

## Review article: comparison of the pharmacokinetics, acid suppression and efficacy of proton pump inhibitors

C. A. M. STEDMAN\* & M. L. BARCLAY\*\*†

\*Departments of Gastroenterology and †Clinical Pharmacology, Christchurch Hospital, Christchurch, New Zealand

Accepted for publication 16 March 2000

### SUMMARY

Proton pump inhibitors have dramatically influenced the management of acid-peptic disorders in recent years. They all have a broadly similar mechanism of action and are extensively metabolized in the liver via cytochromes P450 2C19 and 3A4. There is some variation in their potential for drug interactions due to differences in enzyme inhibition. Relatively few serious adverse effects have been reported for the proton pump inhibitors.

Comparative studies of acid suppression suggest that lansoprazole and pantoprazole have a potency similar to that of omeprazole on a mg for mg basis; however, rabeprazole may have a greater potency than

omeprazole. Lansoprazole and rabeprazole display a more rapid onset of maximal acid suppression than the other proton pump inhibitors.

Comparative studies using proton pump inhibitors for the treatment of reflux oesophagitis, duodenal ulcer healing and *Helicobacter pylori* eradication show little overall difference in outcome between the proton pump inhibitors when used in their standard doses. Lansoprazole and rabeprazole provide earlier and better symptom relief than the other proton pump inhibitors in some studies of peptic ulcer treatment. The few studies of gastric ulcer treatment suggest that there is an advantage in using the proton pump inhibitors that have a higher standard daily dose.

### INTRODUCTION

Proton pump inhibitors have influenced the management of acid-peptic disorders dramatically over the last 10 years. Three of these agents are now widely available; omeprazole (available since 1989), lansoprazole (1995), and pantoprazole (1997). Rabeprazole is now also becoming available in some countries.

These agents selectively and irreversibly inhibit the gastric hydrogen/potassium adenosine triphosphatase ( $H^+/K^+$ -exchanging ATPase), part of the 'proton pump' that performs the final step in the acid secretory process.<sup>1</sup> They thereby inhibit both basal and stimulated secretion of gastric acid, independently of the nature of parietal cell stimulation.<sup>1–2</sup> Clinical uses include the treatment of peptic ulcer disease, gastro-oesophageal

reflux disease, Barrett's oesophagus, Zollinger–Ellison Syndrome, and the eradication of *Helicobacter pylori* as part of combination regimens.

In this review, all four agents are compared with regard to pharmacokinetics, potency, acid suppression, clinical efficacy and toxicity, and potential for drug interactions. There are fewer comparative data available for rabeprazole, but this is included where such data are available. In general, only studies directly comparing two or more of these agents have been included, although other data have been used in some cases when no direct comparison studies were available.

### STRUCTURE AND MECHANISM OF ACTION

Proton pump inhibitors are all substituted benzimidazole derivatives (Figure 1). They function as pro-drugs, accumulating within the parietal cell canaliculus where acid-catalysed conversion of the pro-drug to a tetracy-

Correspondence to: Dr M. L. Barclay, Department of Clinical Pharmacology, Christchurch Hospital, Private Bag 4710, Christchurch, New Zealand.

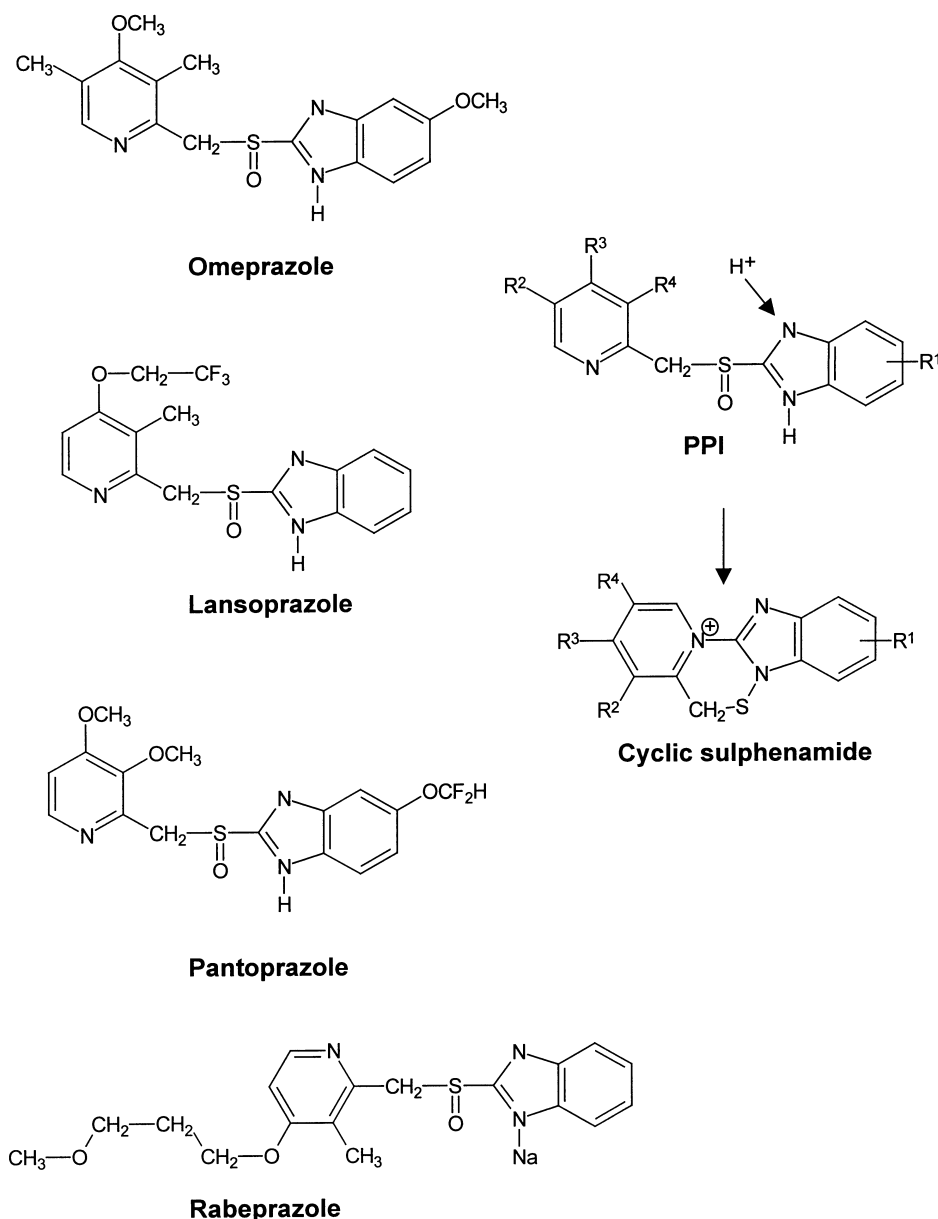


Figure 1. Structural formulae of the proton pump inhibitors omeprazole, lansoprazole, pantoprazole and rabeprazole and the tetracyclic sulphenamide to which they are converted in the parietal cell canaliculus after protonation.

clic planar sulphenamide occurs (Figure 1).<sup>3</sup> The sulphenamide then binds covalently to key cysteine groups on the proton pump to cause prolonged inhibition of gastric acid secretion.<sup>1–2</sup> Acid production by the proton pump can generally only be restored through endogenous synthesis of the H<sup>+</sup>K<sup>+</sup>-exchanging ATPase, which has a half-life of production of approximately 50 h.<sup>1</sup> However, rabeprazole differs because it converts more rapidly to the activated sulphenamide form than the other proton pump inhibitors and also dissociates more

readily from the H<sup>+</sup>K<sup>+</sup>-ATPase, resulting in both a faster rate of inhibition and also a shorter duration of action.<sup>4–5</sup>

The drugs are weak bases and accumulation within the acidic parietal cell canaliculus is dependent on the pH gradient and pK of each agent. The pH of the parietal cell canaliculus is 0.8, whereas that of other acidic compartments such as lysosomes is 4.5–5.<sup>1–3</sup> The important site of protonation for accumulation of these drugs is the pyridine N (Figure 1). All four of the proton pump inhibitors have a pyridine N pK of less than 4.5,

which should favour selectivity of the drugs for the parietal cell. The pK of the pantoprazole pyridine N (3.96) is slightly lower than that of omeprazole (4.13) or lansoprazole (4.01), although this difference has not been shown to be of direct clinical significance.<sup>2</sup> The pK for the N of the benzimidazole rings are all much lower.<sup>1</sup> The drugs all have similar high levels of activation at a very low pH, whereas in the near neutral pH range of 4–6, pantoprazole is more chemically stable and less activated, and rabeprazole is less stable than the other two drugs.<sup>5–6</sup> The conversion rate from the pro-drug to the active sulphenamide is slower for pantoprazole.<sup>1, 2</sup>

Acid inhibition is not necessarily maximal after the first dose. Acid catalysed activation of the drug is necessary, so only activated parietal cells will be inhibited, whereas resting parietal cells (approximately 25% of the cell mass) will escape initial inhibition.<sup>1</sup> Both pantoprazole and omeprazole display an increase in acid inhibitory effect over several days of repeated administration, whereas acid inhibition with lansoprazole is maximal after the first dose.<sup>7–8</sup>

The mechanism of action is similar for all of the proton pump inhibitors, and they all bind to one common distinct site on the alpha subunit of the proton pump (probably cysteine 813 on the luminal loop between transmembrane domains 5 and 6). Pantoprazole may also bind to the adjacent cysteine 822, and omeprazole to cysteine 892. Lansoprazole and rabeprazole both bind to additional sites at cysteine 892 and cysteine 321.<sup>9</sup> Pantoprazole has greater selectivity for the cysteine 813/822 sites, but the clinical significance of these differences is unclear.<sup>1–2</sup>

The drugs are all acid-labile, so when administered orally they must be formulated in an enteric coating to protect them from rapid degradation in the stomach. They are rapidly absorbed in the duodenum.

