Aliment Pharmacol Ther 2005; 22 (Suppl. 3): 25–30.

Review article: immediate-release proton-pump inhibitor therapy – potential advantages

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Accepted for publication 15 September 2005

SUMMARY

The absorption of most oral proton-pump inhibitors is delayed by the enteric coating required to protect the acid-labile proton-pump inhibitor from degradation in the stomach and, as a result, antisecretory effect is also delayed.

This article provides an overview of the pharmacokinetics and pharmacodynamics of a new immediate-release omeprazole [(IR-OME) Zegerid power for oral suspension; Santarus Inc., San Diego, CA, USA] and its potential advantages over delayed-release proton-pump inhibitors.

Immediate-release omeprazole has a higher mean peak plasma omeprazole concentration (C_{max}) and a significantly shorter mean time to reach C_{max} (t_{max}) than delayed-release omeprazole. Immediate-release omeprazole 40 mg has a prolonged antisecretory effect with median intragastric pH above 4.0 for 18.6 h/day at steady-state, after 7 days of once daily dosing. The sodium bicarbonate in immediate-release omeprazole protects the uncoated omeprazole from degradation by gastric acid. The accelerated antisecretory action of immediate-release omeprazole compared with delayed-release omeprazole may be due to the activation of proton pumps by the rapid neutralization of intragastric acid by the sodium bicarbonate. The faster onset of action seen with immediate-release omeprazole is not achieved by using an antacid with a delayed-release proton-pump inhibitor, because administering antacids with conventional delayed-release proton-pump inhibitors does not significantly enhance absorption of the proton-pump inhibitor.

In conclusion, immediate-release omeprazole is associated with rapid absorption of omeprazole and rapid onset of antisecretory effect, without compromising the duration of acid suppression.

DELAYED-RELEASE ENTERIC-COATED PPIs

Currently available delayed-release proton-pump inhibitors (PPIs) are orally administered as enteric-coated preparations. Different formulations have been developed: omeprazole (OME), lansoprazole and esomeprazole are generally administered as gelatine capsules containing enteric-coated granules, whereas pantoprazole and rabeprazole are given as enteric-coated tablets. The different enteric coatings, which are necessary to protect the acid-labile PPI from acid degradation within the stomach, have the potential disadvantage of delaying PPI absorption. An alternative oral formulation of lansoprazole – the lansoprazole orally disintegrating tablet (LODT) – also depends on an enteric coating; the oral pharmacokinetics of lansoprazole after dosing with LODT are essentially identical to those obtained after dosing with capsules of enteric-coated granules of lansoprazole.[1]

The PPIs employing any form of enteric coating for oral administration can be considered to be delayed-release (DR) preparations, as the enteric coating reduces the rate of absorption of the PPI into the systemic circulation. In its standard DR formulation, the proto-

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typical PPI OME has poor absorption after a single dose, and displays marked interindividual variability in the parameters of maximum plasma concentration (C_{max}), time to achieve C_{max} (t_{max}) and area under the plasma concentration/time curve (*AUC*).[2, 3] For single oral doses of 10, 30 and 60 mg of OME, mean t_{max} was, respectively, 3.3, 2.3 and 2.5 h with marked interindividual variability.[2, 3]

Although the DR-PPIs have had an enormous impact on the management of gastro-oesophageal reflux disease (GERD) and other acid-related disorders, they do not achieve maximum effectiveness after a single dose. This may be due in part to their poor absorption with initial dosing. A recent systematic review of the effectiveness of PPIs in relieving symptoms of GERD, found that most patients did not obtain complete relief of daytime or night-time symptoms with the first dose.[4] Lack of a prompt response of GERD to PPI therapy may contribute to patient dissatisfaction with treatment and may lead to unnecessary increases in dose or inappropriate switching to alternate members of the class. There would, therefore, be some clinical utility of a formulation that ensured rapid absorption of the PPI and a more rapid onset of antisecretory activity.

IMMEDIATE-RELEASE OMEPRAZOLE

The recent introduction in the US of immediate-release omeprazole [(IR-OME) Zegerid powder for oral suspension; Santarus Inc., San Diego, CA, USA] may go some way to answering the unmet needs associated with the DR-PPIs. The currently available formulation consists of pure, non-enteric-coated OME powder 40 mg or 20 mg per unit dose along with 1680 mg of sodium bicarbonate (containing 460 mg of sodium). This is designed to be constituted with water to be drunk. It is flavoured with peach and peppermint.

