

Review article: similarities and differences among delayed-release proton-pump inhibitor formulations

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SUMMARY

Proton-pump inhibitors are acid-labile, and require an enteric coating to protect them from degradation in the stomach when given orally. However, this leads to delayed absorption and onset of action of the proton-pump inhibitor.

This article aims to review the similarities and differences between the various formulations of delayed release proton-pump inhibitors. Delayed-release omeprazole and delayed-release lansoprazole have been suspended in sodium bicarbonate for tube administration; however, for omeprazole, absorption is further impaired and antisecretory effects are disappointing. Although such

formulations may be more convenient for clinical use in certain patient groups, absorption of the proton-pump inhibitor is still influenced by residual enteric coating. There are few differences among the currently available delayed-release proton-pump inhibitors with respect to their pharmacodynamic effects during chronic administration. There are minor formulation-based pharmacokinetic differences among these agents, primarily reflected in their bioavailability following the first few doses.

Differences in bioavailability may explain slight differences in the rate of onset of maximal antisecretory effect. However, minor pharmacodynamic and pharmacokinetic differences are not associated with meaningful differences in clinical outcomes.

INTRODUCTION

Proton-pump inhibitors (PPIs) have been very efficacious for the management of a variety of acid-related disorders. However, as PPIs are acid-labile, they need to be protected from the destructive effects of gastric acid when administered orally. Various types of enteric coating have been developed to protect the PPIs, but they all delay PPI absorption and hinder these delayed-release (DR) formulations.

When a DR-PPI enters the stomach, the enteric coating must be destroyed in order for the PPI to be dissolved and then absorbed. Most PPI absorption takes place in the proximal small intestine. Once absorbed,

PPIs circulate widely but are preferentially taken up by parietal cells, particularly when they are actively secreting acid. In the parietal cell, PPIs are excreted via the luminal aspect of the cell into the canalicular space. Therefore, following protonation and conversion to a sulfenamide derivative, the activated PPI molecule binds covalently to cysteine moieties of the membrane-bound H^+,K^+ -ATPase molecule. Although there are differences among the PPIs regarding the cysteine residues to which they bind, these have not been definitively associated with meaningful differences in antisecretory action or clinical outcomes.

ALTERNATIVE DOSE FORMULATIONS FOR ORAL OR NASOGASTRIC (NG) ADMINISTRATION

Although DR-PPIs are usually administered as capsules [omeprazole (OME), lansoprazole, esomeprazole] or

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tablets (pantoprazole, rabeprazole), a variety of alternative oral dosing formulations have been developed for ease of administration in particular patient subgroups. For example, lansoprazole is available as a powder for oral suspension and as lansoprazole orally disintegrating tablet (LODT). LODT is, however, still dependent on an enteric coating on the dispersed granules to protect the lansoprazole from stomach acid degradation. Therefore, the absorption pharmacokinetics of lansoprazole following ingestion of LODT are essentially identical to those following ingestion of the standard capsule formulation.¹ In addition to such specialized formulations, some of the encapsulated DR-PPIs can be administered as non-encapsulated intact enteric-coated granules with certain fluids or mixed with some soft foods. Such administration may make these agents more suitable for some patients with swallowing disorders and for some elderly patients and children, but this is not associated with any acceleration of PPI absorption or onset of antisecretory effect. Some of these reconstituted formulations are suitable for administration through a nasogastric tube. Table 1 contains a list of the various alternative dosing formulations for DR-PPIs.

PER-GASTROSTOMY ADMINISTRATION

Studies have been conducted examining the antisecretory effects of OME^{2, 3} and lansoprazole^{4, 5} when given via gastrostomy tubes. In these experiments, patients with indwelling gastrostomy tubes had 24 h intragastric pH monitoring at baseline and after 7 days of once daily administration of either intact non-encapsulated OME granules in orange juice,² 'simplified omeprazole suspension' (SOS),³ intact non-encapsulated lansoprazole

granules in orange juice⁴ and 'simplified lansoprazole suspension' (SLS).⁵ SOS and SLS are produced by opening a capsule of OME 20 mg or lansoprazole 30 mg, respectively, and dropping the granular contents into 10 mL of 8.4% sodium bicarbonate. The mixtures have to be gently agitated for a few minutes to obtain milky-white suspensions for subsequent tube administration.

Each of the above formulations was found to suppress 24 h intragastric acidity. The degree of acid suppression obtained with intact OME or lansoprazole granules in orange juice and with SLS was similar to what would be expected had the patients ingested capsules of the respective DR-PPIs. However, the level of acid suppression found with SOS was less than would have been expected had the patients been given intact OME capsules.³

For administration of a DR-PPI via a gastrostomy tube, SLS or predisintegrated LODT would be appropriate choices. Administration of intact OME or lansoprazole granules in orange juice (or, potentially, other liquids) is not recommended because of the theoretical risk of tube blockage, although this was not encountered in the studies described above. SOS is not recommended because of poor OME absorption and consequently disappointing antisecretory effects.

