing agents in clinical use. There is now a substantial body of evidence showing improved efficacy of PPIs over the histamine H_2 receptor antagonists and other drugs in acid-related disorders.

Omeprazole 20 mg/day, lansoprazole 30 mg/day, pantoprazole 40 mg/day or rabeprazole 20 mg/day for 2 to 4 weeks are more effective than standard doses of H_2-receptor antagonists in healing duodenal and gastric ulcers. Patients with gastric ulcers should receive standard doses of PPIs as for duodenal ulcers but for a longer time period (4 to 8 weeks). There is no conclusive evidence to support the use of a particular PPI over another for either duodenal or gastric ulcer healing.

For *Helicobacter pylori*–positive duodenal ulceration, a combination of a PPI and 2 antibacterialswill eradicate *H. pylori* in over 90% of cases and significantly

reduce ulcer recurrence. Patients with *H. pylori*-positive gastric ulcers should be managed similarly. PPIs also have efficacy advantages over ranitidine and misoprostol and are better tolerated than misoprostol in patients taking nonsteroidal anti-inflammatory drugs (NSAIDs).

In endoscopically proven gastro-oesophageal reflux disease, standard daily doses of the PPIs are more effective than H_2-receptor antagonists for healing, and patients should receive a 4 to 8 week course of treatment. For severe reflux, with ulceration and/or stricture formation, a higher dose regimen (omeprazole 40mg, lansoprazole 60mg, pantoprazole 80mg or rabeprazole 40mg daily) appears to yield better healing rates. There is little evidence that PPIs lead to resolution of Barrett's oesophagus or a reduction of subsequent adenocarcinoma development, but PPIs are indicated in healing of any associated ulceration. In Zollinger-Ellison syndrome, PPIs have become the treatment of choice for the management of gastric acid hypersecretion.

Proton pump inhibitors (PPIs) have been one of the most important advances in the field of gastroenterology in the past 15 years. Many studies have now demonstrated their greater efficacy in acid-related conditions over other acid reducing drugs. Currently 3 PPIs, omeprazole, lansoprazole and pantoprazole are commercially available worldwide, with rabeprazole (which has been recently licensed in Japan) expected soon in other countries (fig. 1).

1. Pharmacology of the Proton Pump Inhibitors (PPIs)

1.1 Overview of Pharmacology of the H^+, K^+ ATPase Pump

The gastric acid pump (H^+/K^+ ATPase) is the primary target for a group of drugs known as the PPIs. This H^+/K^+ ATPase pump is the final common pathway for acid secretion in the stomach, and inhibitors of this pump are the most effective antisecretory in current use.[1] This enzymatic pump is present in the canalicular membrane of gastric parietal cells where it secretes HCl and H^+ is exchanged for K^+ with ATP breakdown,[1,2] and contains transmembrane alpha and beta sub-units of 1034 and 291 amino acids, respectively. The alpha sub-unit consists of 10 trans-membrane spanning segments and is responsible for the transport and catalytic functions of the pump. It is also present in an inactive form in the cytoplasm and has to be transported to the luminal cell membrane surface of the acid secreting cell for it to become active (fig. 2). PPIs have a pKa of approximately 4, and are concentrated up to 1000-fold on the luminal side of the secretory canaliculus[1,2] where they are activated in the acid environment (fig. 2).

1.2 Comparative Pharmacology of the PPIs

The PPIs are pyridyl methylsulfinyl benzamidazoles which bind to the H^+/K^+ ATPase pump.[1,2] After accumulating in the acid canaliculus, they become active by undergoing acid stimulated conversion to sulphenamides, which enables them to bind to exposed cysteine residues in the luminal alpha domain of the H^+/K^+ ATPase pump. The precise site of binding of individual drugs to the proton pump varies.[3] In their active form, PPIs are membrane impermeable and form disulfide covalent bonds with cysteine residues in the alpha subunit which inhibit the activity of the acid secreting pump.[2] The alpha sub-unit to which they bind contains a total of 28 cysteine residues and there are 9 in the beta sub-unit. In a recent study, using SDS gel separation of digested hog gastric vesicles incubated with PPIs under acid secreting conditions, Besancon et al.[3] have shown that 3 cysteine residues are accessible but that binding by different drugs varies. Thus omeprazole has been shown to bind to cysteine 813 in the fifth to sixth trans-membrane segment (and this correlates with acid inhibiting activity) and to cysteine 892 in the seventh to eighth transmembrane segment.

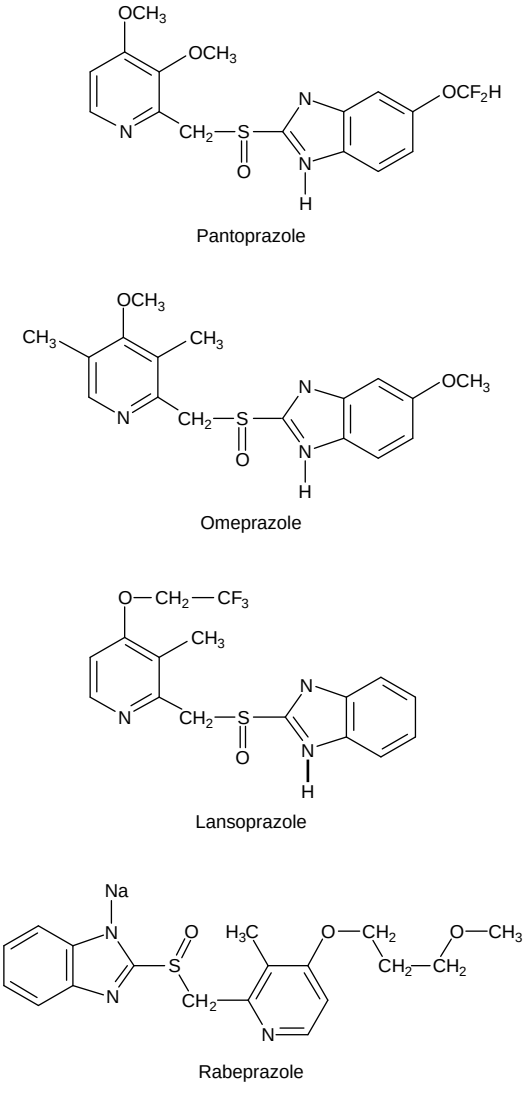

Fig. 1. Structural formulae of the proton pump inhibitors omeprazole, lansoprazole, pantoprazole and rabeprazole.

Lansoprazole was also bound to cysteine residues in these domains and, in addition, to cysteine 321 located towards the extracellular end of the third transmembrane segment. In contrast, pantoprazole only bound to one site (cysteine 813 or 822 in the fifth to sixth transmembrane region). Rabeprazole also bound to this site, which correlated with its ability to inhibit acid secretion, but also bound to cysteines 892 and 321.[3] Thus, all of the PPIs bind to a cysteine residue in the fifth and sixth transmembrane region (probably 813), but whether binding to other cysteine residues is pharmacologically important is at present uncertain.

Such differences between PPIs may contribute to differences in their onset of action. Lansoprazole has, in clinical studies, been shown to inhibit acid secretion more rapidly than omeprazole, albeit at a higher dose.[4] Dose differences may be a more likely explanation of this faster onset than greater lipid solubility (which has been suggested as an alternative explanation) because *in vitro* experiments using isolated vesicles showed no difference in time to activity onset (fig. 3). In these studies, onset of activity with pantoprazole was slower with the other drugs, compatible with its greater resistance to acid catalysed rearrangement to the sulphenamide form. Conversely, activation of rabeprazole was significantly faster, in line with its more unstable chemical structure. Rabeprazole has, like lansoprazole, been reported in clinical studies as

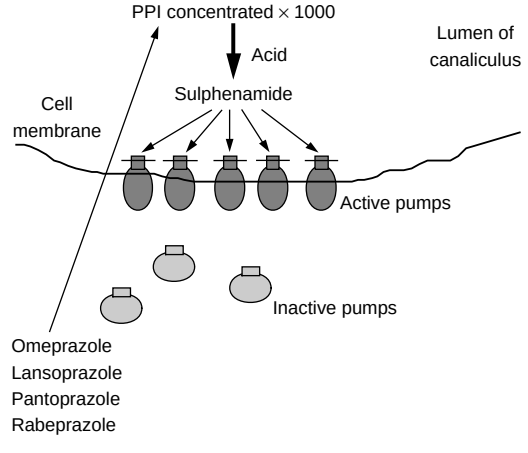

Fig. 2. Simplified schematic representation of the inhibition of the H^+/K^+ ATPase pump by proton pump inhibitors (PPIs). H^+/K^+ ATPase pumps are activated by a receptor-mediated mechanism and insert into the luminal membrane of the parietal acid secreting cell (not shown). PPIs are secreted into the canalicular lumen where they are concentrated and activated by conversion to sulphenamides in the acid environment. In this form they covalently bind to extra-cytoplasmic cysteine residues in the transmembrane alpha sub-unit of the proton pump and inhibit acid secretion into the canalicular lumen.

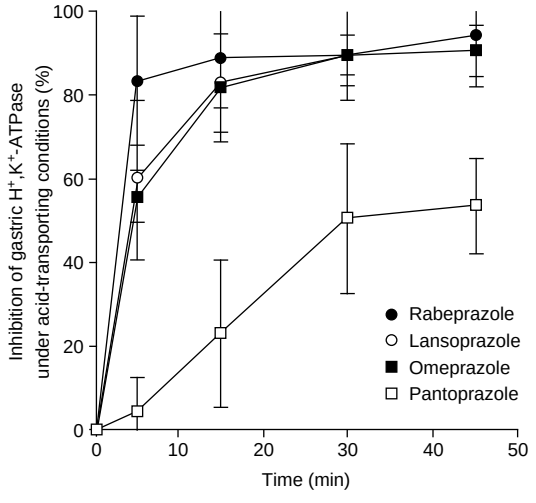

Fig. 3. The rate of inhibition of gastric H^+/K^+ ATPase under acid-transporting conditions by proton pump inhibitors. Isolated hog gastric vesicles were incubated in potassium chloride with valinomycin and activated by the addition of MgATP. Acidification of the gastric vesicles was measured by determination of the quenching of acridine orange. Rabeprazole produced inhibition faster than omeprazole and lansoprazole, which in turn produced inhibition faster than pantoprazole (from Besancon et al.,[3] with permission).

having a greater effect than omeprazole on day one of dosing, and in contrast to omeprazole, this has been shown at similar doses.[5] It is possible that this genuinely reflects its chemical instability, which leads to more rapid sulphenamide formation, since activation *in vitro* was also more rapid.