## PHARMACOKINETICS

The values for the main pharmacokinetic parameters for the proton pump inhibitors are shown in Table 1 for comparison.

There is a poor correlation between maximal plasma drug concentration ( $C_{\max}$ ) and the degree of acid suppression in studies of omeprazole. The maximal plasma drug concentration varies widely depending on the rate of passage in the gastrointestinal tract, release of drug and intraduodenal pH.<sup>8</sup> However, the area under the plasma concentration–time curve (AUC) does correlate well with acid suppression, and the area under the same curves for omeprazole 20 mg ( $0.2\text{--}1.2 \mu\text{g} \cdot \text{h/mL}$ ) and rabeprazole 20 mg ( $0.8 \mu\text{g} \cdot \text{h/mL}$ ) or 40 mg ( $1.0 \mu\text{g} \cdot \text{h/mL}$ ) are significantly lower than for pantoprazole 20 mg ( $2 \mu\text{g} \cdot \text{h/mL}$ ) or 40 mg ( $4.6\text{--}4.9 \mu\text{g} \cdot \text{h/mL}$ ), or lansoprazole 30 mg ( $1.7\text{--}5 \mu\text{g} \cdot \text{h/mL}$ ).<sup>8, 11–12</sup>

The proton pump inhibitors all have similar short plasma half-lives of elimination at approximately 1 h and are therefore unlikely to accumulate even when clearance is significantly reduced.<sup>8–11, 13</sup> However, the duration of acid inhibition is relatively long (48–72 h) because of the irreversible binding of the sulphenamide to the  $\text{H}^+\text{K}^+\text{-ATPase}$ . Rabeprazole has a shorter duration of action as it can dissociate to a greater extent than the other drugs.

Table 1. Comparison of the pharmacokinetics of the proton pump inhibitors (results expressed as reported range)

Pharmacokinetic parameters	Omeprazole <sup>a</sup> 20 mg	Pantoprazole <sup>b</sup> 40 mg	Lansoprazole <sup>c</sup> 30 mg	Rabeprazole <sup>d</sup> 20 mg
AUC ( $\mu\text{g} \cdot \text{h/mL}$ )	0.2–1.2	2–5	1.7–5	0.8
$C_{\max}$ ( $\mu\text{g/mL}$ )	0.08–8	1.1–3.3	0.6–1.2	0.41
$T_{\max}$ (h)	1–3	2–4	1.3–2.2*	3.1†
$t_{1/2}$ (h)	0.6–1	0.9–1.9	0.9–1.6	1
Cl ( $\text{L} \cdot \text{h/kg}$ )	0.45	0.08–0.13	0.2–0.28	0.50
Vd ( $\text{L/kg}$ )	0.31–0.34	0.13–0.17	0.39–0.46	
Bioavailability (%)	Variable 35 → 65 (with repeated doses)	Constant 57–100	Constant 80–91	
Protein binding (%)	95	98	97–99	95–98
Dose linearity	non-linear	linear	linear‡	linear

Data from References: <sup>a</sup> 2, 7, 10, 15, 16, 18, 27, 62; <sup>b</sup> 2, 6, 11, 15, 101; <sup>c</sup> 2, 8, 10, 12, 13, 16, 92; <sup>d</sup> 4.

AUC, area under the concentration curve;  $C_{\max}$ , maximum serum concentration;  $T_{\max}$ , time to maximum serum concentration;  $t_{1/2}$ , elimination half-life; Cl, drug clearance; Vd, apparent volume of distribution.

\*Delayed to 3.5–3.7 with food; †delayed by 1.7 h with food; ‡non-linear in some studies for doses < 20 mg and intravenous administration.

The oral bioavailabilities (F) of the proton pump inhibitors differ significantly. The oral availability of omeprazole is initially low at approximately 35–40% but increases to about 65% on repeated dosing.<sup>7, 10</sup> This may reflect improved drug absorption associated with increases in gastric pH and reduced breakdown of the acid-labile drug in the stomach. In contrast, pantoprazole has a constant bioavailability of approximately 77%, independent of dose.<sup>11</sup> Lansoprazole also has a constant high bioavailability of 80–91% at therapeutic doses, although studies have shown that bioavailability is reduced at doses lower than 20 mg/day.<sup>8, 13</sup>

For pantoprazole and rabeprazole, there is a linear relationship between dose and plasma concentrations after the administration of single and multiple doses.<sup>5, 11, 14, 15</sup> For omeprazole the kinetics are dose-dependent, with non-linear increases in maximal plasma drug concentration occurring with increasing doses.<sup>7</sup> For lansoprazole, there is a linear increase in maximal plasma drug concentration and the area under the plasma concentration–time curve in relation to the dose administered at standard therapeutic doses.<sup>8</sup>

All of the proton pump inhibitors are highly protein bound (> 95%), rapidly metabolized in the liver and have negligible renal clearance.

#### *Pharmacokinetics in special populations*

A summary of the pharmacokinetics of the proton pump inhibitors in special situations is given in Table 2. Food has been shown to result in delayed absorption of lansoprazole, with a reduction in maximal plasma drug concentration and F in some studies but not in others.<sup>8, 12, 16, 17</sup> Similar effects have been seen with omeprazole and pantoprazole, but these have been of

borderline significance.<sup>15</sup> Concurrent administration of antacids has been reported to result in a slight reduction in bioavailability of lansoprazole but this has not been shown for omeprazole or pantoprazole.<sup>8, 18, 19</sup>

Renal impairment would not be expected to significantly alter the pharmacokinetics of these drugs as they are highly metabolized. Whilst there are studies confirming this for the three older drugs, there are some studies with conflicting results for both lansoprazole and pantoprazole.<sup>11, 20–22</sup> However, these small effects are unlikely to be clinically significant.

In contrast, studies have shown that significant hepatic impairment results in a seven to ninefold increase in the area under the plasma concentration–time curve and a prolongation of the half-life to 4–8 h for all proton pump inhibitors.<sup>20–24</sup> This could potentially result in an increase in dose-related side-effects although this has not been confirmed clinically. It is unlikely to result in significant drug accumulation, as these drugs are generally administered once daily. However, it would seem reasonable to use lower doses in this population, as the desired therapeutic effect should be obtainable at a lower dose. Consistent with the expected effects of ageing on physiological function, the area under the plasma concentration–time curve of these drugs also increases by up to 50–100% in the elderly.<sup>11, 25</sup> Drug clearance is reduced with increasing age and the half-life of elimination increases to approximately 1.5 h in the elderly.<sup>11, 26</sup>

Three per cent of the population are poor metabolizers of proton pump inhibitors, with a reduction in clearance that is associated with an increase in half-life and a five to tenfold increase in the area under the plasma concentration–time curve. Studies show that there is co-segregation of S-mephenytoin polymorphism with

Table 2. The effects of different conditions on the pharmacokinetics of the proton pump inhibitors

	Omeprazole <sup>a</sup>	Pantoprazole <sup>b</sup>	Lansoprazole <sup>c</sup>	Rabeprazole <sup>d</sup>
Food-effect on absorption	Minimal	Minimal	Delayed absorption, ↓C <sub>max</sub> , ↓F (some studies)	Minimal
Concurrent antacid use	No change	No change	Conflicting results	—
Renal impairment	No change	Conflicting results	Conflicting results	—
Hepatic impairment	↑AUC +++ ↑t <sub>1/2</sub> +++	↑AUC +++ ↑t <sub>1/2</sub> +++	↑AUC +++ ↑t <sub>1/2</sub> +++	↑AUC + ↑t <sub>1/2</sub> +
Elderly	↓Cl ↑AUC, ↑t <sub>1/2</sub>	↓Cl ↑AUC	↓Cl ↑AUC, ↑t <sub>1/2</sub>	—

Data from References: <sup>a</sup> 6, 16, 18, 23; <sup>b</sup> 6, 11, 15, 18, 19, 22, 23, 26, 62, 92, 101; <sup>c</sup> 6, 8, 12, 16, 17, 20, 23, 25, 92; <sup>d</sup> 24, 111.  
AUC, area under the concentration curve; C<sub>max</sub>, maximum serum concentration; T<sub>max</sub>, time to maximum serum concentration; t<sub>1/2</sub>, elimination half-life; Cl, drug clearance; Vd, apparent volume of distribution; (—), not tested; (+), small change; (+++), large change.

proton pump inhibitor normal and poor metabolizers, suggesting that metabolism is via CYP 2C19.<sup>4, 27–29</sup>

