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

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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.[1] They thereby inhibit both basal and stimulated secretion of gastric acid, independently of the nature of parietal cell stimulation.[1–2] 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.

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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-

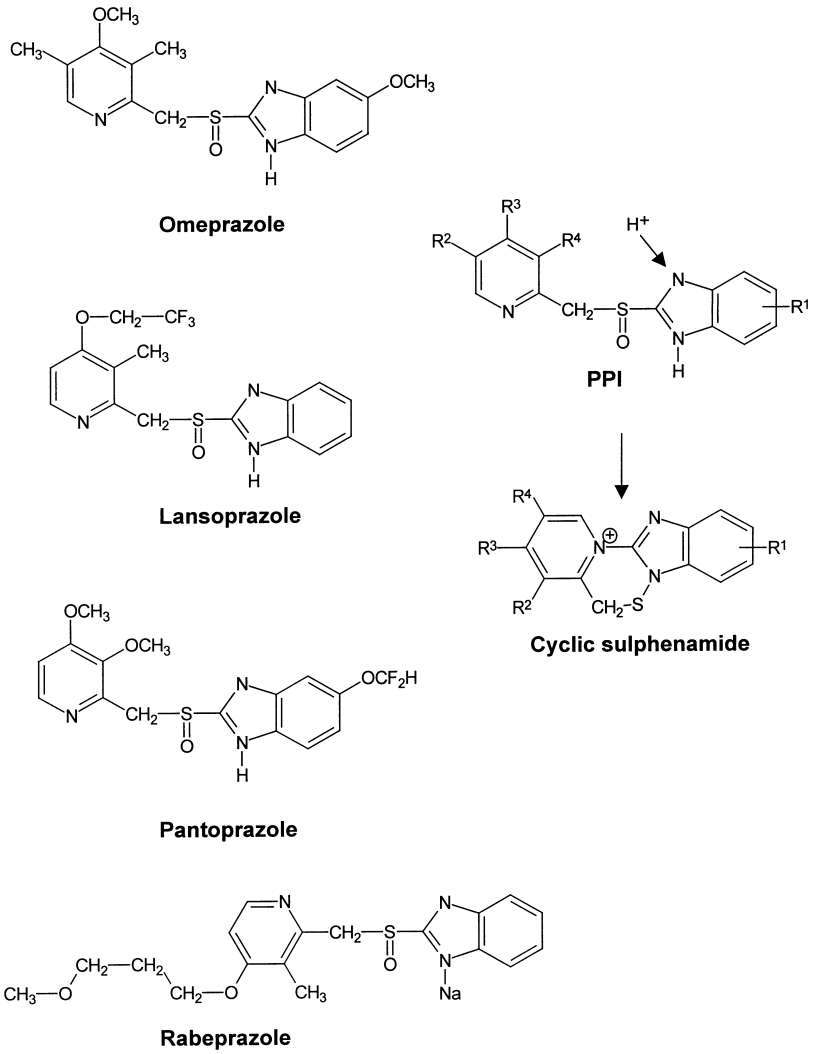

Figure 1. Structural formulae of the proton pump inhibitors omeprazole, lansoprazole, pantoprazole and rabeprazole and the tetracyclic sulphenamide to which they are converted in the parietal cell canaliculus after protonation.

clic planar sulphenamide occurs (Figure 1).[3] The sulphenamide then binds covalently to key cysteine groups on the proton pump to cause prolonged inhibition of gastric acid secretion.[1–2] Acid production by the proton pump can generally only be restored through endogenous synthesis of the H^+K^+-exchanging ATPase, which has a half-life of production of approximately 50 h.[1] 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^+K^+-ATPase, resulting in both a faster rate of inhibition and also a shorter duration of action.[4–5]

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.[1–3] 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.[2] The pK for the N of the benzimidazole rings are all much lower.[1] 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.[5–6] The conversion rate from the pro-drug to the active sulphenamide is slower for pantoprazole.[1, 2]

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.[1] 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.[7–8]

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.[9] Pantoprazole has greater selectivity for the cysteine 813/822 sites, but the clinical significance of these differences is unclear.[1–2]