In line with the inherent instability of the parent molecule, rabeprazole was also less dependent than the other drugs on pH for conversion to the chemically active sulphenamide form. In theory, this could allow subsequent doses of rabeprazole to bind and inhibit the pump at a higher pH than the other drugs resulting in acid suppression that would occur earlier in the process of pump regeneration and lead to greater sustained acid suppression.

Because PPIs bind irreversibly to the pump, their duration of action is more affected by regeneration of new pumps than by the pharmacokinetic properties of the PPIs themselves. Although pump binding is covalent, it is still possible, in theory, for this to be at least partially reversed, as is the case for rabeprazole which has been shown *in vitro* to be reversed by cysteine.[6] A fully reversible PPI might have some appeal, for example, if the drug were ineffective for a few hours each day, allowing a burst of normal acidity which may in turn impact on the risk of enteric infections, the intragastric distribution of *Helicobacter pylori* and possible progression to gastric atrophy.

The precise basis of irreversibility may vary from one drug to another. For omeprazole, stereochemical constraints may prevent access of cysteine[3] while for lansoprazole its high lipid solubility may be a key factor.[4] Under less acid conditions (pH ≈3), pantoprazole is more stable than omeprazole or lansoprazole; this could improve its selectivity against parietal cell H^+/K^+ ATPase and reduce its effects in less acidic compartments such as lysosomes and chromaffin granules[7] and appears to have a confer a lower liability to interfere with biological targets.[8]

It should be stressed that the clinical significance of these observations are highly theoretical and have yet to be determined. In some instances, one advantage may counteract another. For example, if rabeprazole proved truly to be reversible in clinical use, it is likely that second doses would be given at a time when its ability to inhibit the pump at relatively high pH would not be relevant.

1.3 Pharmacokinetic Profiles

Plasma concentrations of PPIs can be measured by reverse-phase high performance liquid chromatography, although this technique is not used routinely in clinical practice. PPIs are rapidly absorbed after oral administration with peak concentrations occurring 2 to 4 hours after administration of enteric coated preparations. The pharmacokinetic profile of each of the PPIs is dependent to a large extent on the dose of drug used and the route of administration and has been reviewed individually recently.[4,5,8,9] For purposes of comparison, selected studies showing their pharmacokinetic profile at usually prescribed oral doses are shown in table I. All are rapidly absorbed with peak plasma concentrations of approximately 0.5 to 2 mg/L

Table I. Summary of pharmacokinetic profiles in selected studies using the recommended dose of proton pump inhibitor

Drug	No. volunteers	Dosage (mg/day)	C_{max} (mg/L)	AUC (mg/L • h)	$t_{1/2}$ (h)
Omeprazole[10]		20	0.66[a] (Estimated)		< 1
Lansoprazole[11]	12	30	1.15	2.98	1.6
Pantoprazole[12]	12	40 x 7d	2.1		1.9
Rabeprazole[13]	25	20	0.406	0.809	1.02

a value derived from graph and converted to mg/L for comparison.

AUC = area under the plasma concentration-time curve; C_{max} = peak plasma drug concentrations; $t_{1/2}$ = elimination half-life.

occurring at 2 to 4 hours. They are subject to relatively low rates of hepatic first pass extraction, with oral bioavailabilities in the range of 50 to 80%. Despite their short half-lives, because of their irreversible mechanism (which may be arguably somewhat different for rabeprazole) the pharmacokinetics have little bearing on their antisecretory action. They are also highly protein bound, thus giving a relatively low volume of distribution.

1.4 Effects of PPIs on Gastric Acid Secretion

Control of gastric acid secretion has been extensively studied *in vivo* in animals and humans. Dose-dependent inhibition of gastric acid secretion by PPIs has been demonstrated in healthy volunteers where pentagastrin-stimulated acid output was reduced by 42, 80 and 92% with omeprazole 30, 60 and 90 mg/day, respectively.[14] Basal and stimulated acid output inhibition with omeprazole approaches 100% after 7 days of therapy with 30 mg/day or 60 mg/day, with a 66% reduction in basal acid output (BAO) 6 to 8 hours post dose.[15] Similar efficacy has been reported for lansoprazole,[16,17] pantoprazole[18] and rabeprazole.[19,20]

There are also comparative data on the efficacy of the individual PPIs in the control of gastric acid secretion. Des Varannes et al.[21] compared lansoprazole 30 mg/day to omeprazole 20 mg/day and found that at these doses, lansoprazole was better in terms of total time spent above pH 3 during 24 hour pH monitoring. A small open study of 12 individuals comparing lansoprazole 30 mg/day and pantoprazole 40 mg/day demonstrated that lansoprazole was superior to pantoprazole at maintaining pH >4 during 24 hour pH monitoring; this was most marked on the first and seventh days of this crossover study.[22] In a study of patients with peptic ulcer disease (PUD) published in abstract form only, the time that the intragastric pH was above 3 on monitoring during treatment with rabeprazole 20 mg/day, omeprazole 20 mg/day and famotidine 40 mg/day was 99, 84 and 65% respectively, with the effect of rabeprazole lasting 2 days compared with 4 days for omeprazole.[23]

1.5 Effects on Gastrin Production

Early studies in rats with omeprazole or high dose histamine H_2 receptor antagonists produced hypergastrinaemia which was associated with gastric enterochromaffin-like cell (ECL) hyperplasia, which in some cases led to development of ECL dysplasia and even carcinoids.[9] However, with more than ten years use, although omeprazole increases serum gastrin levels to approximately 1.5 times that of normal, no clinically significant increased endocrine or parietal cell density has been found.[9,24] It is now recognised that this is a species-specific phenomenon, which is also seen with other PPIs and high doses of H_2-antagonists and appears to be a consequence of profound acid suppression.[25,26]

Lansoprazole also increases serum gastrin levels in human volunteers[17,27] which returned to baseline levels after withdrawal of the drug. In comparative studies, similar increases in gastrin by ≈40% were found after 2 to 4 weeks of pantoprazole and omeprazole 20mg daily,[28] although in a recent study, rabeprazole 20 mg/day produced greater gastrin levels than omeprazole 20 mg/day.[29] Overall, studies have not demonstrated substantial differences in serum gastrin levels among the different PPIs, and gastrin levels return to normal 1 week after stopping the drugs.

By inhibiting acid secretion and raising intragastric pH, PPIs interrupt the normal regulatory feedback effect of acidity on gastrin release. Recent studies have raised the possibility that this further accelerates the progression of gastric atrophy in the body of the stomach associated with *H. pylori* infection in this region.[30,31] These changes were associated with hyperplasia of ECL cells,[30] which in the earlier rodent studies had been a prelude to carcinoid tumour development.[32-35] However, these studies[30,31] are controversial and have been criticised on a number of grounds, including the use of nonstandardised histological endpoints and a control group that was not comparable with the patients receiving omeprazole. Furthermore, these results have not been supported by a recent prospective Swedish study.[36] In this study, patients with reflux oesophagitis were randomised to receive either omeprazole or anti-reflux surgery: the development of atrophic gastritis in *H. pylori*-positive patients with over 1000 days follow-up was no different in the omeprazole compared to surgery groups.[36] The Food and Drug Administration of the US judged that currently available evidence did not require any changes to the indications or labelling of these drugs.

Gastrin receptors have been demonstrated on both gastric[37] and colonic carcinomas,[38] though there is currently no evidence directly linking PPI-induced acid suppression with colonic neoplasia.

1.6 Drug Interactions

PPIs are metabolised by the polymorphic cytochrome P450 (CYP) system, in particular the S-mephenytoin hydroxylase (CYP2C19) and nifedipine hydroxylase (CYP3A4).[39] About 3% of Caucasians will be slow metabolisers due to polymorphic gene variations. Pantoprazole, in contrast to omeprazole and lansoprazole, is also metabolised by a cytosolic sulphotransferase which is a conjugating enzyme and appears to interact less with drugs that are in competition for the same P450 enzyme systems.[39] This may explain why pantoprazole may possible have a lower potential for drug interactions than other members of the group.

Despite a theoretical risk of serious drug interactions, these have not been supported by in clinical studies with drugs such as warfarin,[40] diazepam[41] or phenytoin.[42,43]

Studies in rabeprazole have demonstrated a modest increase in digoxin trough concentrations (≈20%) and drug concentration monitoring when these drugs are used concomitantly is therefore recommended.[44] No interactions have been noted between rabeprazole and phenytoin, warfarin or theophylline,[45,46] although reduction in absorption of the antifungal agent ketoconazole when coadministered with rabeprazole has been reported.[47] Therefore, current data would suggest a theoretical advantage of pantoprazole over the other PPIs for drug interactions but whether this is important in clinical practice remains to be seen.

2. Therapeutic Indications

2.1 Duodenal Ulcer

Eradication of *H. pylori* and prophylaxis against gastroduodenal toxicity of nonsteroidal anti-inflammatory drugs (NSAIDs) in high risk patients are central to modern management of duodenal ulcers. However, most studies to date that have evaluated ulcer healing by PPIs have generally been in patients not taking NSAIDs and have not addressed the role of *H. pylori* eradication in ulcer disease.

2.1.1 Duodenal Ulcer Healing – Placebo Controlled and Dose Ranging Studies

Omeprazole

Omeprazole is superior to placebo in healing duodenal ulcers (41 *vs* 13% at 2 weeks and 75 *vs* 27% at 4 weeks)[48] with better symptom relief. This healing effect is dose-related up to 20mg per/day as omeprazole 20 mg daily healed significantly more duodenal ulcers than 10mg daily (74 *vs* 48% at 2 weeks and 91 *vs* 75% at 4 weeks).[49] In another study, omeprazole 30 mg/day was not significantly better than 20 mg/day with healing rates at 4 weeks of 97 *vs* 93%, respectively.[50] In a large multicentre study involving over 1000 patients[51] healing rates with omeprazole 20 and 40mg daily were 66%, 93%, and 97% *vs* 72, 97 and 99.8% at 2, 4 and 8

weeks respectively. Although there was an overall statistically significant difference in favour of the 40mg dose, this was not thought to be generally clinically relevant. However, omeprazole 40 mg/day may be useful for the small proportion of patients in whom healing is not achieved with standard doses for a period of 8 weeks.