### Cytochrome P450 enzyme metabolism

Proton pump inhibitors are metabolized in the liver by P450 cytochromes and this subject has been reviewed previously.<sup>18, 29–31</sup> All four proton pump inhibitors are metabolized by CYPs 2C19 and 3A4 to varying degrees. Omeprazole is metabolized predominantly by CYP 2C19 (responsible for 80% of clearance) with dose-dependent enzyme saturation, and has a lower affinity for CYP 3A4, which may function as a high capacity enzyme that prevents very high omeprazole concentrations.<sup>31–33</sup> Lansoprazole is also metabolized by CYPs 2C19 and 3A4, although the relative importance of each enzyme is less clear.<sup>28, 31, 33</sup> Although pantoprazole is metabolized by both CYPs 2C19 and 3A4, it differs in that it has a lower affinity for P450, and is also subsequently metabo-

lized by a sulphotransferase, which is non-saturable and not part of the CYP system.<sup>2, 34–36</sup>

Table 3 shows the results of studies that have investigated possible interactions between the proton pump inhibitors and other drugs that may result via effects on the CYP450 enzymes. There is some evidence that omeprazole and lansoprazole may be weak inducers of CYPs 1A1 and 1A2. Concurrent administration of lansoprazole results in increased theophylline metabolism (area under the plasma concentration–time curve decreases by 13%).<sup>37–38</sup> In addition, caffeine metabolism is increased in people on high doses of omeprazole, although other studies have shown little or no effect on caffeine metabolism when using low doses of omeprazole in extensive metabolisers.<sup>39–42</sup> At present these interactions appear unlikely to be of clinical significance. CYP 3A4 is induced by omeprazole and lansoprazole in human hepatocyte cultures but no clinically significant interactions with drugs metabolized by CYP

Table 3. Proton pump inhibitor interactions with other drugs via CYP 450 metabolism

CYP 450 enzyme/drug tested	Omeprazole <sup>a</sup>	Lansoprazole <sup>b</sup>	Pantoprazole <sup>c</sup>	Rabeprazole <sup>d</sup>
<b>CYP 1A2</b>				
Theophylline	No interaction	?↑Cl	No interaction	No interaction
Caffeine	↑Cl*	—	No interaction	—
<b>CYP 2C9</b>				
Phenytoin	↓Cl (by 15–20%)	No interaction	No interaction	No interaction
S Warfarin	?↓Cl (3%)	No interaction	No interaction	No interaction
Carbamazepine	↓Cl	—	No interaction	—
Diclofenac	—	—	No interaction	—
Tolbutamide	↑AUC (by 10%)	—	—	—
<b>CYP 2C19</b>				
Diazepam	↓Cl (by 26–54%)	No interaction	No interaction	No interaction
Mephenytoin	↓Cl	—	No interaction	—
R warfarin	↑concentration ×2	No interaction	No interaction	No interaction
<b>CYP 2D6</b>				
Debrisoquine	No interaction	—	No interaction	—
Propranolol	No interaction	No interaction	—	—
Metoprolol	No interaction	—	No interaction	—
<b>CYP 3A4</b>				
Nifedipine	?↓Cl	—	No interaction	—
Cyclosporin	No interaction	—	—	—
Quinidine	No interaction	—	—	—
Lignocaine	No interaction	—	—	—
Contraceptives	No interaction	?effect on ovulation	No interaction	—
Erythromycin	No interaction	—	—	—

Data from References: <sup>a</sup> 30, 31, 39–42, 44, 45, 112; <sup>b</sup> 18, 30, 31, 37, 38, 40, 46; <sup>c</sup> 18, 19, 30, 31, 47, 48; <sup>d</sup> 4, 43, 49, 51, 52.

CYP, Cytochrome P450; Cl, drug clearance; AUC, area under the concentration curve; (—), not tested; (?), result not clear; \*, in high doses or in CYP 2C19 poor metabolisers.

3A4 have been documented.<sup>31</sup> Pantoprazole has little or no potential for enzyme induction and rabeprazole does not affect theophylline metabolism.<sup>19, 43</sup>

Omeprazole inhibits CYPs 2C9 and 2C19 and in those with the extensive metaboliser phenotype there is evidence that omeprazole administration results in significant decreases in the clearance of diazepam, phenytoin, and possibly carbamazepine and S-warfarin.<sup>44–45</sup> Lansoprazole may reduce the efficacy of the oral contraceptive, but otherwise there have been no clinically significant interactions reported for lansoprazole, pantoprazole or rabeprazole.<sup>19, 43, 46–49</sup>

Proton pump inhibitors may alter the absorption of some other drugs by increasing the gastric pH. Omeprazole and rabeprazole use results in small increases in the absorption of digoxin, and similar effects would be expected with the other proton pump inhibitors.<sup>31, 50–51</sup> However, the difference did not reach statistical significance in studies of digoxin with pantoprazole.<sup>19</sup> Proton pump inhibitors may increase the absorption of acid-labile antibiotics, such as penicillin V and erythromycin, by increasing gastric pH. Rabeprazole reduces the absorption of ketoconazole, resulting in reductions in the maximal plasma drug concentration and the area under the plasma concentration–time curve of ketoconazole.<sup>52</sup>

In summary, the proton pump inhibitors, as a group, are extensively metabolized via the cytochrome P450 system, and some drug interactions of probable clinical significance have been reported for omeprazole. Lansoprazole and rabeprazole have less potential for drug interactions and no interactions of clinical relevance have been reported for pantoprazole.

## EFFICACY

### *Acid suppression/pH studies*

The primary effect of the proton pump inhibitors is gastric acid suppression, the degree of which has been shown to correlate with healing rates for reflux oesophagitis (good healing when the gastric pH is greater than 4 for 16 h/day) and peptic ulcer (healing when pH > 3).<sup>53</sup> The degree of acid suppression is probably the best *in vivo* parameter with which to compare the potency of the proton pump inhibitors. Omeprazole, lansoprazole and pantoprazole have been marketed in different standard doses, and few studies compare their potency on a mg for mg basis.

Table 4 summarizes the results of studies comparing the acid suppressing effects of the proton pump inhibitors. A number of studies have examined the effect on gastric pH of lansoprazole compared with omeprazole. Three studies have shown that lansoprazole 30 mg taken orally on a daily basis maintained the pH at greater than 3 for a significantly greater time than omeprazole 20 mg, and two studies have shown a higher median 24-h pH for lansoprazole.<sup>10, 54, 55</sup> Three other studies found no significant difference overall in any pH parameters when comparing omeprazole and lansoprazole and their results conflicted with respect to the effects of these proton pump inhibitors on daytime and night-time pH.<sup>56–58</sup>

One study has shown that gastric pH was greater than 3 for 76% of the time with lansoprazole 60 mg/day and 69% with omeprazole 40 mg/day ( $P = 0.002$ ).<sup>59</sup> Omeprazole 40 mg was significantly superior to lansoprazole 30 mg at maintaining the pH above 5, but not above 3. These results suggest that on a mg for mg basis, the potency of lansoprazole and omeprazole is similar.

Two studies compare equal doses (40 mg) of pantoprazole and omeprazole. In one study, no significant difference was found in any measured parameters for pH.<sup>60</sup> In the other, the mean nocturnal pH was higher for pantoprazole (3.4) than for omeprazole (1.7), but there was no difference in other measurements of pH.<sup>61</sup> Pantoprazole 40 mg has also been compared with omeprazole 20 mg and the results showed a significantly higher daytime and 24 h pH on both days 1 and 7 with pantoprazole, although there was no difference in mean night-time pH. There was a markedly increased rise in intragastric pH with repeated administration of both drugs.<sup>62</sup>

Overall these results suggest that pantoprazole and omeprazole have a similar potency on a mg for mg basis.

In one study, daytime pH, median 24-h pH and percentage time that pH was greater than 4 were significantly higher with lansoprazole 30 mg than pantoprazole 40 mg. Night-time pH was significantly higher with lansoprazole 30 mg at day 1 only. It was also noted that the antisecretory effect appears to be maximal after the first dose of lansoprazole, whereas for pantoprazole, antisecretory activity increased significantly from the first to the 7th day.<sup>63</sup>

Rabeprazole 20 mg results in a significantly faster onset of antisecretory action than omeprazole 20 mg,