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.[8] 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 (0.2–1.2 $\mu g \cdot h/mL$) and rabeprazole 20 mg (0.8 $\mu g \cdot h/mL$) or 40 mg (1.0 $\mu g \cdot h/mL$) are significantly lower than for pantoprazole 20 mg (2 $\mu g \cdot h/mL$) or 40 mg (4.6–4.9 $\mu g \cdot h/mL$), or lansoprazole 30 mg (1.7–5 $\mu g \cdot h/mL$).[8, 11–12]

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.[8–11, 13] However, the duration of acid inhibition is relatively long (48–72 h) because of the irreversible binding of the sulphenamide to the H^+K^+-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[a] 20 mg	Pantoprazole[b] 40 mg	Lansoprazole[c] 30 mg	Rabeprazole[d] 20 mg
AUC ($\mu g \cdot h/mL$)	0.2–1.2	2–5	1.7–5	0.8
C_{max} ($\mu g/mL$)	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 ($L \cdot h/kg$)	0.45	0.08–0.13	0.2–0.28	0.50
Vd (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: [a] 2, 7, 10, 15, 16, 18, 27, 62; [b] 2, 6, 11, 15, 101; [c] 2, 8, 10, 12, 13, 16, 92; [d] 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.[7, 10] 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.[11] 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.[8, 13]

For pantoprazole and rabeprazole, there is a linear relationship between dose and plasma concentrations after the administration of single and multiple doses.[5, 11, 14, 15] For omeprazole the kinetics are dose-dependent, with non-linear increases in maximal plasma drug concentration occurring with increasing doses.[7] 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.[8]

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.[8, 12, 16, 17] Similar effects have been seen with omeprazole and pantoprazole, but these have been of borderline significance.[15] 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.[8, 18, 19]

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.[11, 20–22] 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.[20–24] 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.[11, 25] Drug clearance is reduced with increasing age and the half-life of elimination increases to approximately 1.5 h in the elderly.[11, 26]

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[a]	Pantoprazole[b]	Lansoprazole[c]	Rabeprazole[d]
Food-effect on absorption	Minimal	Minimal	Delayed absorption, $\downarrow C_{max}$, $\downarrow$F (some studies)	Minimal
Concurrent antacid use	No change	No change	Conflicting results	—
Renal impairment	No change	Conflicting results	Conflicting results	—
Hepatic impairment	$\uparrow AUC$ +++ $\uparrow t_{1/2}$ +++	$\uparrow AUC$ +++ $\uparrow t_{1/2}$ +++	$\uparrow AUC$ +++ $\uparrow t_{1/2}$ +++	$\uparrow AUC$ + $\uparrow t_{1/2}$ +
Elderly	$\downarrow$Cl $\uparrow AUC$, $\uparrow t_{1/2}$	$\downarrow$Cl $\uparrow AUC$	$\downarrow$Cl $\uparrow AUC$, $\uparrow t_{1/2}$	—

Data from References: [a] 6, 16, 18, 23; [b] 6, 11, 15, 18, 19, 22, 23, 26, 62, 92, 101; [c] 6, 8, 12, 16, 17, 20, 23, 25, 92; [d] 24, 111.
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; (–), not tested; (+), small change; (+++), large change.

proton pump inhibitor normal and poor metabolizers, suggesting that metabolism is via CYP 2C19.[4, 27–29]

Cytochrome P450 enzyme metabolism

Proton pump inhibitors are metabolized in the liver by P450 cytochromes and this subject has been reviewed previously.[18, 29–31] 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.[31–33] Lansoprazole is also metabolized by CYPs 2C19 and 3A4, although the relative importance of each enzyme is less clear.[28, 31, 33] 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 metabolized by a sulphotransferase, which is non-saturable and not part of the CYP system.[2, 34–36]

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%).[37–38] 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.[39–42] 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[a]	Lansoprazole[b]	Pantoprazole[c]	Rabeprazole[d]
CYP 1A2				
Theophylline	No interaction	?↑Cl	No interaction	No interaction
Caffeine	↑Cl*	—	No interaction	—
CYP 2C9				
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* (by10%)	—	—	
CYP 2C19				
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
CYP 2D6				
Debrisoquine	No interaction	—	No interaction	—
Propranolol	No interaction	No interaction	—	—
Metoprolol	No interaction	—	No interaction	—
CYP 3A4				
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: [a] 30, 31, 39–42, 44, 45, 112; [b] 18, 30, 31, 37, 38, 40, 46; [c] 18, 19, 30, 31, 47, 48; [d] 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.

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