Lansoprazole

A dose finding study comparing lansoprazole 7.5, 15 and 30 mg/day produced cumulative healing rates of 48, 59 and 74%, respectively at 2 weeks and 75, 84 and 95% at 4 weeks.[52] Pain relief was similar in all groups as was the relapse rate at 6 months. In another dose finding study involving 296 patients comparing placebo with lansoprazole 15, 30, and 60 mg/day, respective healing rates at 4 weeks were 46, 89, 92, and 90%.[53] There were no significant difference between the different doses of lansoprazole which were all superior to placebo. In a Japanese study, treatment with lansoprazole 30 mg/day for a 4 week period gave duodenal ulcer healing rates of 97.1%[54] and in a review of a number of trials utilising a similar dose of lansoprazole, healing rates of 90 to 95% were achieved.[55] Therefore, 30mg/day appears to be the optimal duodenal ulcer healing dose for lansoprazole.

Pantoprazole

In a dose finding study of 219 patients, duodenal ulcer healing was faster with 40mg than 20mg (89 *vs* 58% at 2 weeks, 99 *vs* 93% at 4 weeks), with better symptom relief,[56] although no advantage for 80 mg/day was demonstrated. The time to symptom relief was shorter in the 40 and 80mg groups compared to the 20 mg/day group (6 *vs* 5 days, respectively).

Rabeprazole

In a study published in abstract form, rabeprazole 20 and 40 mg/day was more effective than placebo, with healing rates of 44 and 42% *vs* 21% at 2 weeks and 79 and 91% *vs* 39% at 4 weeks.[57] Both rabeprazole doses were significantly better than placebo but there was no difference between the rabeprazole doses.

2.1.2 Comparisons of PPIs and Histamine H_2 Receptor Antagonists

A number of well constructed randomised double-blind trials have consistently demonstrated improved duodenal ulcer healing with PPIs compared to standard doses of histamine H_2 receptor antagonists (table II). A recent meta-analysis of 16 randomised trials including 3504 patients gave a therapeutic gain (the average difference in favour of omeprazole) of 15.2 percentage points [confidence intervals (CI) 8.1 to 13.7] in favour of omeprazole at 2 weeks, and 10.9 (CI 8.1 to 13.7) points at 4 weeks with faster symptom relief than the H_2 antagonists.[76]

In comparison with cimetidine, analysis of 6 studies including 1363 patients gave therapeutic gains for omeprazole of 20.6 (CI 15.4 to 25.8) at 2 weeks and 12.3 (CI 8.1 to 16.5) percentage points at 4 weeks. Another meta-analysis has shown that lansoprazole 30 mg/day resulted in healing rates of 85% for duodenal ulcers at 4 weeks, a 10% therapeutic advantage over standard doses of ranitidine or famotidine, again with better symptom relief at 2 weeks.[77] More recent studies comparing pantoprazole 40 mg/day to ranitidine 300 mg/day gave respective healing rates of 61 to 81% *vs* 35 to 53% at 2 weeks and 92 to 97% *vs* 81 to 85% at 4 weeks. These studies demonstrated significantly better healing rates and resolution of symptoms in favour of pantoprazole.[72-74]

Rabeprazole 20 mg/day was compared to ranitidine 150mg twice daily in an American multicentre study involving 376 patients with endoscopically demonstrated duodenal ulceration.[78] Rabeprazole was significantly better than ranitidine at 2 and 4 weeks, with healing rates of 40 *vs* 26% and 83 *vs* 73%, respectively.

The above data indicate that all of the currently available PPIs at standard doses demonstrate superior efficacy over H_2-antagonists with regard to overall healing rates and time to healing of duodenal ulcers.

2.1.3 Comparisons Between Individual PPIs

There are fewer studies comparing individual PPIs for duodenal ulceration and as 4- and 8-week

Table II. Duodenal ulcer healing: double-blind comparisons of proton pump inhibitors and histamine H_2 receptor antagonists

Reference	Additional study design	No. of patients	Dosage regimens (mg/day)	% patients healed (weeks)			Comments
				2	4	6	
Lauritsen et al.[58]	rc	132	O 30 C 1g	73* 46	92* 74		Pain relief at 1 wk O > C
Barbara et al.[59]	rc,mc	121	O 20 R 150 bid	66* 53	97* 84	100* 92	At 4 and 6/52 p < 0.05
Archambault et al.[60]	rc	169	O 20 C 600 bid	58 46	84 80	88 89	Pain relief O > C p = 0.056 at 2wk
McFarland et al.[61]	pg,mc	248	O 20 R 300	79* 62	91* 80		Pain relief at 2/52 O = 77%, R = 59%, p = 0.005
Popovic et al.[62]	rc,mc	139	O 20 F 20 bid	68* 43	95* 76		Similar number of adverse effects reported
Hui et al.[63]	rc	270	O 10 O 20 R 150 bid	77 86 63	95 96 93		Healing rates lower in smokers Relapse rates at 1year O = R
Crowe et al.[64]	pg	98	O 20 C 800	62* 33	85* 61		p < 0.001 2 wks p < 0.001 4 wks
Valenzuela et al.[65]	rc,mc	309	O 20 R 150 bid	42 34	82* 63		Omeprazole more effective especially in ulcers >1cm
Kager et al.[66]	mc	143	O 30 R 400 bid	70* 55			Relapse rates not significantly different at 6/12; O = 39%, R = 47%
Marks et al.[67]	rc,mc	206	O 20 R 300 evening dose	80* 52	95* 85		By 2 wks O > R for symptomatic relief. At 4 wks no difference in symptoms
Delle Fave et al.[68]	rc,mc	241	O 20 F 40	62* 33	92* 80	99* 92	Per protocol analysis
Zaterka et al.[69]	rc,mc	241	O 20 R 300	67* 40	93* 82		Non smoking, small ulcers and O treatment predicted healing
Londong et al.[54]	rc,mc	314	L 7.5 L 15 L 30 R 300	48 59 74 51	75 84 95 89		L 30 significantly better than L 7.5 (p = 0.001). Similar pain relief and relapse rates at 6 months
Hawkey et al.[70]	rc,mc	289	L 30 L 60 R 300	78 80 60	93 97 81		Both L doses gave significantly improved healing and symptom relief. No difference between L30 and L60
Lanza et al.[71]	rc,mc	289	L 15 L 30 R 300 Placebo		92 80 70 47		R *vs* placebo (p < 0.05) L 30 *vs* placebo (p < 0.05) L 15 *vs* placebo and R, (p < 0.05) Greater symptom relief for L
Judmaier et al.[72]	rc,mc	202	P 40 R 300	81* 53	97* 83		Pantoprazole provided quicker symptomatic relief
Van Rensberg et al.[73]	rc,mc	199	P 40 R 300	61* 35	97* 81		No significant difference in pain relief at 2/52
Schepp et al.[74]	rc,mc	266	P 40 R 300	68* 44	96* 85		Pain relief significantly better in P group at 2/52 (p < 0.01)
Nakazawa et al.[75]	rc,mc	240	Rab 20 F 40	58* 34	92* 77	96* 89	Rab showed significantly greater efficacy than F at all time points

bid = twice daily; **C** = cimetidine; **F** = famotidine; **L** = lansoprazole; **mc** = multicentre; **O** = omeprazole; **P** = pantoprazole; **pg** = parallel group; **R** = ranitidine; **Rab** = rabeprazole; **rc** = randomised controlled; *p < 0.05.

healing rates are high with individual PPIs, it is not surprising that significant differences between PPIs are difficult to demonstrate (table III). For the newer PPIs (especially pantoprazole and rabeprazole), it has been necessary to demonstrate at least equal efficacy rather than superiority over omeprazole and lansoprazole in clinical trials.

In a study of 279 patients with duodenal ulcer, there were no significant differences in healing at 2 or 4 weeks for lansoprazole 30 mg/day (86 and 97%) compared to omeprazole 20 mg/day (82 and 96%), with similar symptom relief for both treatments.[79] Indirect evidence from non-comparative studies in a recent meta-analysis suggests that at standard doses there is little difference in efficacy with respect to healing rates or symptomatic relief between lansoprazole 30 mg/day and omeprazole 20 mg/day.[77]

A randomised double-blind trial comparing pantoprazole 40 mg/day to omeprazole 20 mg/day in endoscopically proven duodenal ulceration has shown healing rates of 71 *vs* 74% at 2 weeks and 96 *vs* 91% at 4 weeks, respectively; these differences were not significantly different.[82] Another study using the same dosing regimen also failed to detect a significant difference between treatment groups.[81] A further study of 96 duodenal ulcer patients demonstrated 2 and 4 week healing rates for pantoprazole 40 mg/day and omeprazole 20 mg/day of 72 and 97% *vs* 62% and 91%, respectively. In addition, no differences in adverse events were observed between the groups.[80]

A recent small European study comparing rabeprazole 20 mg/day and omeprazole 20 mg/day in active duodenal ulceration recorded similar healing rates at 2 and 4 weeks, 69 *vs* 61% and 98 *vs* 93%, respectively.[29]

2.1.4 Maintenance Therapy

On cessation of treatment, relapse rates of 50 to 80%/year for PUD have been reported.[83] *H. pylori* infection is now generally accepted as the principal factor for peptic ulcer relapse and eradication of the organism greatly reduces relapse rates.