Table 4. Studies comparing the PPIs with respect to gastric acid suppression

Reference	Number of patients	Drug & dosage (mg/day)	Duration (days)	Median 24 h pH	Median percentage of time (%)			Overall efficacy (significance)
					pH > 3	pH > 4	pH > 5	
<b>Omeprazole vs. lansoprazole</b>								
Timmer <i>et al.</i> <sup>59</sup>	(20)	L30 mg	9	4.1 <sup>m</sup>	65 <sup>m</sup>		37 <sup>m</sup>	L60 ≥ O40
		L30 mg b.d.		4.6	76		48	O40 ≥ L30
		L45 mg b.d.	7	4.7	78		49	
		L60 mg b.d.		4.8	81		52	
		O20 mg b.d.		4.4	69		46	
Verdu <i>et al.</i> <sup>56</sup>	(18)	L30 mg	7	5.4	85–87			L30 = O20
(HP +ve)		O20 mg	7	5.5	84–86			
Tolman <i>et al.</i> <sup>10</sup>	(17)	L15 mg	5	4.0 <sup>m</sup>	L30 > O20, O15**			
		L30 mg		4.9*				L30 > L15,O20
		O20 mg		4.2				
Blum <i>et al.</i> <sup>55</sup>	(29)	L15 mg	5	4.0 <sup>m</sup>	64 <sup>m</sup>	48 <sup>m</sup>		
		L30 mg		4.5*	75*	63*		L30 > L15,O20
		O20 mg		4.0	63	51		
Bruley Des	(12)	L30 mg	7	NS	L > O*	NS		L30 ≥ O20
Varannes <i>et al.</i> <sup>54</sup>		O20 mg						
Geus <i>et al.</i> <sup>57</sup>	(16)	L30 mg	7	3.7	60	46	32	L30 = O20
		L30 mg b.d.		5.1	88	70	51	O40 > L60
		O20 mg		4.2	68	53	29	(night pH)
		O20 mg b.d.		5.4	94	78	61	
Seensalu <i>et al.</i> <sup>58</sup>	(16)	L15 mg	5	2.9				O20 = L15,L30
		L30 mg		3.0				O40 = L60
		L60 mg		3.8				
		O20 mg		3.0				
		O40 mg		4.2				
Dammann <i>et al.</i> <sup>113</sup>	(10)	L15 mg						
		L30 mg						L30 > O20 <sup>#</sup>
		O20 mg						L30 = O40
		O40 mg						
<b>Omeprazole vs. pantoprazole</b>								
Brunner <i>et al.</i> <sup>60</sup>	(12)	P40 mg	7	6.4	91	87		O40 = P40
		O40 mg		6.4	88 NS	83 NS		
Hartmann <i>et al.</i> <sup>62</sup>	(16)	P40 mg	7	3.2				P40 > O20**
		O20 mg		2.1				
Koop <i>et al.</i> <sup>61</sup>	(7)	P40 mg	7	4.2		54		P40 = O20
		O40 mg		4.0		50		(except night pH)
<b>Omeprazole vs. rabeprazole</b>								
Williams <i>et al.</i> <sup>5</sup>	(24)	R20 mg	1	3.2	55	44		R20 ≥ O20***
			8	4.7	69	60		
		O20 mg	1	2.0	37	25		
			8	4.2	60	51		
<b>Lansoprazole vs. pantoprazole</b>								
Florent <i>et al.</i> <sup>63</sup>	(12)	L30 mg	1	3.8*	65	51	22	L30 > P40
			7	3.8	61	49	23	
		P40 mg	1	2.5	35	23	8	
			7	3.4	49	34	12	
<b>Lansoprazole vs. pantoprazole/omeprazole</b>								
Scholtz <i>et al.</i> <sup>64</sup>	(18)	P40 mg	5	3.2		41		L > O
		L30 mg		3.7		46		L = P
		O20 mg		2.8		35		

Abbreviations: \* =  $P < 0.05$ , \*\* =  $P < 0.01$ , \*\*\* =  $P < 0.001$ , > = significantly superior to comparator agent on all efficacy parameters, ≥ = significantly superior to comparator agent in some efficacy parameters, = = comparable efficacy to comparator agent, NS = no significant difference, m = mean values, L = lansoprazole, O = omeprazole, P = pantoprazole, # = meal stimulated acid secretion measured rather than pH.

with a greater percentage of time for which the pH is above 3 and 4 at days 1 and 8, but no significant difference in median 24-h pH at 8 days.<sup>5</sup>

There is one published abstract comparing three proton pump inhibitors with respect to the effects on gastric pH.<sup>64</sup> In order of decreasing potency, this study ranked lansoprazole 30 mg > omeprazole 20 mg, and lansoprazole 30 mg was ranked equal to pantoprazole 40 mg, although the pH values were slightly higher for lansoprazole 30 mg. However, the study population was small and there was no comment regarding the statistical significance of the results.

Overall, these studies support equivalent potency for omeprazole vs. lansoprazole, and also omeprazole vs. pantoprazole. However, one study has shown that 30 mg of lansoprazole gave better acid suppression than 40 mg of pantoprazole, suggesting that lansoprazole has a greater potency. In some studies, omeprazole 20 mg has a lesser effect on pH than the other two drugs in standard doses, which would be consistent with its lower dose. One study suggests that rabeprazole has a greater potency than omeprazole when compared on a mg for mg basis. The significance of these differences can only be fully assessed in trials examining clinical outcomes as endpoints.

#### *Gastro-oesophageal reflux disease*

**Treatment.** Table 5 summarizes the results of studies comparing the clinical efficacy of the proton pump inhibitors for the treatment of reflux oesophagitis. There are at least nine reported studies comparing lansoprazole with omeprazole for the treatment of reflux oesophagitis. Of those comparing lansoprazole 30 mg with omeprazole 20 mg, six studies out of seven show no significant difference in endoscopic healing rates at 4 and 8 weeks.<sup>65–70</sup> One study showed lansoprazole 30 mg to be superior in endoscopic healing at 4 weeks, although the published details of this study are limited.<sup>71</sup> There are trends in three studies for lansoprazole 30 mg to provide earlier symptom relief than omeprazole 20 mg.<sup>66, 68, 69</sup> Lansoprazole 30 mg has been compared with omeprazole 40 mg, and no significant differences were found in healing rates or symptom relief.<sup>72</sup>

Both lansoprazole 30 mg and omeprazole 20 mg have been shown to be superior to lansoprazole 15 mg for the healing of oesophagitis.<sup>66</sup> No studies have shown any difference between pantoprazole 40 mg and omeprazole

20 mg for healing rates or symptom relief in patients with reflux oesophagitis.<sup>73–75</sup>

In one study of 202 patients with GERD, rabeprazole 20 mg and omeprazole 20 mg had equivalent healing rates and symptom relief at 4 and 8 weeks.<sup>76</sup>

**Maintenance of remission.** When maintenance of remission was assessed in patients with treated oesophagitis, there was no significant difference between omeprazole 20 mg and lansoprazole 30 mg.<sup>77</sup>

One small study of remission maintenance compared omeprazole 40 mg, lansoprazole 60 mg and pantoprazole 80 mg and showed a dramatic difference in remission rates in favour of omeprazole 40 mg.<sup>78</sup> However, the number of patients was very small compared with other larger studies that showed no significant difference between omeprazole and lansoprazole in standard doses for remission maintenance.<sup>77</sup>

#### *Peptic ulcer disease*

**Gastric ulcer.** The studies comparing the efficacy of proton pump inhibitors for the treatment of peptic ulcer disease are summarized in Table 6. There have been at least three studies comparing different proton pump inhibitors for gastric ulcer healing.<sup>79–81</sup> Rates of ulcer healing were significantly greater with lansoprazole 30 mg than omeprazole 20 mg, on an intention-to-treat analysis at 8 weeks ( $P = 0.04$ ), and a trend favoured lansoprazole treatment at 4 weeks ( $P = 0.06$ ).<sup>79</sup> The time to relief of symptoms was shorter with lansoprazole (mean 6.6 days compared with 11 days) and the trend for the overall percentage of patients with symptom relief favoured lansoprazole.

Gastric ulcer healing rates were greater at 4 weeks with pantoprazole 40 mg than with omeprazole 20 mg when analysed on a per protocol basis (87.7% compared with 76.7%,  $P < 0.05$ ), but the difference was not significant on an intention-to-treat analysis.<sup>80</sup> There was no significant difference in symptom relief, although the trend favoured pantoprazole.

In a 6-week study of 227 patients with active gastric ulcer treated with omeprazole 20 mg or rabeprazole 20 mg, there was no significant difference in healing rates at 3 or 6 weeks, but the results favoured rabeprazole with regard to ulcer pain frequency, and severity of daytime and night-time pain.<sup>81</sup>



Table 5. Studies comparing the clinical efficacy of PPIs: gastro-oesophageal reflux disease

Reference	Number of patients	Drug & dosage (mg/day)	Duration (weeks)	Outcome		
				Healing	Symptoms	Other
<b>Omeprazole vs. lansoprazole</b>						
Vcev <i>et al.</i> <sup>65</sup>	60	L 30 O 20	8	NS	NS	
Castell <i>et al.</i> <sup>66</sup>	1284	L 15 L 30 O 20 Placebo	8	L30 = O20 > L15** L,O > placebo	L30 ≥ O20* L,O > placebo*	Nausea L15 > O20,L30 AE:L30,O20 > L15
Corallo <i>et al.</i> <sup>67a</sup>	145	L 30 O 20	8	NS	NS	
Hatlebakk <i>et al.</i> <sup>68</sup>	229	L 30 O 20	4,8	NS	L ≥ O @ 4 weeks*	Headache O > L*
Mee <i>et al.</i> <sup>69</sup>	604	L 30 O 20	8	NS	L ≥ O @ 3,7 days*	
Cordova-Villabos <i>et al.</i> <sup>70a</sup>	20	L 30 O 20	4	NS	NS	
Sekiguchi <i>et al.</i> <sup>71</sup>	68	L 30 O 20	4	L > O	—	
Mulder <i>et al.</i> <sup>72</sup>	211	L 30 O 40	8	NS	NS	
Carling <i>et al.</i> <sup>77</sup> (remission maintenance)	248	L 30 O 20	48	NS (relapse rates)	NS	
<b>Omeprazole vs. pantoprazole</b>						
Corinaldesi <i>et al.</i> <sup>73</sup>	241	P 40 O 20	8	NS	NS	
Hotz <i>et al.</i> <sup>74a</sup>	521	P 40 O 20	8	NS	NS	
Mossner <i>et al.</i> <sup>75</sup>	286	P 40 O 20	4,8	NS	NS	
<b>Omeprazole vs. rabeprazole</b>						
Dekkers <i>et al.</i> <sup>76</sup>	202	R 20 O 20	4,8	NS	NS	↑ALT/SGPT O > R* Flatulence O > R*
<b>Omeprazole vs. lansoprazole vs. pantoprazole</b>						
Jasperson <i>et al.</i> <sup>78</sup> (remission maintenance)	36	O 40 L 60 P 80	4	O > P,L**	O > P,L**	

Abbreviations: \* =  $P < 0.05$ , \*\* =  $P < 0.01$ , > = significantly superior to comparator agent; ≥ = significantly superior to comparator agent in some efficacy parameters; ' = comparable efficacy to comparator agent; NS = no significant difference; L = lansoprazole; O = omeprazole; P = pantoprazole; R = rabeprazole; a = abstract only; AE = proportion of patients experiencing any adverse event.