Omeprazole absorption from 'simplified omeprazole suspension'

The relative bioavailability of OME from SOS has been found to be less than that of intact capsules.^{6, 7} This likely explains the poorer than expected antisecretory effect seen with per-gastrostomy administration of SOS.² After 5 days of once daily oral dosing with intact OME

Table 1. Different administration options for delayed-release PPIs

Formulations	Lansoprazole	Esomeprazole	Rabeprazole	Pantoprazole	Omeprazole
Capsule or tablets	x	x	x	x	x
Capsule granules sprinkled on selected soft foods	x	x			x
Capsule granules mixed into selected beverages	x				
Capsule granules flushed through a nasogastric tube with apple juice or water, depending on product	x	x			
IV formulation	x	x		x	-†
Packet for oral suspension	x				
Orally disintegrating tablet	x				
Available as OTC preparation					x*

Includes only US FDA approved options.

OTC, over-the-counter; IV, intravenous; PPI, proton-pump inhibitor; FDA, Food and Drug Administration.

*Omeprazole OTC available only as 20 mg formulation.

†IV omeprazole is available in some countries.

20 mg capsules, mean maximum plasma concentration (C_{\max}) increased from 222 to 430 ng/mL ($P < 0.05$) whereas mean C_{\max} only increased from 172 to 198 ng/mL with 5 days of SOS 20 mg (N.S.).⁶ Mean area under the plasma OME concentration/time curve (AUC) increased from 197 to 454 ng·h/mL with 5 days of once daily dosing with intact OME capsules 20 mg ($P < 0.05$), but only increased from 198 to 265 ng·h/mL with repeated doses of SOS 20 mg (N.S.).⁶ Similarly, Song *et al.* found that the OME AUC was higher after intact OME capsules than after SOS and noted the expected increase in AUC after 7 days of dosing with the capsules but not with SOS.⁷ It should be clearly understood that SOS is a different preparation than sodium bicarbonate-containing immediate-release (IR) OME (Zegerid powder for oral suspension; Santarus, Inc., San Diego, CA, USA) powder for oral suspension, which is discussed in detail elsewhere in this supplement.

PHARMACOKINETICS OF DR-PPIs

Table 2 compares the pharmacokinetic properties of currently available DR-PPIs. Rates of absorption after oral ingestion are highly variable for the DR-PPIs; time to achieve maximum plasma concentration (t_{\max}) can be up to 3 h for individual DR-PPIs. Absolute bioavailability is also highly variable within the class of DR-PPIs. For OME and esomeprazole, bioavailability is not maximal after a single oral dose. All PPIs are extensively protein-bound, and all undergo hepatic metabolism. All of the currently available DR-PPIs have a short elimination half-life ($t_{1/2}$) of between 1 and 2 h. Aside from bioavailability in the first few days of oral dosing, there are no substantive differences among currently available DR-PPIs with respect to pharmacokinetics.

PHARMACODYNAMICS OF DR-PPIs

There have been numerous studies comparing the antisecretory effects of DR-PPIs. Typically, these have

been reported as mean or median 24 h pH or suppression of 24 h intragastric acidity expressed as time above a predetermined pH threshold. Gastric pH has been determined either through frequent aspiration of small quantities of gastric juice with *ex vivo* measurement of pH and subsequent titration, or by continuous intragastric pH monitoring using an indwelling pH electrode.

The proportion of time during which intragastric pH can be maintained above 3 has been correlated with the ability of antisecretory drugs to heal duodenal ulcer.⁸ Maintenance of intragastric pH above 4 has been correlated with the ability to heal gastric ulcer^{9, 10} and erosive oesophagitis.¹¹

Using single oral doses of DR-PPIs, Pantoflickova *et al.* reported that 24 h intragastric pH was maintained above 4 for 8.0 h with rabeprazole 20 mg, 7.4 h with lansoprazole 30 mg, 4.9 h with pantoprazole 40 mg, 2.9 h with OME 20 mg and 3.0 h with OME 20 mg multiunit pellet suspension (MUPS).¹² However, different investigators have reported different rank orders for the effects of DR-PPIs on intragastric pH. In five-way crossover study of the effects of 5 days of different DR-PPIs on 24 h intragastric acidity, Miner *et al.* found that esomeprazole 40 mg produced the greatest effect on intragastric pH, maintaining pH >4 for 14.0 h of the 24-h period.¹³ Corresponding results for rabeprazole 20 mg, OME 20 mg, lansoprazole 30 mg and pantoprazole 40 mg were, 12.1, 11.8, 11.5 and 10.1 h, respectively ($P < 0.05$, esomeprazole vs. all other DR-PPIs; Figure 1). Therefore, with the possible exception of esomeprazole, there are only small differences among existing DR-PPIs for antisecretory effect when chronically administered as standard doses.