In a study of 128 patients with duodenal ulceration who were randomised to receive either omeprazole or placebo after ulcer healing,[84] a substantial increase in disease free maintenance for omeprazole 20mg/day over placebo was reported, with highly significant remission rates of 94 *vs* 9% at 1 year. In this study, the role of *H. pylori* eradication maintaining remission was not addressed. Studies investigating varying dosing regimens of omeprazole in daily, alternate day or weekend therapy only strategies, have demonstrated daily dosing regimens were the most effective.[9] Additionally, a daily dose of 10 mg/day was marginally better than 3 days of 20 mg/day for maintenance therapy.[85] Two further studies with omeprazole 20mg daily as opposed to weekend or alternate day therapy have demonstrated superior efficacy of daily administration.[86,87]

Table III. Duodenal ulcer healing: double-blind, randomised controlled trials of individual comparisons between proton pump inhibitors

Reference	No. of patients	Dosage (mg/day)	% patients healed (weeks)		Comments
			2	4	
Ekstrom et al.[79]	279	L 30	86	97	L = O in efficacy and symptom relief
		O 20	82	96	
Bianchi Porro et al.[80]	96	P 40	72	97	Efficacy, symptomatic relief and adverse effects equivalent
		O 20	62	91	
Becker et al.[81]	270	P 40	71	96	No difference in healing and symptomatic relief
		O 20	65	89	
Rehner et al.[82]a	276	P 40	71	96	No significant difference on healing rates or symptom relief
		O 20	74	91	
Beker et al.[29]	205	Rab 20		99	Rab associated with greater relief of pain
		O 20		96	

a Multicentre trial.

L = lansoprazole; **O** = omeprazole; **P** = pantoprazole; **Rab** = rabeprazole.

A study of 71 patients with gastric and duodenal ulcers demonstrated less frequent relapses in patients treated with lansoprazole 15 mg/day compared to those treated with 30 mg/day at weekends only; compliance was also better in 15mg/day group.[88] In a more recent study, 12 month ulcer relapse rates were 17% for lansoprazole 15mg daily and 61% for placebo regardless of *H. pylori* status.[89] The role of PPIs for maintenance treatment in duodenal ulcer disease will need to be re-evaluated in future studies which take the role of *H. pylori* into account.

2.2 Gastric Ulcer Healing

2.2.1 Placebo Controlled and Dose Ranging Studies

Omeprazole

In a study of 26 patients with gastric ulcers > 5mm diameter, omeprazole 30 mg/day resulted in healing rates of 27, 69, and 92% of ulcers at 2, 4 and 6 weeks, respectively.[90] For the conventionally prescribed dose of omeprazole, gastric ulcer healing rates in 34 Filipino patients at 2, 4, 6 and 8 weeks for 22 patients given omeprazole 20 mg/day were 50, 70, 85, and 95%, respectively, and for the other 12 patients given omeprazole 40 mg/day they were 50, 75, 92 and 92%, respectively, where no difference in efficacy or symptomatic relief for the 2 dosing regimens was noted.[91] In a large multicentre double-blind American study of 520 patients using similar dosing regimens, in comparison to placebo significantly improved healing rates for both omeprazole 20 and 40 mg/day were seen at 4 and 8 weeks. At 8 weeks the healing rates for the 40 mg/day regimen were significantly greater than the 20 mg/day regimen (82.7 *vs* 74.8%), and in particular were better at healing large (>1cm) ulcers.[92]

Lansoprazole

A multicentre double-blind study involving 268 patients with gastric ulcers showed lansoprazole 15 and 30 mg/day to be superior to placebo at 4 weeks (65 and 58% *vs* 37%) and 8 weeks (92 and 97% *vs* 77%), respectively.[93] A multicentre study involving 118 patients with gastric ulcers using lansoprazole 30 and 60 mg/day yielded respective healing rates at 4 weeks of 63 *vs* 66% and at 8 weeks 83 *vs* 81%, but there was no significant difference between the 2 dosing groups.[94]

Rabeprazole

At doses of 20 and 40 mg/day, rabeprazole has been compared to placebo in a 6 week study in 94 patients.[95] Respective healing rates were 32, 32 and 29% at 3 weeks and 90, 86 and 39% at 6 weeks, both rabeprazole doses being of similar efficacy and significantly better than placebo.

2.2.2 Comparisons of PPIs with Histamine H_2 Receptor Antagonists and Other Treatment Modalities for Gastric Ulcer Healing

A number of studies have demonstrated improved healing rates of omeprazole over ranitidine,[96-98] famotidine 20mg twice daily,[99] and cimetidine.[100,101] In a meta-analysis of 3 randomised trials totalling 374 patients, therapeutic gain for omeprazole over ranitidine at standard doses were 11.0 (CI 3.9 to 18.1) percentage points at 4 weeks and 5.9 (CI 1.2 to 10.6) percentage points at 8 weeks.[76] Omeprazole 40 mg/day was shown to be more effective than sucralfate 2g twice daily, with healing rates at 2, 4 and 6 weeks of 49 *vs* 23%, 83 *vs* 59%, and 90 *vs* 70 %, respectively, and omeprazole provided significantly better symptom relief.[102]

Lansoprazole at the recommended dose of 30 mg/day has been demonstrated to have significantly greater efficacy in gastric ulcer healing than ranitidine 150mg twice daily, with reported healing rates of 80 *vs* 62% at 4 weeks and 98 *vs* 86% at 8 weeks, respectively.[103] Smaller studies have shown greater efficacy of lansoprazole over famotidine 20mg twice daily[104] and cimetidine 400mg twice daily.[105]

In a multicentre trial[106] pantoprazole 40 mg/day was shown to be significantly superior to ranitidine in gastric ulcer healing; respective healing rates at 2, 4 and 8 weeks were 37, 87, and 97% in the pantoprazole group, compared to 19, 58 and 80% in the ranitidine treated group. In a Japanese study comparing gastric ulcer healing rates in 241 patients treated with rabeprazole 20mg/day or fam-

otidine 20mg twice daily, healing rates at 2, 4, 6 and 8 weeks were superior with rabeprazole (19.1 *vs* 6% at 2 weeks, 73 *vs* 30% at 4 weeks, 94 *vs* 65% at 6 weeks and 97 *vs* 78% at 8 weeks).[107]

Thus, as with duodenal ulcers, current data from clinical trials favour all PPIs over H_2 receptor antagonists for benign gastric ulcer healing. A summary of the results obtained in the trials mentioned in this section is outlined in table 4.

2.2.3 Comparisons Between Individual PPIs

In a study involving 126 patients comparing the efficacy of lansoprazole 30 mg/day and omeprazole 20 mg/day in gastric ulceration, cumulative healing rates assessed on an intent-to-treat basis were 82 *vs* 68% and 93 *vs* 82% at 4 and 8 weeks, respectively ($p = 0.04$), although on a per-protocol analysis healing rates were similar.[108] However, the time to symptom relief was shorter with lansoprazole (6.6 *vs* 11 days).

Omeprazole 20 mg/day was compared with pantoprazole 40 mg/day in 219 patients with benign gastric ulcer.[109] Per-protocol analysis suggested an advantage for pantoprazole at 4 weeks (88 *vs* 77%, $p < 0.05$) but not 8 weeks (97 *vs* 96%), although in the intention-to-treat analysis there was no statistically significant difference in healing rates at either time point. Four week symptom relief was 88% with omeprazole and 81% with pantoprazole (not statistically significant).[109]

Another 6 week study of 227 patients with active gastric ulceration compared healing rates between rabeprazole 20 mg/day and omeprazole 20 mg/day. On an intent-to-treat analysis, healing rates were 58 *vs* 61% at 3 weeks and 91 *vs* 91% at 6 weeks for rabeprazole and omeprazole, respectively, which were not significantly different at the 3 week time point.[110]

In summary, there is little if any difference between standard doses of the various PPIs for gastric ulcer healing, and what little differences there are appear to depend on the dose of drug used and the type of study analysis.

2.2.4 Refractory Ulceration

Refractory ulcers are classed as those that have failed to heal despite the use of H_2-antagonists or other treatment modalities at adequate doses for at

Table IV. Gastric ulcer healing: double-blind, randomised controlled comparisons of proton pump inhibitors and other treatment modalities. (doses of drugs are mg/day unless stated)

Reference	No. of patients	Dosage (mg/day)	% patients healed (weeks)				Comments
			2	4	6	8	
Lauritsen et al.[100]	176	O 30	54*	81		86	Quicker symptomatic relief for O *vs* C
		C 1g	39	73		78	during first week of treatment
Walan et al.[96]a	602	O 20		69*		89	O 20 v R (p = 0.01)
		O 40		80*		96	O 40 v R (p < 0.0005)
		R 300		59		85	O induced quicker healing
Bate et al.[101]	189	O 20		73*		84	Quicker symptomatic relief with O
		C 800		58		75	
Sorensen et al.[102]	104	O 40	49	83		90	Superior symptomatic relief with O
		Sucralfate 4g	23	59		70	Higher remission rate at 1 year for O
Michel et al.[103]a	158	L 30	80*		98*		No serious adverse events reported for L
		R 300	62		86		
Okai et al.[104]b	24	L 30		80		100	Healing to Sakita's S2 stage significantly
		F 40		40		73	greater for L (p < 0.05)
Hotz et al.[106]a	248	P 40	37*	87*		97*	Faster symptomatic relief with P
		R 300	19	58		80	
Nakazawa et al.[107]a	241	Rab 20	19*	73*	94*	97*	Rab > R at all time points
		F 40	6	30	65	78	

a Multicentre trial.

b Single centre trial.

C = cimetidine; **F** = famotidine; **L** = lansoprazole; **O** = omeprazole; **P** = pantoprazole; **R** = ranitidine; **Rab** = rabeprazole; * p < 0.05.

least 6 weeks. This definition accounts for between 5 to 10% of duodenal ulcers,[111] although this definition probably needs to be revised with the recognition of the importance of *H. pylori* in ulcer recurrence. There is now good evidence to demonstrate the efficacy of the PPIs in this setting and also to confirm their superiority over the H_2-antagonists.

A small Asian study employing omeprazole 40 mg/day in 27 patients with H_2-antagonist refractory PUD produced healing rates of 79% at 2 weeks and 100% at 4 week.[112] Improved efficacy of omeprazole over H_2-antagonists was also demonstrated in a European study of 107 patients who were randomised to receive either omeprazole 20 mg/day or to continue with a H_2-antagonist.[113] In this study, respective healing rates of 85 *vs* 34% at 4 weeks and 96 *vs* 57% at 8 weeks were reported (all highly significantly in favour of omeprazole) as was the time to symptomatic improvement.