There are few trials comparing proton pump inhibitors on a mg for mg basis for the treatment of gastric ulcer, and therefore it is difficult to make firm conclusions about differences in potency and effectiveness in this context. However, any differences seen in the available studies would be consistent with the differences in the standard dose administered.

**Duodenal ulcer.** Several studies have compared lansoprazole with omeprazole in the treatment of acute

duodenal ulcer.<sup>82–86</sup> None of these studies have shown a statistically significant difference in healing rates at 4 weeks, although in two studies lansoprazole 30 mg was associated with an increased healing rate at 2 weeks compared with omeprazole 20 mg.<sup>85–86</sup> One study showed a trend in favour of lansoprazole for the relief of pain at 4 weeks.<sup>84</sup>

Lansoprazole 30 mg has been compared with omeprazole 40 mg for the initial healing of duodenal ulcer, and no significant difference was found between the

Table 6. Studies comparing the clinical efficacy of the PPIs: Peptic ulcer disease

Reference	Number of patients	Drug & dosage (mg/day)	Duration (weeks)	Outcome		
				Healing	Symptoms	Other
<b>Gastric ulcer</b>						
Florent <i>et al.</i> <sup>79</sup>	(126)	L 30 O 20	8	L > O*ITT	NS	
Witzel <i>et al.</i> <sup>80</sup>	(219)	P 40 O 20	8	P > O @ 4 weeks*PP	NS	
Dekkers <i>et al.</i> <sup>81</sup>	(227)	R 20 O 20	3,6	NS	R ≥ O**	
<b>Duodenal ulcer</b>						
<b>Omeprazole vs. lansoprazole</b>						
Chang <i>et al.</i> <sup>82</sup>	(111)	L 30 O 20	4	NS	NS	
Dobrilla <i>et al.</i> <sup>83</sup>						
—ulcer healing	(251)	L 30 O 40	4	NS	NS	
—remission maintenance	(218)	L 15 L 30 O 20	52	NS	NS	
Ekstrom <i>et al.</i> <sup>84</sup>	(279)	L 30 O 20	4	NS	L > O @ 4 weeks*	↑S-ALAT L > O**
Petite <i>et al.</i> <sup>85</sup>	(144)	L 30 O 20	4	L > O @ 2 weeks*	NS	
Louw <i>et al.</i> <sup>86a</sup>	(143)	L 30 O 20	4	L > O @ 2 weeks*	—	
<b>Omeprazole vs. pantoprazole</b>						
Beker <i>et al.</i> <sup>87</sup>	(270)	P 40 O 20	4	NS	NS	
Rehner <i>et al.</i> <sup>88</sup>	(276)	P 40 O 20	2,4	NS	NS	
Italian Group <sup>89</sup>	(96)	P 40 O 20	4	NS	NS	
<b>Rabeprazole vs. omeprazole</b>						
Dekkers <i>et al.</i> <sup>90</sup>	(205)	R 20 O 20	2,4	NS	R ≥ O*	↑Gastrin R > O*

Abbreviations: \* =  $P < 0.05$ , \*\* =  $P < 0.01$ , > = significantly superior to comparator agent, ≥ = significantly superior to comparator agent in some efficacy parameters, NS = no significant difference between comparator agents, L = lansoprazole, O = omeprazole, P = pantoprazole, R = rabeprazole, a = abstract only; ITT = Intention-to-treat analysis only, PP = per-protocol analysis only.

two drugs.<sup>83</sup> Lansoprazole in 15 mg and 30 mg doses was also compared with omeprazole 20 mg for remission maintenance therapy in this study. At 1 year there were no relapses in the lansoprazole 30 mg group, 3.3% in the lansoprazole 15 mg group and 3.5% in the omeprazole 20 mg group, with no statistically significant difference overall between the three groups.

These results are consistent with the results of the studies assessing drug effect on gastric pH and suggest that lansoprazole and omeprazole have a similar potency, giving lansoprazole 30 mg a slight advantage

over omeprazole 20 mg. Lansoprazole does appear to have a slightly faster onset of symptom relief in acute disease at these doses.

At least three reported studies compare pantoprazole 40 mg with omeprazole 20 mg, and none show a significant difference in healing rates or symptom relief.<sup>87–89</sup>

A recent European study comparing rabeprazole 20 mg and omeprazole 20 mg in active duodenal ulcer recorded similar healing rates of 69% and 62% at 2 weeks and 98% and 93%, respectively, at 4 weeks. Rabeprazole-treated patients had significantly greater

improvement in daytime pain symptom relief than those treated with omeprazole.<sup>90</sup>

In peptic ulcer disease, there appears to be a modest advantage in using lansoprazole 30 mg or pantoprazole 40 mg over omeprazole 20 mg for healing of gastric ulceration. With regard to symptom relief, some studies in patients with gastric or duodenal ulceration show an advantage for lansoprazole 30 mg and rabeprazole 20 mg when compared with omeprazole 20 mg, but there is little overall difference in duodenal ulcer healing rates. Pantoprazole 40 mg and omeprazole 20 mg have very similar efficacy in duodenal ulcer healing.

*Helicobacter pylori eradication.* Proton pump inhibitors have been used successfully in triple therapy regimens for the eradication of *Helicobacter pylori*. Interestingly, the proton pump inhibitors possess intrinsic antibacterial activity *in vitro*, with lansoprazole displaying the greatest bactericidal activity, followed by omeprazole then pantoprazole.<sup>91</sup> However, it is believed that this intrinsic antibacterial effect is of minor, if any, importance in the triple therapies and that the primary effect of the proton pump inhibitors relates to elevation of gastric pH which improves the efficacy of the antibiotics.

The use of proton pump inhibitors in triple therapy regimens has been reviewed.<sup>92–93</sup> Of nine trials comparing omeprazole with lansoprazole, three favoured lansoprazole, two favoured omeprazole, and four trials favoured neither agent. Overall, regimens containing lansoprazole appear to be similar to those containing omeprazole, in achieving *H. pylori* eradication.<sup>92–96</sup>

Fewer studies directly compare pantoprazole with the other proton pump inhibitors for *H. pylori* eradication. In one study of 278 patients treated with clarithromycin, amoxycillin and either omeprazole, lansoprazole or pantoprazole, there was no significant difference in eradication rates although a trend for better results was observed with the omeprazole regimen.<sup>97</sup>

Rabeprazole 20 mg b.d. has recently been compared with omeprazole 20 mg b.d. and lansoprazole 30 mg b.d. in 1-week triple therapy regimens, with cure rates of 88%, 85% and 84%, respectively.<sup>98</sup> In a recent review of 1-week triple therapy regimens, it was concluded that there was no significance between different proton pump inhibitor-based regimens.<sup>93</sup>

At present there is no evidence to indicate a clinically significant difference in *H. pylori* eradication rates when different proton pump inhibitors are used in triple therapy regimens.

#### *Non-ulcer dyspepsia*

One study has compared lansoprazole 15 mg/day with omeprazole 10 mg for the treatment of non-ulcer dyspepsia in a general practice setting.<sup>99</sup> Lansoprazole provided significantly better relief of overall primary symptoms at 2 weeks than omeprazole. Whilst the trend for symptom relief continued to favour lansoprazole at 4 weeks, the difference was not significant, although antacid usage remained significantly lower in the lansoprazole group.

#### ADVERSE EFFECTS

Common adverse effects reported for all proton pump inhibitors include headache, diarrhoea, rash, nausea, and constipation, with incidences of 1–3%.<sup>4, 12, 92, 100, 101</sup> Minor increases in aspartate transaminase (AST) and alanine transaminase (ALT) have also been reported. In most studies, the withdrawal rate because of adverse effects was 1–2%. Overall, most studies report no significant differences between the proton pump inhibitors.

Serious adverse effects are very uncommon with the proton pump inhibitors, but there are reports of hepatitis associated with omeprazole and lansoprazole, and interstitial nephritis with omeprazole.<sup>102–104</sup> Visual disturbance has been associated with the use of high dose parenteral omeprazole, and there is one report of this occurring with oral pantoprazole.<sup>105</sup> However, the strength of this association has been debated, and the higher number of reports of visual disturbance with omeprazole compared with the other proton pump inhibitors may simply reflect greater omeprazole usage.<sup>106</sup> The results from one large cohort study failed to show a major increased risk for ocular disorders associated with the use of omeprazole or other anti-ulcer drugs.<sup>107</sup>

Owing to their potent antisecretory properties, proton pump inhibitors are associated with moderate dose-related rises (two to fourfold) in serum gastrin concentration.<sup>10, 108</sup> The magnitude of the rise is similar for all the proton pump inhibitors in standard doses, although in one study the gastrin output was slightly lower with

pantoprazole than omeprazole, and in another study it was higher with lansoprazole than omeprazole 5 and 10 min after a meal.<sup>54, 61, 108</sup> Rabeprazole use resulted in significantly greater plasma gastrin levels compared with an equivalent dose of omeprazole in one study.<sup>5</sup> The potential for possible long-term consequences from sustained hypergastrinaemia has been the subject of recent debate.<sup>109–110</sup> The greatest experience to date is with omeprazole, which has been given for up to 11 years in some patients; some caution is still advised when life long proton pump inhibitor treatment is being considered.