SUMMARY AND CONCLUSIONS

The DR-PPIs effectively suppress gastric acid secretion and successfully treat acid-related disorders. There are only minor differences among existing members of the class, and these have not been translated into

Table 2. Pharmacokinetics of delayed-release proton-pump inhibitors (PPIs)

	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Absolute bioavailability (%)	64–90	>80	40	77	52
Time to peak plasma level (h)	1.5	1.7	0.5–3.5	2–4	2–5
Plasma half-life (h)	1.0–1.5	1.5	0.5–1.0	1.0	1–2
Plasma protein binding (%)	97	97	95	98	96
Hepatic metabolism	Yes	Yes	Yes	Yes	Yes

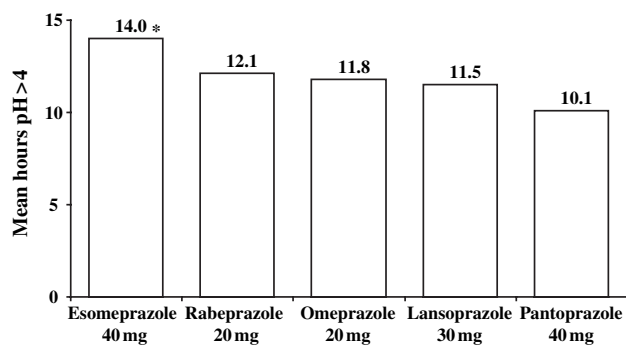


Figure 1. Effects of standard doses of currently available delayed-release proton-pump inhibitors (PPIs) on intragastric acidity. Data from a five-way crossover study in 35 patients with gastro-oesophageal reflux disease (GERD), during which each PPI was administered once daily for 5 days. * $P < 0.001$ vs. all others (adapted from Miner *et al.*¹³).

consistent, clinically meaningful advantages for any individual DR-PPI. The drugs' enteric coatings impair their systemic absorption, and may delay the onset of maximal antisecretory effect. Alternative dosing formulations may be more convenient for some specific groups of patients but still rely on some form of enteric coating.

DISCUSSION

What are the pros and cons of different delayed-release PPI formulations?

Differences among existing DR-PPIs formulations are of small absolute magnitude and are not associated with any consistently demonstrable differences in clinical outcomes. Currently, lansoprazole has the greatest number of alternative dosing formulations approved by the US Food and Drug Administration (FDA; Table 1). Omeprazole has the lowest absolute bioavailability after the first dose. Bioavailability increases progressively with repeated once daily doses of OME due to auto-inhibition of its metabolism. Lansoprazole has the highest absolute bioavailability after the first dose (Table 2). In standard marketed doses, esomeprazole may have the greatest antisecretory effect at pharmacodynamic steady-state (Figure 1). Omeprazole, lansoprazole and esomeprazole are easier to administer in liquids or soft foods than rabeprazole or pantoprazole because the first three are given as capsules of enteric-coated granules while the latter two are enteric-coated tablets.

Are there meaningful advantages for any one DR-PPI over the others?

Absolute differences among the DR-PPIs are of small magnitude and have not been demonstrated to be of clinical relevance. When clinical end points such as the healing of ulcers or oesophagitis are compared, there are small and inconsistent differences seen between DR-PPIs. Esomeprazole has demonstrated slightly better healing rates compared with OME, lansoprazole or pantoprazole in erosive oesophagitis.^{14–16} However, the differences are small in magnitude and appear to offer only limited clinical benefit. Furthermore, there is no clinically significant difference between esomeprazole and lansoprazole in improving symptoms of gastro-oesophageal reflux disease (GERD).^{15, 17–19}

To what extent does the formulation of a PPI influence its use?

In the US, the two DR-PPIs that are currently most often prescribed are esomeprazole and lansoprazole. As both are usually given as capsules of enteric-coated granules, it could be argued that formulation has little influence. However, alternative dosing formulations are important for particular groups of patients. For example, elderly patients may have difficulty swallowing intact capsules or tablets; if a PPI is clinically indicated, IR-OME or the LODT may be more appropriate choices. For administration of a PPI through a nasogastric or gastrostomy tube, preparations consisting of intact granules in a liquid carry the potential concern of tube blockage as does lansoprazole DR oral suspension. IR-OME or predisintegrated LODT may be preferable for enteral tube administration.

How do simplified omeprazole suspension and the lansoprazole orally disintegrating tablet compare with immediate-release omeprazole?

The IR-OME is unique among the PPIs in that it has no form of enteric coating; it is protected from acid degradation by an excipient, sodium bicarbonate (see other article in this supplement for a full discussion of IR-OME). IR-OME is fundamentally different from SOS, which is formed by allowing enteric-coated granules of OME to disintegrate in a solution of 8.4% sodium bicarbonate. SOS requires compounding and takes longer to prepare than IR-OME. IR-OME is packaged

in single-dose packets (both 40 and 20 mg) that can be constituted with water. IR-OME is associated with a more rapid absorption of OME than conventional DR-OME capsules and has a faster onset of antisecretory activity.²⁰ Absorption of OME from SOS is actually less than from DR capsules and its antisecretory effect is relatively disappointing.^{6, 7}

The LODT contains enteric-coated granules of lansoprazole. Although the granules of lansoprazole in LODT are much smaller than those in the capsules, they still have some residual enteric coating that affects lansoprazole absorption. The pharmacokinetic profile of lansoprazole from LODT is virtually identical to that from standard DR capsules.¹ Therefore, LODT offers no advantage over lansoprazole capsules for rate of drug absorption and – by extension – rate of onset of antisecretory activity.

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