In 22 patients with H_2 antagonist-refractory gastric ulcers, lansoprazole 30 mg/day provided greater healing rates than the prostaglandin analogue misoprostol, alone or with a H_2-antagonist, at 8 weeks (88 *vs* 60% respectively).[114] Pantoprazole is also effective in healing ulcers resistant to H_2-antagonists. Pantoprazole 40 to 80 mg/day for 2 to 8 weeks healed ulcers in 96.7% of ulcers unresponsive to ranitidine, and prevented ulcer recurrence in 88 out of 98 patients in up to 3 years of follow-up.[8,115]

2.3 *Helicobacter pylori*

H. pylori has been established in recent years to be the major aetiological factor associated with PUD.[116-118] There is also epidemiological evidence associating *H. pylori* with gastric carcinoma[119-121] and gastric mucosal-associated lymphoid tissue (MALT) lymphoma.[122] *H.pylori* is invariably associated with chronic active gastritis when present in the stomach.[123] Once *H.pylori* colonises the gastric mucosa it produces a profound inflammatory response mediated in part by chemotactic cytokines such as interleukin-8 (IL-8).[124] Patients with documented duodenal or gastric ulceration who are not taking NSAIDs should have *H. pylori* eradicated.[125]

No single agent to date has been identified which will successfully eradicate *H. pylori.* Current treatment regimens consist of the administration of at least 3 agents, two of which are antibacterials coprescribed with an antisecretory drug or a bismuth-containing compound. Eradication of *H. pylori* can be difficult because of the emergence of resistance to various antibacterials and problems with delivering bactericidal concentrations of antibacterials. Additionally, *H. pylori* can assume a resting coccoid form which does not make it amenable to antibacterial therapy.

PPIs have assumed a major role in recent years as part of triple therapy for *H. pylori* eradication, and PPI-based triple therapy is now regarded as the gold standard here.[126]

2.3.1 In vitro *Pharmacological Effects of PPIs on* H. pylori

As a group, the PPIs have demonstrated powerful anti-*H. pylori* properties *in vitro.*[127-131] The precise mechanism of action of PPIs in inhibiting *H. pylori* growth *in vitro* is still unclear, although it has been suggested that the anti–*H. pylori* properties of PPIs maybe due to inhibition of the urease enzyme,[132-134] perhaps as a result of the blockade of SH group of the *Helicobacter* ureas.[132] However this effect is not just due to inhibition of urease alone as both omeprazole and lansoprazole, in addition to their acid-activated derivative (AG-2000), inhibited both urease positive and their urease negative *H. pylori* derivatives[135] and omeprazole has been shown to inhibit growth *in vitro* of non-urease producing *H. pylori* mutants.[133] In a recent study, the anti-bacterial activity of omeprazole appeared to be dependent upon the growth conditions of the bacteria: omeprazole covalently bound to a large range of *H. pylori* proteins at a pH of 5.0 but when the pH was increased to 7, binding was enhanced 15-fold.[136]

2.3.2 In vivo *Effects of PPIs on* H. pylori

Early clinical studies with PPIs suggested that they might be sufficient to eradicate *H. pylori*.[137] However, with more rigorous definitions of eradi-

cation of *H. pylori* it became apparent that PPIs alone did not eradicate *H. pylori*, but only suppressed its activity.[138,139] The currently accepted definition for eradication of *H. pylori* is that tests for eradication, including urea breath test, biopsy and culture and urease tests, are negative at least 4 weeks after eradication therapy.[126]

Some studies have demonstrated that the distribution of *H. pylori* in the stomach appears to be altered after treatment with PPIs, in that it is found preferentially in the corpus compared with the antrum after treatment with omeprazole or lansoprazole,[140,141] although another recent study could not identify any change in distribution of *H. pylori* after antisecretory therapy.[142] The possible explanation for the 'migration' of *H. pylori* into the corpus post-treatment with PPIs has been suggested by Mayer-Rosenberg et al.,[143] who found that *H. pylori in vitro* can grow at a neutral pH. The corpus under normal circumstances is more acidic than the antrum. After PPI therapy, the pH of the corpus is raised to approximately 4.0, allowing growth of the organism in the corpus, whereas the pH of the antrum will be too high to facilitate growth of *H. pylori*.[143] Another anti–*H. pylori* effect of PPIs *in vivo* is that they enhance the bioactivity of a number of antibacterials, including amoxicillin and clarithromycin.

Additionally, omeprazole has recently been demonstrated to alter absorption of other antibacterials. In human volunteers, Goddard et al.[144] demonstrated that coadministration of omeprazole enhanced secretion of amoxicillin and clarithromycin without effecting the absorption of metronidazole.

2.3.3 Eradication of H. pylori *Using PPI-Based Drug Regimens*

Rates of eradication of *H. pylori* depend to a large extent on the method of assessment of a particular treatment with respect to timing, one or more tests and per protocol *vs* intention-to-treat analysis of clinical trials.[126] As a result, early studies may have overestimated eradication rates compared to recent ones. At present, an ideal single anti-*H. pylori* treatment does not exist. Current problems with the treatment of *H. pylori* relate to its resistance to various antibacterials and patient intolerance of the different drug regimens used.

Dual Therapy

In 1992, Bayerdorffer et al.[145] reported an eradication rate of 82% in patients given dual therapy with high dose omeprazole and amoxicillin making dual therapy briefly fashionable. However, subsequent studies using omeprazole- and lansoprazole-based regimens have reported erratic eradication rates for *H. pylori* ranging from 0 to 92%.[146] In a recent meta-analysis of 120 studies published from 1990 to 1995 reporting eradication rates following omeprazole and amoxicillin dual therapy, the overall eradication rate in 5725 patients treated was 61% (95% CI 58 to 61) on an intention-to-treat basis.

Dual therapy with lansoprazole and amoxicillin has also been investigated. Although some studies have shown a greater *in vitro* potency of lansoprazole against *H. pylori*, pooled data from dual therapy studies (lansoprazole with amoxicillin) have reported an eradication rate of 48%.[146]

PPIs have also been combined with clarithromycin and dual therapy with omeprazole and clarithromycin has yielded somewhat higher eradication rates of 58 to 83%.[147,148] In a recent study comparing different *H. pylori* eradication regimes with rabeprazole, dual therapy with rabeprazole and clarithromycin gave an eradication rate of 60%.[149] Currently available data on *H. pylori* eradication rates for dual therapy, regardless of the PPI or antibacterial used, would not support the use of dual therapy as a definitive treatment as eradication rates have been unacceptably low.[126]

PPI-Based Triple Therapy

Standard antisecretory-based triple therapy currently refers to the combination of a PPI with two of a combination of a nitroimidazole, clarithromycin, amoxicillin or tetracycline. Of particular interest are the one week PPI-based triple therapies, and this regimen is currently recommended in Europe.[126] A recent meta-analysis of 79 studies with PPI-based triple therapy (39% of which were randomised controlled trials) gave an overall eradication rate of 87% (95% CI 86 to 87) in a total of 5513 patients treated.[146]

The largest single one week PPI-based triple therapy study for the eradication of *H. pylori* in duodenal ulcer disease is the European MACH-1 study in which 787 duodenal ulcer patients were randomised to receive omeprazole (O) with two of three other drugs, amoxicillin (A), metronidazole (M) or clarithromycin (C). Highest eradication rates were 96% OAC (95% CI 93 to 100) and 95% OMC (95% CI 90 to 99), where omeprazole 20mg, amoxicillin 500mg, metronidazole 400mg or clarithromycin 250mg were given twice daily.[150] In this study, 96% of patients complied with medication and only 2.3% withdrew because of adverse events.

Lansoprazole (L)-based triple therapy regimens have also been studied. In a recent study of 496 patients, eradication rates of patients receiving LAC, LAM, LCM and OAM were reported to be 86, 66.4, 87.3 and 74.6%, respectively; LAC and LCM eradication rates were judged to be significantly different from the LAM scores but there was no significant difference between LAM and OAM.[151] Initial metronidazole sensitivity had an effect on efficacy of metronidazole-containing regimens but no effect on LAC.

Less information is available for pantoprazole in eradicating *H. pylori*, although *H. pylori* was eradicated in 95% of patients given one week of pantoprazole with amoxicillin and clarithromycin.[152] A recent study of rabeprazole (R)-based 1-week *H. pylori* eradication regimens in 78 patients gave eradication rates of (on intent-to-treat analysis) RCM 100%, RAC 95%, RAM 90% and RC 63%.[149] Although this rabeprazole study contained small patient numbers, rabeprazole might have theoretical advantages over the other PPIs for one-week *H. pylori* eradication regimens because of its slightly faster onset of action. Among the other PPIs, currently there is little evidence of differences in *H. pylori* eradication rates with different PPIs in 1- or 2-week triple therapy regimens,[153] where compliance with medications[146] and antibacterial resistance[154,155] are the most important factors in achieving high eradication rates.

Quadruple Therapy

In *H. pylori* quadruple therapy regimens, a PPI is added to standard bismuth based triple therapy (with metronidazole and amoxicillin or tetracycline). However, results with these regimens are variable and they are often reserved for patients who fail to have *H. pylori* eradicated using standard triple therapy. Seven day treatment with a PPI in combination with bismuth has been reported to eradicate *H. pylori* in >95% of patients regardless of metronidazole resistance.[156] However, in patients who had previously received unsuccessful *H. pylori* eradication therapy, 51% had *H. pylori* eradicated with quadruple therapy.[157] Additionally, studies have been performed using quadruple therapy over shorter periods of time (1 to 4) days where eradication rates of 72 to 91% have been reported.[156] With *H. pylori* eradication rates of over 90% currently being described using standard PPI-based triple therapy, the addition of bismuth as a first line treatment does not appear necessary. However future studies will clarify the role of quadruple therapy, especially in eradication failures using standard triple therapy regimens.