## CONCLUSIONS

The proton pump inhibitors have a common mechanism of action, but pantoprazole and rabeprazole have greater selectivity for the cysteine 813/822 sites of the proton pump. Rabeprazole converts rapidly to the activated sulphenamide form and dissociates more readily from the H<sup>+</sup>K<sup>+</sup>-ATPase than the other drugs, resulting in a faster rate of inhibition and shorter duration of action. All proton pump inhibitors have short half-lives and good oral bioavailability. Omeprazole demonstrates an increase in bioavailability with repeated administration.

All proton pump inhibitors are metabolized by CYPs 2C19 and 3A4. Pantoprazole has a lower affinity to the P450 enzymes and is also metabolized by a sulphotransferase. No significant interactions have been reported for pantoprazole. Omeprazole and lansoprazole may induce CYPs 1A1 and 1A2, and omeprazole may inhibit CYP 2C19, resulting in some drug interactions. The absorption of other drugs may be altered by changes in gastric pH. Hepatic impairment and old age reduce clearance of the proton pump inhibitors, but renal impairment has little significant effect.

Acid suppression studies comparing omeprazole and lansoprazole, and omeprazole and pantoprazole suggest equivalent potency. In other studies, lansoprazole 30 mg resulted in greater acid suppression than pantoprazole 40 mg and rabeprazole gave greater acid suppression than omeprazole. Lansoprazole and rabeprazole display a more rapid onset of maximal acid suppression than the other proton pump inhibitors.

Most studies have not shown a significant difference between the four proton pump inhibitors used in standard doses for the healing of reflux oesophagitis or

duodenal ulcer. However, trends for earlier symptom relief from oesophagitis and more rapid healing of duodenal ulcers were seen with lansoprazole. The few reported studies of proton pump inhibitor use in gastric ulcer healing suggest that there may be an advantage in using the proton pump inhibitors that have a higher standard dose. In addition, however, rabeprazole gave better symptomatic relief than omeprazole in the same dose in several studies of peptic ulcer treatment. *H. pylori* eradication rates are similar when the different proton pump inhibitors are used in triple therapy regimens.

## REFERENCES

- 1 Sachs G, Shin JM, Briving C, *et al.* The pharmacology of the gastric acid pump: the H<sup>+</sup>,K<sup>+</sup> ATPase. *Annu Rev Pharmacol Toxicol* 1995; 35: 277–305.
- 2 Huber R, Kohl B, Sachs G, *et al.* Review article: the continuing development of proton pump inhibitors with particular reference to pantoprazole. *Aliment Pharmacol Ther* 1995; 9: 363–78.
- 3 Sachs G, Shin JM, Besancon M, *et al.* The continuing development of gastric acid pump inhibitors. *Aliment Pharmacol Ther* 1993; 7(Suppl. 1): 4–12.
- 4 Prakash A, Faulds D. Rabeprazole. *Drugs* 1998; 55: 261–7.
- 5 Williams MP, Sercombe J, Hamilton MI, *et al.* A placebo-controlled trial of the effects of 8 days of dosing with rabeprazole versus omeprazole on 24-h intragastric acidity and plasma gastrin concentrations in young healthy male subjects. *Aliment Pharmacol Ther* 1998; 12: 1079–89.
- 6 Parsons ME. Pantoprazole, a new proton-pump inhibitor, has a precise and predictable profile of activity. *Eur J Gastroenterol Hepatol* 1996; 8(Suppl. 1): S15–20.
- 7 Andersson T, Andren K, Cederberg C, *et al.* Pharmacokinetics and bioavailability of omeprazole after single and repeated oral administration in healthy subjects. *Br J Clin Pharmacol* 1990; 29: 557–63.
- 8 Delhotal-Landes B, Petite JP, Flouvat B. Clinical pharmacokinetics of lansoprazole. *Clin Pharmacokinet* 1995; 28: 458–70.
- 9 Besancon M, Simon A, Sachs G, *et al.* Sites of reaction of the gastric H, K-ATPase with extracytoplasmic thiol reagents. *J Biol Chem* 1997; 272: 22 438–46.
- 10 Tolman KG, Sanders SW, Buchi KN, *et al.* The effects of oral doses of lansoprazole and omeprazole on gastric pH. *J Clin Gastroenterol* 1997; 24: 65–70.
- 11 Huber R, Hartmann M, Bliesath H, *et al.* Pharmacokinetics of pantoprazole in man. *Int J Clin Pharmacol Therapeut* 1996; 34: 185–94.
- 12 Spencer CM, Faulds D. Lansoprazole. A reappraisal of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy in acid-related disorders. *Drugs* 1994; 48: 404–30.

- 13 Gerloff J, Mignot A, Barth H, *et al.* Pharmacokinetics and absolute bioavailability of lansoprazole. *Eur J Clin Pharmacol* 1996; 50: 293–7.
- 14 Reill L, Erhardt F, Heinzerling H, *et al.* Dose–response of pantoprazole 20, 40 and 80 mg on 24-hour intragastric pH, serum pantoprazole and serum gastrin in man. *Gastroenterology* 1994; 106(Suppl.): A165(Abstract).
- 15 Benet LZ, Zech K. Pharmacokinetics—a relevant factor for the choice of a drug? *Aliment Pharmacol Ther* 1994; 8(Suppl. 1): 25–32.
- 16 Blum RA. Lansoprazole and omeprazole in the treatment of acid peptic disorders. *Am J Health-Syst Pharm* 1996; 53: 1401–15.
- 17 Brummer R-JM, Geerling BJ, Stockbrugger RW. Initial and chronic gastric acid inhibition by lansoprazole and omeprazole in relation to meal administration. *Dig Dis Sci* 1997; 42: 2132–7.
- 18 Andersson T. Pharmacokinetics, metabolism and interactions of acid pump inhibitors. Focus on omeprazole, lansoprazole and pantoprazole. *Clin Pharmacokinet* 1996; 31: 9–28.
- 19 Steinijans VW, Huber R, Hartmann M, *et al.* Lack of pantoprazole drug interactions in man: an updated review. *Int J Clin Pharmacol Therapeut* 1996; 34(Suppl. 1): S31–50.
- 20 Delhotal-Landes B, Flouvat B, Duchier J, *et al.* Pharmacokinetics of lansoprazole in patients with renal or liver disease of varying severity. *Eur J Clin Pharmacol* 1993; 45: 367–71.
- 21 Naesdal J, Andersson T, Bodemar G, *et al.* Pharmacokinetics of [ $^{14}\text{C}$ ] omeprazole in patients with impaired renal function. *Clin Pharmacol Ther* 1986; 40: 344–51.
- 22 Lins RL, De Clercq I, Hartmann M, *et al.* Pharmacokinetics of the proton pump inhibitor pantoprazole in patients with severe renal impairment. *Gastroenterology* 1994; 106: A126(Abstract).
- 23 Danz-Neeff H, Brunner G. Comparative kinetic studies with the three proton pump inhibitors omeprazole, lansoprazole and pantoprazole in patients with complete liver cirrhosis. *Gastroenterology* 1996; 110: A90(Abstract).
- 24 Hoyumpa AM, Trevino-Alanis H, Grimes I, *et al.* Rabeprazole: pharmacokinetics in patients with stable, compensated cirrhosis. *Clin Ther* 1999; 21: 691–701.
- 25 Flouvat B, Delhotal-Landes B, Cournot A, *et al.* Single and multiple dose pharmacokinetics of lansoprazole in elderly subjects. *Br J Clin Pharmacol* 1993; 36: 467–9.
- 26 Breuel HP, Hartmann M, Bondy S, *et al.* Pantoprazole in the elderly: no dose-adjustment. *Gut* 1994; 35(Suppl. 4): A77(Abstract).
- 27 Andersson T, Regardh C-G, Dahl-Puustinen ML. Slow omeprazole metabolisers are also poor S-mephenytoin hydroxylators. *Ther Drug Monit* 1990; 12: 415–6.
- 28 Sohn MD, Kwon J-T, Kim H-K. Influence of S-mephenytoin phenotype on the lansoprazole metabolism. *Clin Pharmacol Ther* 1996; 59: 137(Abstract).
- 29 Tucker GT. The interaction of proton pump inhibitors with cytochromes P450. *Aliment Pharmacol Ther* 1994; 8(Suppl. 1): 33–8.
- 30 Unge P, Andersson T. Drug interactions with proton pump inhibitors. *Drug Safety* 1997; 16: 171–9.
- 31 Meyer UA. Interaction of proton pump inhibitors with cytochrome P450: consequences for drug interactions. *Yale J Biol Med* 1996; 69: 203–9.
- 32 Andersson T, Miners JO, Veronese ME, *et al.* Identification of human liver cytochrome P450 isoforms mediating omeprazole metabolism. *Br J Clin Pharmacol* 1993; 36: 521–30.
- 33 Curi-Pedrosa R, Pichard L, Bonfils C, *et al.* Major implication of cytochrome P4503A4 in the oxidative metabolism of the antisecretory drugs omeprazole and lansoprazole in human liver microsomes and hepatocytes. *Br J Clin Pharmacol* 1993; 36: 156P.
- 34 Kromer S, Postius R, Riedal WA, *et al.* BY 1023/SK & F 96022 INN pantoprazole, a novel gastric proton pump inhibitor, potently inhibits acid secretion but lacks relevant cytochrome P450 interactions. *J Pharmacol Exp Ther* 1990; 254: 129–35.
- 35 Simon WA, Budingen C, Fahr S, *et al.* The  $\text{H}^+/\text{K}^+$ -ATPase inhibitor pantoprazole (BY1023/SK & F96022) interacts less with cytochrome P450 than omeprazole and lansoprazole. *Biochem Pharmacol* 1991; 42: 347–55.
- 36 Meyer UA. Metabolic interactions of the proton-pump inhibitors lansoprazole, omeprazole and pantoprazole with other drugs. *Eur J Gastroenterol Hepatol* 1996; 8(Suppl. 1): S21–5.
- 37 Kokufu T, Ihara N, Sugioka N, *et al.* Effects of lansoprazole on pharmacokinetics and metabolism of theophylline. *Eur J Clin Pharmacol* 1995; 48: 391–5.
- 38 Granneman G, Winters EP, Locke CS, *et al.* Lack of effect of concomitant lansoprazole on steady-state theophylline pharmacokinetics. *Gastroenterology* 1991; 100: A75(Abstract).
- 39 Rost KL, Roots I. Accelerated caffeine metabolism after omeprazole treatment is indicated by urinary metabolite ratios: coincidence with plasma clearance and breath test. *Clin Pharmacol Ther* 1994; 55: 402–11.
- 40 Rizzo N, Padoin C, Palombo S, *et al.* Omeprazole and lansoprazole are not inducers of cytochrome P4501A2 under conventional therapeutic conditions. *Eur J Clin Pharmacol* 1996; 49: 491–5.
- 41 Rost KL, Brosicke H, Brockmoller J, *et al.* Increase of cytochrome P4501A2 activity by omeprazole: evidence by the  $^{13}\text{C}$ -[N-3-methyl]-caffeine breath test in poor and extensive metabolizers of S-mephenytoin. *Clin Pharmacol Ther* 1992; 52: 170–80.
- 42 Andersson T, Bergstrand R, Cederberg C, *et al.* Omeprazole treatment does not affect the metabolism of caffeine. *Gastroenterology* 1991; 101: 943–7.
- 43 Humphries TJ, Nardi RV, Spera AC, *et al.* Coadministration of rabeprazole sodium (E3810) does not effect the pharmacokinetics of anhydrous theophylline or warfarin. *Gastroenterology* 1996; 110: A138(Abstract).
- 44 Gugler R, Jensen JC. Omeprazole inhibits oxidative drug metabolism. Studies with diazepam and phenytoin *in vivo* and 7-ethoxycoumarin *in vitro*. *Gastroenterology* 1985; 89: 1235–41.
- 45 Prichard PJ, Walt RP, Kitchingman GK, *et al.* Oral phenytoin pharmacokinetics during omeprazole therapy. *Br J Clin Pharmacol* 1987; 24: 543–5.