It is important to distinguish IR-OME from another formulation containing OME and sodium bicarbonate called 'simplified omeprazole suspension' (SOS). While IR-OME has no form of enteric coating, SOS is prepared by opening standard capsules of DR-OME, dropping the granular contents into 8.4% sodium bicarbonate solution and agitating the mixture until the enteric coating of the granules disintegrates and a suspension is formed.[5] When administered via gastrostomy once daily for 7 days, this formulation produced an antisecretory effect that was lower than would have been predicted had the patients been given standard DR-OME capsules.[5] A subsequent study of comparative pharmacokinetics, found that the absorption of OME from SOS was less efficient than from intact DR-OME capsules.[6] The bioavailability of OME from SOS relative to standard capsules of DR-OME was 81.2% [95% confidence interval (CI): 59.1–103.3] after a single-dose but fell to 58.4% (95% CI: 30.5–86.3) after 5 days of once daily dosing.[6] Other investigators have confirmed impairment of OME absorption from SOS.[7] Thus, the lower than expected antisecretory effect of SOS was likely due to impaired absorption of OME when given in that form.

PHARMACOKINETICS OF OMEPRAZOLE WHEN ADMINISTERED AS IR-OME

There is rapid absorption of OME when IR-OME is administered orally. In a comparative study with DR-OME, IR-OME (prototype formulation) displayed a significantly shorter t_{max} and a higher C_{max} (Figure 1).[8] Mean t_{max} was 25 min with IR-OME and 127 min with DR-OME ($P < 0.01$); mean C_{max} was 1019 ng/mL with IR-OME and 544 ng/mL with DR-OME. The *AUC* for OME was not significantly different between the IR and DR formulations; mean values were 1120 and 1170 ng·h/mL, respectively.

Both C_{max} and *AUC* increased between 1 and 7 days of once daily dosing with IR-OME (commercial formulation). For the 20 mg dose, mean C_{max} increased from 672 to 902 ng/mL between days 1 and 7, while mean *AUC* increased from 825 to 1446 ng·h/mL.[9] For the 40 mg dose, mean C_{max}increased from 1412 ng/mL on day 1 to 1954 ng/mL on day 7, while mean *AUC* increased from 2228 to 4640 ng·h/mL. There was no

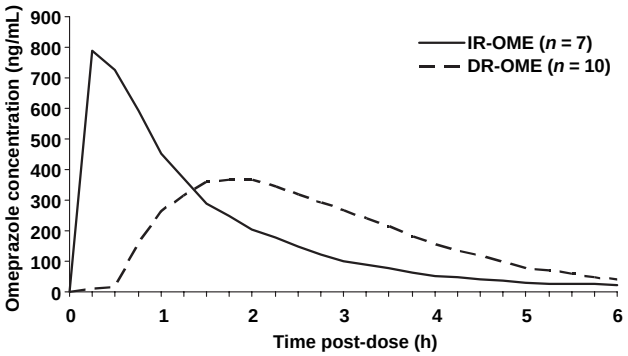

Figure 1. Mean plasma concentration from fasting subjects with immediate-release omeprazole (IR-OME) 40 mg prototype formulation ($n = 7$) and delayed-release (DR)-OME 40 mg ($n = 10$; adapted from Hepburn and Goldlust[8]).

significant change in mean t_{max} between days 1 and 7 for either the 20 mg or the 40 mg dose. For the 20 mg dose, mean t_{max} was 29.8 min on day 1 and 28.3 min on day 7. Corresponding values for the 40 mg dose were 26.6 and 34.7 min.[9] Similarly, mean plasma elimination half-life ($t_{1/2}$) was dose-independent and did not change significantly with repeated dosing. For the 20 mg dose, $t_{1/2}$ was 0.86 h on day 1 and 1.08 h on day 7. Corresponding values for the 40 mg dose were 1.00 and 1.38 h.[9]

The sodium bicarbonate is critical to the effective absorption of OME from IR-OME because it protects the uncoated OME from acid degradation within the stomach. When uncoated OME 40 mg was administered without sodium bicarbonate to 10 healthy volunteers 1 h before ingestion of a standardized meal, the median C_{max} was 186.4 ng/mL and the median *AUC* was 225 ng·h/mL.[10] However, when the same dose of uncoated OME was given with 30 mmol of sodium bicarbonate, median C_{max} was 911.5 ng/mL and median *AUC* was 965.7 ng·h/mL.

PHARMACODYNAMIC STUDIES WITH IR-OME

Just as with the pharmacokinetics, the sodium bicarbonate content is critical to understanding the pharmacodynamics of IR-OME. When pure, uncoated OME powder was administered to 10 healthy volunteers 1 h before a meal, median integrated intragastric acidity from 0 to 210 min was 35 mmol·h/L. When the same dose was given with 30 mmol of sodium bicarbonate, median integrated intragastric acidity over the same time period was only 0.5 mmol·h/L.[10]

In a crossover trial, 10 healthy volunteers received a single 40 mg dose of DR-OME; after a washout period of at least 1 week, seven of the subjects received 40 mg of uncoated IR-OME (prototype formulation).[8] Intragastric acidity was monitored from 0 to 30 min and from 4 to 6 h after ingestion. Within the first 30 min, DR-OME had no measurable effect on intragastric acidity, while IR-OME reduced the mean gastric acid concentration by 78% from baseline. From 4 until 6 h after ingestion, there was a mean gastric acid concentration reduction from baseline of 27% for DR-OME and 65% for IR-OME. Thus, the antisecretory effect of IR-OME was detectable earlier than that of DR-OME and lasted at least as long. While the effect seen within the first 30 min may have been due largely to the neutralizing capacity of the sodium bicarbonate, the more profound suppression seen from 4 to 6 h after dosing likely reflects enhanced and accelerated absorption of OME from the IR formulation.