2.4 Prevention of Nonsteroidal Anti-Inflammatory Drug (NSAID)-Induced Ulceration

2.4.1 PPIs and NSAIDs

NSAIDs are estimated to cause approximately 30% of ulcers.[158] Their contribution to ulcer bleeding may even be greater than this, particularly if aspirin is taken into account. Prescribing of low dose aspirin is currently enhancing the number of bleeds associated with non-aspirin and aspirin NSAIDs. It can be calculated that non-aspirin NSAIDs account for approximately 1200 deaths per annum in the UK in this way. Although problems associated with NSAIDs can often be avoided by non-use, this is not a realistic option in many patients. Those who are at high risk require protective co-therapy. Recent studies have shown advantages for omeprazole over ranitidine and misoprostol in the management of such patients.[159-160]

2.4.2 Acute Studies

In human volunteers, omeprazole has been very effective in reducing acute gastric erosions or gastric micro bleeding provoked by aspirin.[161] This appears to reflect pH since H_2 receptor antagonists are capable of achieving reductions in acute gastric injury, but only at higher than normal concentrations.[162] Such observations led to assessment of omeprazole and high dose famotidine in patients continuing to take NSAIDs.[159,160,163] The demonstration that high dose famotidine (40mg twice daily) but not the normal 20mg twice daily dose reduces the development of both gastric and duodenal ulcers was essentially a surrogate for what could be achieved with PPIs.[163] Recently, the results of 4 large studies comparing omeprazole with placebo, misoprostol and ranitidine, involving over 2000 patients, have been reported.[159,160,164,165] A smaller open study on ulcer healing in NSAID users with lansoprazole has also recently been reported[166]

2.4.3 Healing of Ulcers and Erosions

In these studies, omeprazole 20mg healed gastric and duodenal ulcers faster than either misoprostol 200μg qid or ranitidine 150mg twice daily.[159,160] There appeared to be no advantage for omeprazole 40mg daily. Interestingly, misoprostol was more effective than omeprazole in healing multiple superficial erosions.[159] Omeprazole was more effective than ranitidine in this respect.[160] For lansoprazole, in 47 chronic NSAID users with endoscopic gastric or duodenal ulceration, most patients (45/47) reached scarring (defined as stage I healing) within 6 to 8 weeks, and 35% achieved good healing (defined as stage 2 healing) over this time.[166]

2.4.4 Prophylaxis

When used empirically (no initial endoscopy) over 3 months, omeprazole 20mg once daily reduced the development of peptic ulcer from 16 to 4.7% and dyspepsia from 20 to 8.2%, compared to placebo.[164] A similar result was seen if omeprazole was used as prophylactic treatment following healing of demonstrated ulcers. In this group of patients, 64% of those receiving omeprazole 20mg daily remained in remission over 6 months compared to 51% of those receiving misoprostol ($p = 0.0001$) and 33% of those receiving placebo ($p < 0.0001$).[159] In this study, omeprazole was also significantly better tolerated than misoprostol. Likewise, when compared with ranitidine 150mg twice daily, 74% of those receiving omeprazole remained in remission compared with 62% of those receiving ranitidine ($p = 0.004$).[160] Omeprazole was also effective in patients in whom initial endoscopy showed no ulcer and showed fewer than 10 erosions at any one site. In this study, 78% of patients remained in remission over 6 months compared to 53% on placebo ($p = 0.004$).[161]

2.4.5 Who Should Receive PPIs?

As most of the trials with PPIs in NSAID users have been performed with omeprazole, firm recommendations in NSAID users can only be made for this drug. These data suggest that omeprazole should be used as the first line of treatment for patients with established gastric or duodenal ulcers who are continuing to take NSAIDs. Misoprostol may be preferred for multiple erosions. Whether both drugs together would be better than either separately has not been studied. Omeprazole 20mg daily should be considered as prophylactic treatment for patients at high risk of NSAID ulcer complications. The main risk factors for NSAID ulceration are past history, old age, use of particular NSAIDs including azaproprazone and piroxicam, use of high dose NSAIDs and co-prescription of warfarin or corticosteroids.

2.4.6 Role of H. pylori Eradication in NSAID Users

The role of *H. pylori* eradication in NSAID users is currently a controversial area. One study in patients without a past history of either ulcer or exposure to NSAIDs has suggested a role for *H. pylori* eradication in protecting NSAID users.[167] Another has shown no benefit in long term users with a current or previous documented peptic ulcer or moderate to severe dyspepsia.[168] These studies suggest that once an ulcer has occurred, local mucosal factors may be the most important determinants of enhanced relapse rates in patients who have had a previous ulcer. Patients naturally unin-

fected with *H. pylori* and those who have undergone *H. pylori* eradication are less responsive to omeprazole than those with continuing infection, perhaps because of the known greater effect of omeprazole on intragastric pH in *H. pylori*-infected individuals.[159,160,168] Currently, there are no clear grounds for using *H. pylori* eradication as either an alternative or a supplement to omeprazole in NSAID users and for bleeding ulcers. Indeed, it has been recently shown in a Hong Kong study that omeprazole is superior to *H. pylori* eradication for prevention of ulcer bleeding in non-aspirin NSAID users.[169]

2.5 Reflux Oesophagitis

Reflux oesophagitis results from prolonged and repeated exposure of the oesophagus to gastric contents.[170] Oesophageal reflux is a problem that may respond to lifestyle changes, for example cessation of smoking, weight reduction and modification and timing of dietary intake. However, many cases will require drug treatment, with some form of acid-lowering medication, or prokinetic agent at some time. All of the available PPIs have been tested in clinical trials in patients with reflux oesophagitis, and omeprazole and lansoprazole are licensed for maintenance use for this condition in Europe.

2.5.1 Placebo Controlled and Dose Ranging Studies

In a dose ranging study little overall benefit for omeprazole 40 mg/day over 20 mg/day was demonstrated in a study of 313 patients treated for 4 weeks with 20mg daily and a second 4 weeks with either 20 or 40mg.[171] Accumulated healing rates at the end of the study period were 74 *vs* 65% for the 20/20mg and 20/40mg groups. Taking the second treatment period in isolation from the first treatment period, healing rates were 64 *vs* 45% ($p < 0.02$). However, this difference was not large enough to permit recommending routine use of this higher dose for healing.

In an open study of 38 patients with ulcerative reflux oesophagitis,[172] endoscopic healing rates of 76, 97, and 97% at 2, 4 and 8 weeks with lansoprazole 30 mg/day were recorded. In another study in 50 patients whose oesophagitis had not healed despite at least 12 weeks of H_2 antagonist treatment at recommended doses, no advantage of lansoprazole 60 mg/day over 30 mg/day with respect to healing rates and symptomatic relief was noted.[173]

Van Rensburg et al.[174] reported that pantoprazole 40 and 80 mg/day have similar efficacies in healing endoscopic reflux changes after 4 (78 *vs* 72%) and 8 weeks (95 *vs* 94%).

2.5.2 Comparisons of PPIs and Histamine H_2 Receptor Antagonists

As for PUD, there are substantial data from randomised controlled trials demonstrating superior efficacy for PPIs over histamine H_2 receptor antagonists in the treatment of reflux oesophagitis. Omeprazole, in doses varying from 20 to 60 mg/day, has been shown to be more efficacious for both endoscopic healing and symptom relief[175-179] compared to standard doses of H_2-antagonists. In a meta-analysis of 5 studies including 935 patients, the healing rate was 23.2 percentage points higher with omeprazole 20 mg/day compared to ranitidine 300 mg/day at 4 weeks, and 28.6 points higher at 8 weeks.[76]

Similar studies have been published for lansoprazole[180-182] and pantoprazole.[183] The results of these studies are shown in detail in table V. Rabeprazole 20 mg/day has been compared to ranitidine 150mg qid in 338 patients with modest to severe oesophagitis and was found to be significantly better in both healing (58 *vs* 36% at 4 weeks and 88 *vs* 65% at 8 weeks) and symptomatic improvement (75 *vs* 58% at 4 weeks and 79 *vs* 68% at 8 weeks).[184]

2.5.3 Comparisons of PPIs and Cisapride

Omeprazole has also recently been compared in different treatment regimens with cisapride (a prokinetic agent) for healing and maintenance treatment of reflux oesophagitis. In a study of 225 patients with Savory-Gillard grade I or II oesophagitis, patients were randomised to receive either omeprazole 20 mg/day alone or with cisapride 10mg 3 times daily for 8 weeks, and when healed to receive placebo or cisapride for a further 12 months.[187] There was a tendency for greater heal-

Table V. Gastro-oesophageal reflux disease healing rates: double-blind, randomised controlled trials comparing proton pump inhibitors to histamine H_2 receptor antagonists

Reference	No. of patients	Dosage (mg/day)	% patients healed (weeks)				Comments
			2	4	6	8	
Bate et al.[177]	270	O 20		56*		71*	O superior both endoscopically and histologically
		C 1600		26		35	
Vantrappen et al.[176]	61	O 40		85*		96*	Significantly faster and more profound symptom relief with O
		R 300		40		52	
Zeitoun et al.[185]a	157	O 20		81*		95*	
		R 300		45		65	
Sandmark et al.[186]a	152	O 20		67*		85*	Better symptom relief with O
		R 300		31		50	
Feldman et al.[180]a	202	L 30	71*	80*	88*	89*	p<0.001 at all time points. Greater symptomatic relief with L
		R 300	21	33	45	38	
Bardhan et al.[181]a	229	L 30		84*		92*	L 30 and L 60 significantly superior to R with respect to healing and symptom relief
		L 60		72*		91*	
		R 300		39		53	
Koop et al.[183]a	249	P 40		69		82*	Symptoms more effectively and faster controlled with P
		R 300		57		67	
Humphries et al.[184]a	338	Rab 20		58*		88*	Heartburn resolved more completely in the Rab treated group
		R 600		36*		65*	

C = cimetidine; **L** = lansoprazole; **O** = omeprazole; **P** = pantoprazole; **R** = ranitidine; **Rab** = rabeprazole; ***** $p < 0.05$.

ing in the more severe cases with combined therapy compared to omeprazole alone and cisapride was better than placebo for maintenance. In a 5 way comparison of omeprazole (O), cisapride (C), ranitidine (R), O+C and R+C for maintenance therapy over 12 months after healing with omeprazole 40mg for 4 to 8 weeks, remission rates were O+C = 89%, O = 80% and C = 54% ($p < 0.005$ for C versus O+C).[188] In a more recent study comparing omeprazole to cisapride for relief of reflux symptoms in 424 patients, maintenance therapy with both 10mg and 20mg daily provided better relief than cisapride 10mg 4 times daily.[189] Comparative studies with the other PPIs and prokinetic agents are awaited.