- 46 Lefebvre RA, Flouvat B, Karolac-Tamisier S, *et al.* Influence of lansoprazole treatment on diazepam plasma concentrations. *Clin Pharmacol Ther* 1992; 52: 458–63.
- 47 Steinijans VW, Huber R, Hartmann M, *et al.* Lack of pantoprazole drug interactions in man. *Int J Clin Pharmacol Ther* 1994; 32: 385–99.
- 48 Gugler R, Hartmann M, Rudi J, *et al.* Lack of interaction of pantoprazole and diazepam in man. *Gastroenterology* 1992; 102: A77(Abstract).
- 49 Humphries TJ, Spera AC, Laurent AL, *et al.* Rabeprazole sodium (E3810), 20 mg daily does not affect the pharmacokinetics of phenytoin sodium in normal volunteers. *Am J Gastroenterol* 1996; 91: 1914(Abstract).
- 50 Oosterhuis B, Jonkman JHG, Andersson T, *et al.* Minor effect of multiple dose omeprazole on the pharmacokinetics of digoxin after a single oral dose. *Br J Clin Pharmacol* 1991; 32: 569–72.
- 51 Humphries TJ, Spera AC, Laurent AL, *et al.* Coadministration of rabeprazole sodium (E3810) and digoxin results in a predictable interaction. *Am J Gastroenterol* 1996; 91: 1914(Abstract).
- 52 Humphries TJ, Nardi RV, Spera AC, *et al.* Coadministration of rabeprazole sodium (E3810) and ketoconazole results in a predictable interaction with ketoconazole. *Gastroenterology* 1996; 110: A138(Abstract).
- 53 Bell NJV, Burget D, Howden CW, *et al.* Appropriate acid suppression for the management of gastroesophageal reflux disease. *Digestion* 1992; 51(Suppl. 1): 59–67.
- 54 Bruley Des Varannes S, Levy P, Lartigue S, *et al.* Comparison of lansoprazole with omeprazole on 24-hour intragastric pH, acid secretion and serum gastrin in healthy volunteers. *Aliment Pharmacol Ther* 1994; 8: 309–14.
- 55 Blum RA, Shi H, Karol MD, *et al.* The comparative effects of lansoprazole, omeprazole and ranitidine in suppressing gastric acid secretion. *Clin Ther* 1997; 19: 1013–23.
- 56 Verdu EF, Fraser R, Armstrong D, *et al.* Effects of omeprazole and lansoprazole on 24-hour intragastric pH in *Helicobacter pylori*-positive volunteers. *Scand J Gastroenterol* 1994; 29: 1065–9.
- 57 Geus WP, Mulder PG, Nicolai JJ, *et al.* Acid-inhibitory effects of omeprazole and lansoprazole in *Helicobacter pylori*-negative healthy subjects. *Aliment Pharmacol Ther* 1998; 12: 329–35.
- 58 Seennsalu R, Iwarzon M, Janczewska I, *et al.* Dose–response comparison of lansoprazole and omeprazole on 24-hour gastric acidity and plasma gastrin in healthy volunteers. *Gastroenterology* 1995; 108: A215(Abstract).
- 59 Timmer W, Ripke H, Kleist P, *et al.* Effect of four lansoprazole dose levels and one dosage regimen of omeprazole on 24-hour intragastric pH in healthy subjects. *Meth Find Exp Clin Pharmacol* 1995; 17: 489–95.
- 60 Brunner G, Danz-Neeff H, Athmann N, *et al.* Comparison of pantoprazole (40 mg SID) versus omeprazole (40 mg SID) on intragastric pH and serum gastrin in healthy volunteers. *Can J Gastroenterol* 1997; 11(Suppl. A): S2.
- 61 Koop H, Kuly S, Flug M, *et al.* Comparison of 24-h intragastric pH and 24-h gastrin profiles during therapy with the proton pump inhibitors pantoprazole and omeprazole. *Gut* 1994; 35(Suppl. 4): A79(Abstract).
- 62 Hartmann M, Theiss U, Huber R, *et al.* Twenty-four-hour intragastric pH profiles and pharmacokinetics following single and repeated oral administration of the proton pump inhibitor pantoprazole in comparison to omeprazole. *Aliment Pharmacol Ther* 1996; 10: 359–66.
- 63 Florent C, Forestier S. Twenty-four-hour monitoring of intragastric acidity: comparison between lansoprazole 30 mg and pantoprazole 40 mg. *Eur J Gastroenterol Hepatol* 1997; 9: 195–200.
- 64 Scholtz HE, Meyer BH, Luus HG. Comparison of the effects of lansoprazole, omeprazole and pantoprazole on 24-hour gastric pH in healthy males. *SA Med J* 1995; 85: 915(Abstract).
- 65 Vcev A, Stimac D, Vceva A, *et al.* Lansoprazole versus omeprazole in the treatment of reflux esophagitis. *Acta Med Croatica* 1997; 51: 171–4.
- 66 Castell DO, Richter JE, Robinson M, *et al.* Efficacy and safety of lansoprazole in the treatment of erosive reflux esophagitis. *Am J Gastroenterol* 1996; 91: 1749–57.
- 67 Corallo J, Vicari F, Forestier S, *et al.* Lansoprazole in acute treatment of reflux esophagitis. *Gastroenterology* 1993; 104: A58(Abstract).
- 68 Hatlebakk JG, Berstad A, Carling L, *et al.* Lansoprazole versus omeprazole in short-term treatment of reflux oesophagitis. *Scand J Gastroenterol* 1993; 28: 224–8.
- 69 Mee AS, Rowley JL, the Lansoprazole Clinical Research Group. Rapid symptom relief in reflux oesophagitis: a comparison of lansoprazole and omeprazole. *Aliment Pharmacol Ther* 1996; 10: 757–63.
- 70 Cordova-Villabos JA, Ramirez-Barba EJ, Ramirez-Covarrubias JC. Reflux esophagitis: a comparative study of lansoprazole and omeprazole as short-term therapy. Preliminary report. *Revista Gastroenterol Mexico* 1996; 61: 306–9.
- 71 Sekiguchi T, Horikoshi T, Nishioka T, *et al.* Clinical effect of proton pump inhibitors on oesophagitis [in Japanese]. *Nipp Rinsho* 1992; 50: 131–7.
- 72 Mulder CJ, Dekker W, Gerretsen M. Lansoprazole 30 mg versus omeprazole 40 mg in the treatment of reflux oesophagitis grade II, III and IVa (a Dutch multicenter trial). *Eur J Gastroenterol Hepatol* 1996; 8: 1101–6.
- 73 Corinaldesi R, Valentini M, Belaiche J, *et al.* Pantoprazole and omeprazole in the treatment of reflux oesophagitis: a European multicenter study. *Aliment Pharmacol Ther* 1995; 9: 667–71.
- 74 Hotz J, Gangl A, Heinzerling H. Pantoprazole vs omeprazole in acute reflux esophagitis. *Gastroenterology* 1996; 110: A136(Abstract).
- 75 Mossner J, Holscher AH, Herz R, *et al.* A double-blind study of pantoprazole and omeprazole in the treatment of reflux oesophagitis: a multicentre trial. *Aliment Pharmacol Ther* 1995; 9: 321–6.
- 76 Dekkers CPM, Beker JA, Thjodleifsson B, *et al.* Double-blind, placebo-controlled comparison of rabeprazole 20 mg vs omeprazole 20 mg in the treatment of erosive or ulcerative gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1999; 13: 49–57.