2.5.4 Comparisons Between PPIs in the Healing of Reflux Oesophagitis

Published studies comparing healing rates of omeprazole 20 mg/day and lansoprazole 15 to 30 mg/day showed that lansoprazole 30 mg/day and omeprazole 20 mg/day were significantly better than lansoprazole 15 mg/day, and although there was no statistically significant differences in healing rates between omeprazole 20mg and lansoprazole 30mg, there was a small trend in favour of lansoprazole to quicker symptomatic relief (table VI).[190,191] No significant difference between lansoprazole 30 mg/day and omeprazole 40 mg/day with respect to healing rates and symptomatic relief was demonstrated in a multicentre study involving a total of 211 patients.[193] This would suggest that the trend towards better symptom relief with lansoprazole 30mg compared to omeprazole 20mg daily may be dose-dependent. In addition, in a recent study in volunteers, lansoprazole 30 mg/day blocked acid secretion to a greater extent than the 15mg dose or omeprazole 20mg daily.[197]

In a double-blind randomised trial of pantoprazole 40mg daily and omeprazole 20mg daily, healing rates at 4 and 8 weeks of treatment were 74 *vs* 78% and 90 *vs* 94%, respectively, in 286 patients,[194] where differences in healing rates and symptomatic relief were not statistically significant. Another study gave healing rates at 4 and 8 weeks for omeprazole 20 mg/day and pantoprazole 40 mg/day of 79 *vs* 78.6% and 91.4 *vs* 94.2%, respectively.[195]

A European multicentre study comparing rabeprazole 20 mg/day and omeprazole 20 mg/day in 202 patients with moderate to severe oesophagitis

at endoscopy has recently been reported.[196] On an intent-to-treat analysis, healing rates were similar, 81 *vs* 81% at 4 weeks and 92 *vs* 94% at 8 weeks, and both groups also gave equivalent symptomatic relief. Therefore, comparative studies performed thus far have not demonstrated substantial differences between the different PPIs when individual dosing regimens have been taken into account.

2.5.5 Maintenance Therapy

This is the largest and most competitive market for overall PPI use as reflux oesophagitis is a condition with a high relapse rate without maintenance therapy. PPIs have been compared to placebo, to other treatment modalities and to other PPIs for maintenance therapy. Omeprazole at both 10 mg/day and 20 mg/day has been demonstrated to reduce relapse rates compared to placebo[197] and ranitidine.[198,199] A study of 193 patients showed an endoscopic remission at 12 months of 50 and 74% for omeprazole 10 and 20 mg/day, respectively, with only 14% for placebo.[200] It can be concluded from this study that the higher omeprazole dose should be reserved for those patients in which the lower dose proves ineffective.

Superiority over H_2 antagonists for maintenance therapy has also been demonstrated. Ninety eight patients who still experienced erosive or ulcerative oesophagitis, despite receiving at least 3 months treatment with cimetidine ≥1200 mg/day or ranitidine ≥300 mg/day, were randomised in a double-blind study to receive omeprazole 40 mg/day or ranitidine 300mg twice daily. Complete endoscopic healing rates at 4 and 12 weeks were 63 *vs* 17% and 90 *vs* 47% for omeprazole and ranitidine, respectively.[201]

For the prevention of relapse of reflux oesophagitis, omeprazole has also been demonstrated to be superior to ranitidine where over a 12-month period 67% of patients treated with omeprazole 20 mg/day remained in clinical and endoscopic remission compared with only 10% of patients treated with ranitidine 150mg twice daily ($p = 0.0001$).[202] Even at the 10mg dose omeprazole is superior to ranitidine in the long term treatment of reflux oesophagitis, as evidenced by a study of 392 patients with healed reflux oesophagitis who were randomised to receive omeprazole 20 or 10 mg/day or ranitidine 150mg twice daily. Twelve month remission rates for each dosage were 72, 62 and 45%,

Table VI. Gastro-oesophageal reflux disease: double-blind, randomised, multicentre controlled trials featuring individual comparisons between proton pump inhibitors

Reference	No. of patients	Dosage (mg/day)	% of patients healed (weeks)				Comment
			2	4	6	8	
Petite et al.[191]	?	L 30		81		83	L *vs* O by 1 day to achieve pain relief
		O 20		74		77	
Castell et al.[190]	1284	L 30	65	83	89	90	All active treatment better than
		L 15	56	75	80	79	placebo $p < 0.05$
		O 20	60	82	90	91	L 30 > L 15, $p = <0.05$
		Placebo	23*	33*	37*	40*	O 20 = L 30 for healing rates L 30 gave quicker symptomatic relief
Mee et al.[192]	604	L 30		70		87	L > O in time to symptomatic relief
		O 20		63		82	($p = 0.05$) at 3 days
Mulder et al.[193]	211	L 30		88		96	No significant differences in healing
		O 40		81		93	rates or symptomatic relief
Mossner et al.[194]	286	P 40		74		90	P equally effective as O in symptom
		O 20		78		94	relief
Corinaldesi et al.[195]	208	P 40		79		94	
		O 20		79		91	
Thjodleifsson et al.[196]	202	Rab 20		81		92	Similar adverse events and symptom
		O 20		81		94	relief

L = lansoprazole; **O** = omeprazole; **P** = pantoprazole; **Rab** = rabeprazole; * $p < 0.05$.

respectively (both omeprazole doses were significantly better than ranitidine, $p < 0.001$ and $p < 0.005$, respectively.[203]

Different dosing regimens of omeprazole have also been studied for this indication; weekend-only regimens of omeprazole 20 mg/day, omeprazole 20 mg/day and ranitidine 150mg twice daily yielded 12-month remission rates of 32, 89 and 25%, respectively. Daily omeprazole was significantly better than the other 2 treatment regimens.[204]

Lansoprazole at 30 and 15 mg/day, compared with placebo, gave endoscopic remission rates at 1 year of 90, 79 and 24%, respectively, and symptomatic remission rates of 72, 67 and 35%, respectively. There was no statistically significant differences between either dose of lansoprazole with respect to maintaining healing or symptomatology,[205] and both doses were superior to placebo.

The similar efficacy of lansoprazole 15 and 30 mg/day in maintenance therapy was supported by another UK-based study which demonstrated better relapse prevention for both lansoprazole doses over ranitidine 600 mg/day (respective remission rates at 12 months being 69, 80 and 32%). Both lansoprazole treatment arms were significantly superior to ranitidine but there was no significant difference between the 2 lansoprazole regimens.[206]

2.5.6 Reflux Symptoms Without Oesophagitis at Endoscopy

A proportion of patients with clinical histories suggestive of gastro-oesophageal reflux disease will have a normal endoscopy and recent placebo-controlled studies have addressed this problem. In a well designed study, improvement in symptom scores, reduction in antacid use and improved quality of life scores in patients with a clinical history of oesophageal reflux but normal endoscopy treated with omeprazole in comparison to placebo has been demonstrated.[207] These results supported previous data in patients with an endoscopically normal oesophagus, who also demonstrated significantly better responses with omeprazole 20 mg/day compared to placebo with respect to heartburn, acid regurgitation and symptoms.[208]

In a study by Lind et al.,[209] 509 patients with heartburn without endoscopic oesophagitis were randomised to receive omeprazole 20 or 10mg daily or placebo. At 4 weeks, the respective proportion of patients with complete absence of heartburn was 41% (95% CI 39-53), 31% (25 to 38%), and 13% (7 to 20%). In a more recent study of similar design, the proportion of symptom-free patients at 4 weeks was 41, 35 and 19% for omeprazole 20mg, 10 mg daily and placebo, respectively.[210] Superior efficacy for omeprazole 10mg daily over placebo has also been demonstrated in a primary care-based study of 495 patients without erosive oesophagitis whose symptoms were controlled and then randomised to receive omeprazole 20 or 10mg daily for 6 months.[211] Cumulative relapse rates were 27% for omeprazole and 52% for placebo ($p = 0.0001$).

For relief of symptoms of heartburn, omeprazole has also been compared to ranitidine in a primary care setting where 994 patients were randomised to receive either omeprazole 20 or 10mg daily or ranitidine 150mg twice daily. Symptom relief at 4 weeks were was 61, 49 and 40%, respectively, where both doses of omeprazole provided significantly symptom relief than ranitidine and 20mg of omeprazole was significantly better than 10mg daily.[212]

Indeed, omeprazole has also been evaluated in a double-blind study as a 'diagnostic tool' for reflux oesophagitis, where 160 patients were randomised to receive 1 week of omeprazole 20mg daily or placebo with their response correlated to endoscopic findings. This test was sensitive for omeprazole (71 to 81% *vs* 36 to 47% for placebo), but not specific (≈55% for omeprazole).[213]

2.5.7 Cost Effectiveness

Cost effectiveness studies have suggested that the gain in efficacy with omeprazole may outweigh the influence of this additional drug cost to make it more cost effective than ranitidine in the management of reflux oesophagitis.[214,215] Additionally, a starting dose of omeprazole 20 mg/day appears to be more cost effective than 40 mg/day.[216] Subsequent studies have supported these initial

observations, demonstrating cost effectiveness with respect to cost per patient healed, cost per patient rendered asymptomatic and cost in terms of improved quality of life assessments in comparison to H_2-antagonists alone or in combination with metoclopramide.[217-219] Finally, in a recent cost effectiveness analysis comparing PPIs with high dose and standard dose H_2 antagonists, PPIs were found to be most cost effective where patients were significantly bothered by symptoms and in institutional settings where the differences between drug cost were small.[220]

2.5.8 PPIs In Barrett's Oesophagus

In Barretts oesophagus, the normal squamous epithelium is replaced by columnar epithelium, probably as a consequence of long term exposure of the distal oesophagus to gastric acid. The importance of the condition is the associated increased incidence of adenocarcinoma. As effective acid suppressants, it was hoped that long term PPI therapy could lead to regression of Barrett's oesophagus and thus reduce the incidence of associated adenocarcinoma.

A case report in 1988 described the rapid healing of an oesophageal ulcer and regression of Barrett's oesophagus in a patient with scleroderma, with reduction in both the intragastric pH and time of oesophageal exposure to acid.[221] This encouraging report has not really been substantiated in clinical trials although studies have described the appearance of squamous islands in the Barrett's segment after treatment with PPIs. However, it has recently been suggested that these islands may be merely covering gastric mucosa and may thus mask subsequent malignant transformation.[222-224] In contrast, studies in small groups of patients followed for short periods described regression of the length of Barrett's oesophagus in response to long term acid suppression of omeprazole 40 to 60 mg/day.[225,226]

It still remains to be determined in long term follow-up studies whether PPIs reduce the overall incidence of oesophageal adenocarcinoma in Barrett's oesophagus.

3. Other Indications

3.1 Zollinger-Ellison Syndrome

This rare condition with a prevalence of approximately 0.1 to 3 per million in the US,[227] is characterised by hypergastrinaemia due to gastrin secreting tumours most commonly located in the pancreas or small bowel. Hypergastrinaemia leads to increased acid secretion and ultimately severe peptic ulceration. The diagnosis should be considered in persistent recurrent duodenal ulceration or in complex or post surgical ulceration. Approximately 20% of patients will be cured surgically but the remaining 80% will require long term acid suppression by medical means.

Omeprazole 20 to 80 mg/day has been shown to be effective in a study involving 49 patients, 68% of whom were maintained on 20 mg/day.[228] High initial doses of omeprazole 60 mg/day were used and the dose titrated to basal acid output and clinical recordings.

In another study, an initial dose of 60 mg/day of lansoprazole in 26 patients with the syndrome was titrated to reduce the basal acid output to <5 mmol/hour for those with intact stomachs and to <1 mmol/hour in those with previous gastric surgery or co-existent oesophagitis.[229] The same group recorded a reduced basal acid output of approximately 95% and there was a dramatic clinical improvement.[230]

PPIs are the medical treatment of choice for Zollinger-Ellison syndrome. High starting doses should be used and the subsequent maintenance dose titrated against basal acid output.

3.2 Crohn's Disease

Gastro-oesophageal involvement by Crohn's disease is uncommon. Omeprazole was effective in reducing inflammation in a small study involving 4 patients at a dose of 40 mg/day, and after an 8 week course a mean bodyweight gain of 6kg was recorded.[231] An interesting observation was noted in a series of 7 patients with active colitis in which the addition of omeprazole to the treatment regimen led to clinical improvement in six of the

group; the similar chemical structure of omeprazole to metronidazole was cited as a possible mechanism of action.[232]

3.3 Prevention of Stress Ulceration

Stress-induced mucosal damage is typically characterised by superficial erosion,[233] and is thought to be precipitated mainly by reduced mucosal blood flow in seriously ill patients.[234] Antisecretory prophylaxis against ulceration is widespread, although a large retrospective multicentre study of greater than 3000 patients by Cook et al.[235] in 1994 suggested its use should only be for those patients needing mechanical ventilation or those with a coagulopathy. Experimentally, omeprazole has also been shown to be more effective than famotidine in reducing induced mucosal injury in rats.[236,237]

In a study of 67 high risk patients in intensive care, patients were randomised to receive omeprazole 40 mg/day orally or ranitidine 150 mg/day intravenously. Bleeding occurred in 31% of the ranitidine group and 6% of the omeprazole group ($p < 0.05$).[238] In a study of 82 patients undergoing surgery, the ability of lansoprazole 15 or 30 mg/day given intravenously to reduce gastric hypersecretion was assessed and 66% of patients in the 15mg group and 76% of the 30mg group were described as having 'excellent' responses.[239] However, in a recent review of all available treatments for stress ulcer prophylaxis, PPIs could not be recommended routinely in intensive care because of a lack of evidence for a significant benefit.[240]

3.4 PPIs and Upper Gastrointestinal Bleeding

Over the past 50 years mortality from upper gastrointestinal bleeding has remained at ≈5 to 10%[241] despite developments in modern medicine, including the emergence of acid-blocking drugs. Although PPIs effectively heal peptic ulcers, there are conflicting reports as to their role when used acutely in reducing deaths and other complications in ulcer bleeds. In a UK study by Daneshmend et al.[242] of 1147 patients with acute upper gastrointestinal bleeding from any cause randomised to receive intravenous followed by oral omeprazole or placebo, no advantage in terms of surgery, rebleeding or death was seen in the actively treated group, although omeprazole did reduce the amount of blood seen in the stomach at endoscopy.

In a Scandinavian study of endoscopically proven bleeding ulcers in 274 patients, intravenous followed by oral omeprazole reduced the need for further endoscopic therapy, operations, and duration and severity of bleeding compared to placebo, but no differences in death rates were seen;[243] in fact, in a Dutch multicentre study using a similar design, death rates were actually greater in the omeprazole treated group (11 omeprazole versus 1 placebo) in 333 patients with bleeding ulcers although need for surgery, quantity and duration of bleeding was decreased.[244] However, it should be added that even in the omeprazole group the death rate was 7%, which is below average for bleeding ulcer.[241] In a recent study of 220 patients with bleeding ulcers, Khuroo et al.[245] reported that oral omeprazole also decreased the rate of rebleeding (10.9% for omeprazole; 36.4% for placebo) and the need for further surgery compared to placebo. Death rates were numerically lower in the omeprazole-treated group (2 patients died in the omeprazole group compared to 6 in the placebo group). In this study, patients were somewhat younger (mean age 57) and had fewer co-existing illnesses than might be expected in bleeding ulcer patients from Europe or the US. Whether these differences in outcome are due to inherent differences in the populations studied remains to be determined, and further studies are needed to clarify what group(s) of patients benefit most from PPIs in acute bleeding.

4. Tolerability and Adverse Events

In pooled data from published trials involving 2818 patients, omeprazole was reported as causing headache (2.4%), diarrhoea (1.9%), nausea (0.9%) and rash (1.1%), which was similar to adverse effects with ranitidine and cimetidine.[246] For lansoprazole, in a prospective follow-up study of 5669 daily users, the most common adverse events re-

ported were diarrhoea (4.1%), headache (2.9%) and nausea (2.6%).[247] Studies with pantoprazole have demonstrated a fairly similar adverse effect profile with diarrhoea (1.5%), headache (1.3%), dizziness (0.7%), pruritus (0.5%) being the most frequent adverse effects.[8]

It has also been demonstrated that profound acid suppression leads to colonisation of the stomach by bacteria.[248] In a small study of 20 patients, a 4 week course of omeprazole 20 mg/day led to small bowel colonisation by predominantly oral and colonic flora and significantly speeded up small bowel transit time, with 20% of patients experiencing diarrhoea.[249] Increases in fungal growth rates have also been recorded in patients treated with omeprazole compared to cimetidine and famotidine, although the clinical relevance of these observations has yet to be determined;[250] the incidence of *Campylobacter jejuni* enteritis appears to be also slightly increased by proton pump inhibition.[251] Overall, the PPIs as a group are a very well tolerated class of drugs in clinical practice.

5. Role of PPIs in the Management of Acid Related Disorders

PPIs are now the drugs of choice in the management of acid-related gastrointestinal disorders. They have proved more effective than histamine H_2 receptor antagonists in reducing basal and stimulated acid output, and in the treatment of gastric and duodenal ulceration, reflux oesophagitis and Zollinger-Ellison syndrome.

For the treatment of duodenal ulceration, the 2-week healing rate is in the order of 65% for PPIs compared with 45% for H_2 antagonists. Four- and 6-week healing rates for PPIs are consistently over 90%. Although it is generally more difficult to heal gastric ulcers, again PPIs have a proven superior efficacy here compared with other treatment modalities with healing ranges of 70 to 80% at 4 weeks and over 90% at 8 weeks. As these healing rates are already so high, it is no surprise that comparative studies often fail to demonstrate differences in efficacy among the different PPIs, where very large numbers would be required to demonstrate real differences. For this reason, studies with the newer PPIs that have come on the market, namely pantoprazole and rabeprazole have shown equivalence rather than superiority in controlled trials of ulcer healing.

As *H. pylori* is now regarded to be the most important factor underlying PUD, PPIs have assumed a pre-eminent role in eradication regimens. In Europe, PPI-based antibacterial triple therapy regimens are now regarded as the gold standard for *H. pylori* eradication and have been recommended as such by the European Working Party on *H. pylori*.[76] Although a plethora of studies on different PPI-based eradication regimens have been published in recent years, even in large comparative studies it has been difficult to detect differences in *H. pylori* eradication rates, where rates of over 90% are frequently reported.

The most frequent indication for PPIs in clinical is reflux oesophagitis, and as this condition is associated with a high relapse rate, they have also recently assumed a major role in maintenance therapy. All PPIs have demonstrated superior efficacy over H_2 receptor antagonists for both acute healing and maintenance treatment. Healing rates of over 80% in 8 weeks with PPIs have become the norm with similar rates of symptomatic relief. For maintenance therapy, studies are beginning to show good efficacy with daily use of half of the standard healing dose (for example, omeprazole 10mg and lansoprazole 15mg), although weekend, or alternate day dosing with standard doses, appears to be less effective for maintenance therapy.

A relatively new indication for PPIs is in NSAID-induced ulcer prophylaxis. Next to *H. pylori*, NSAIDs are the most important cause of peptic ulceration, and may be even more important for ulcer complications such as perforations and bleeding. The recent demonstration that omeprazole was more effective than ranitidine for both healing and maintenance, and superior to misoprostol for maintenance therapy in chronic NSAID users, is likely to have major prescribing implications.

PPIs as a group have largely been shown to be well tolerated. Initial worries regarding a theoreti-

cal risk of inducing enterochromaffin-like tumours have not materialised, with over 10 years of omeprazole use in some cases. There has been more recent interest in the possible development of gastric dysplasia in long term PPI users infected with *H. pylori*, and although these studies have been criticised methodologically, further long term studies are required to clarify this issue. Although more recently launched PPIs are often marketed on the basis of less frequent drug interactions than 'older' PPIs, the real significance of this in clinical practice remains to be determined, bearing in mind the long term experience with omeprazole.

In conclusion, PPIs are now the most important drugs for acid-related diseases, including duodenal and gastric ulceration, gastro-oesophageal reflux disease and Zollinger-Ellison syndrome, where they have proven superior to the histamine H_2 receptor antagonists. One- and 2-week PPI-based triple therapy regimens have become the gold standard for *H. pylori* eradication. Choosing which PPI to use for any of these indications is largely dependent on balancing the cost of the individual PPI versus longer term clinical experience, as most comparative studies between PPIs to date have demonstrated comparable efficacies.

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Correspondence and reprints: Dr *William A Stack*, Division of Gastroenterology, University Hospital, Queens Medical Centre, Nottingham, NG7 2UH, England.
E-mail: william.stack@nottingham.ac.uk