- 77 Carling L, Axelsson CK, Forssell H, *et al.* Lansoprazole and omeprazole in the prevention of relapse of reflux oesophagitis: a long-term comparative study. *Aliment Pharmacol Ther* 1998; 12: 985–90.
- 78 Jaspersen D, Diehl KL, Schoeppner H, *et al.* A comparison of omeprazole, lansoprazole and pantoprazole in maintenance treatment of severe reflux oesophagitis. *Aliment Pharmacol Ther* 1998; 12: 49–52.
- 79 Florent C, Audigier JC, Boyer J, *et al.* Efficacy and safety of lansoprazole in the treatment of gastric ulcer: a multicentre study. *Eur J Gastroenterol Hepatol* 1994; 6: 1135–9.
- 80 Witzel L, Gutz H, Huttemann W, *et al.* Pantoprazole versus omeprazole in the treatment of acute gastric ulcers. *Aliment Pharmacol Ther* 1995; 9: 19–24.
- 81 Dekkers CPM, Beker JA, Thjodleifsson B, *et al.* Comparison of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of gastric ulcer—a European multicentre study. *Aliment Pharmacol Ther* 1998; 12: 789–95.
- 82 Chang F-Y, Chiang C-Y, Tam T-N, *et al.* Comparison of lansoprazole and omeprazole in the short-term management of duodenal ulcers in Taiwan. *J Gastroenterol Hepatol* 1995; 10: 595–601.
- 83 Dobrilla G, Piazzzi L, Fiocca R. Lansoprazole versus omeprazole for duodenal ulcer healing and prevention of relapse: a randomized, multicenter, double-masked trial. *Clin Ther* 1999; 21: 1321–32.
- 84 Ekstrom P, Carling L, Unge P, *et al.* Lansoprazole versus omeprazole in active duodenal ulcer. *Scand J Gastroenterol* 1995; 30: 210–5.
- 85 Petite J-P, Slama J-L, Licht H, *et al.* Comparison of lansoprazole (30 mg) and omeprazole (20 mg) in the treatment of duodenal ulcer. *Gastroenterol Clin Biol* 1993; 17: 334–40.
- 86 Louw JA, van Rensburg C, Simjee AE, *et al.* Lansoprazole versus omeprazole in duodenal ulcer healing. *Safr Med J* 1993; 83: 777.
- 87 Beker JA, Porro GB, Bigard M-A, *et al.* Double-blind comparison of pantoprazole and omeprazole for the treatment of acute duodenal ulcer. *Eur J Gastroenterol Hepatol* 1995; 7: 407–10.
- 88 Rehner M, Rohner HG, Schepp W. Comparison of pantoprazole versus omeprazole in the treatment of acute duodenal ulceration—a multicentre study. *Aliment Pharmacol Ther* 1995; 9: 411–6.
- 89 Italian Group for the Study of Pantoprazole. Efficacy and tolerability of pantoprazole vs omeprazole in the treatment of duodenal ulcer. *Argument Gastroenterol Clin* 1994; 7: 271–5.
- 90 Dekkers CPM, Beker JA, Thjodleifsson B, *et al.* Comparison of rabeprazole 20 mg versus omeprazole 20 mg in the treatment of active duodenal ulcer: a European multicentre study. *Aliment Pharmacol Ther* 1999; 13: 179–86.
- 91 Dattilo M, Figura N. *Helicobacter pylori* infection, chronic gastritis, and proton pump inhibitors. *J Clin Gastroenterol* 1998; 27(Suppl. 1): S163–9.
- 92 Langtry HD, Wilde MI. Lansoprazole. An update of its pharmacological properties and clinical efficacy in the management of acid-related disorders. *Drugs* 1997; 54: 473–500.
- 93 Pipkin GA, Williamson R, Wood JR. One-week clarithromycin triple therapy regimens for eradication of *Helicobacter pylori*. *Aliment Pharmacol Ther* 1998; 12: 823–37.
- 94 Mullhaupt B, Fluckiger T, Frohli P, *et al.* One week low dose triple therapies with lansoprazole or omeprazole are equally effective for *H pylori* eradication and ulcer healing. *Gastroenterology* 1996; 110: A202(Abtract).
- 95 Spinzi GC, Berti L, Bortoli A, *et al.* Comparison of omeprazole and lansoprazole in short-term triple therapy for *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 1998; 12: 433–8.
- 96 Catalano F, Privitera U, Branciforte G, *et al.* Omeprazole vs. two different doses of lansoprazole in triple therapy on *H. pylori* positive duodenal ulcer. *Gut* 1996; 39(Suppl. 2): A32(Abtract).
- 97 Rinaldi V, Zullo A, De Francesco V, *et al.* *Helicobacter pylori* eradication with proton pump inhibitor-based triple therapies and re-treatment with ranitidine bismuth citrate-based triple therapy. *Aliment Pharmacol Ther* 1999; 13: 163–8.
- 98 Miwa H, Ohkura R, Murai T, *et al.* Impact of rabeprazole, a new proton pump inhibitor, in triple therapy for *Helicobacter pylori* infection—comparison with omeprazole and lansoprazole. *Aliment Pharmacol Ther* 1999; 13: 741–6.
- 99 Jones R, Crouch SL. Low-dose lansoprazole provides greater relief of heartburn and epigastric pain than low-dose omeprazole in patients with acid-related dyspepsia. *Aliment Pharmacol Ther* 1999; 13: 413–9.
- 100 Wilde MI, McTavish D. Omeprazole. An update on its pharmacology and therapeutic use in acid-related disorders. *Drugs* 1994; 48: 91–132.
- 101 Fitton A, Wiseman L. Pantoprazole. A review of its pharmacological properties and therapeutic use in acid-related disorders. *Drugs* 1996; 51: 460–82.
- 102 Koury SI, Stone CK, La Charite DD. Omeprazole and the development of acute hepatitis. *Eur J Emerg Med* 1998; 5: 467–9.
- 103 Viana de Miguel C, Alvarez Garcia M, Sanchez Sanchez A, *et al.* Lansoprazole-induced hepatitis [in Spanish]. *Med Clin (Barc)* 1997; 108: 599.
- 104 Yip D, Kovac S, Jardine M, *et al.* Omeprazole-induced interstitial nephritis. *J Clin Gastroenterol* 1997; 25: 450–2.
- 105 Schonhofer PS, Werner B. Ocular damage associated with proton pump inhibitors. *Br Med J* 1997; 314: 1805.
- 106 Lessell S. Omeprazole and ocular damage. Concerns on safety of drug are unwarranted. *Br Med J* 1998; 316: 67.
- 107 Garcia Rodriguez LA, Mannino S, Wallander MA, *et al.* A cohort study of the ocular safety of anti-ulcer drugs. *Br J Clin Pharmacol* 1996; 42: 213–6.
- 108 Londong W. Effect of pantoprazole on 24-h intragastric pH and serum gastrin in humans. *Aliment Pharmacol Ther* 1994; 8(Suppl. 1): 39–46.
- 109 Yeomans ND, Dent J. Personal review: alarmism or legitimate concerns about long-term suppression of gastric acid secretion? *Aliment Pharmacol Ther* 2000; 14: 267–271.

- 110 Waldum HL, Brenna E. Personal review: is profound acid inhibition safe? *Aliment Pharmacol Ther* 2000; 14: 15–22.
- 111 Yasuda S, Ohnishi A, Ogawa T, *et al.* Pharmacokinetic properties of E3810, a new proton pump inhibitor, in healthy male volunteers. *Int J Clin Pharmacol Ther* 1994; 32: 466–73.
- 112 Zomorodi K, Houston JB. Diazepam–omeprazole inhibition interaction: an in vitro investigation using human liver microsomes. *Br J Clin Pharmacol* 1996; 42: 157–62.
- 113 Dammann HG, Fuchs W, Richter G, *et al.* Lansoprazole versus omeprazole: influence on meal-stimulated gastric acid secretion. *Aliment Pharmacol Ther* 1997; 11: 359–64.