The more rapid onset of antisecretory action with IR-OME is not achieved at the expense of any shortening of effect. Healthy volunteers received 7 days of once daily dosing with IR-OME (commercial formulation) 20 mg ($n = 28$) or 40 mg ($n = 24$); 24 h intragastric acidity was monitored on day 7 (at pharmacodynamic steady-state). The primary end point was the time during which the intragastric pH was maintained above 4. IR-OME 20 mg maintained intragastric pH above 4 for 51% (12.2 h), while IR-OME 40 mg kept intragastric pH above 4 for 77% (18.6 h) of the 24-h recording period (Figure 2).[9, 10]

Morning administration of IR-OME is associated with profound control of postprandial acidity throughout the day, which is seen as early as day 1 and is maintained

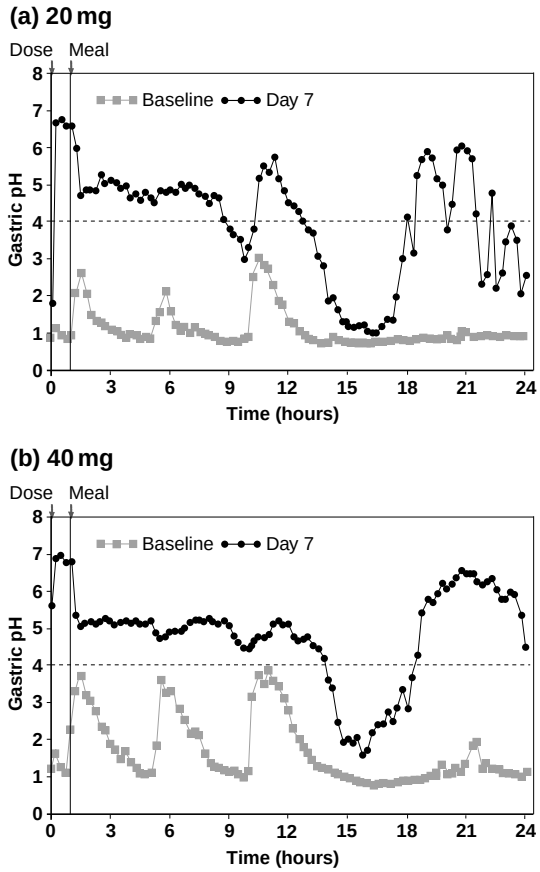

Figure 2. Effect of 7 days of once daily dosing with immediate-release omeprazole (IR-OME) 20 mg (a) and 40 mg (b) on 24 h intragastric pH (Zegerid Package Insert and data on file; Santarus[9, 10]).

at day 7. IR-OME 40 mg dosed once daily controlled intragastric acidity following breakfast and lunch (98% and 100% reductions on days 1 and 7, respectively for both meals), as well as dinner (92% and 100% reductions on days 1 and 7, respectively).[10]

According to Goldlust *et al.*, 17 healthy subjects received IR-OME 20 mg (commercial formulation) each morning for 7 days; on day 8, they received two doses of 20 mg in the morning and at bedtime. The addition of the bedtime dose maintained intragastric pH above 4 for significantly longer than the morning dose alone, over both the nocturnal and entire 24-h period (Figure 3).[11]

POSSIBLE MECHANISM OF ACTION OF IR-OME

As noted above, both the absorption of OME and the onset of its antisecretory effect are more rapid when administered as IR-OME than as DR-OME. The putative mechanism of action to explain these observations is as follows. Following ingestion of IR-OME as an oral suspension, the sodium bicarbonate causes a prompt rise in intragastric pH. While this serves the primary function of protecting the uncoated OME from acid degradation within the stomach, it may also provide a temporary stimulus to gastrin release from antral G cells. Sodium bicarbonate solution has previously been shown to raise circulating gastrin levels within 30 min of oral ingestion.[12] The rise in circulating gastrin may stimulate the parietal cell mass and promote the insertion of functioning molecules of H^+,K^+-ATPase into the secretory canaliculi. Since the peak plasma concentration of OME occurs around 30 min after ingestion of IR-OME, this allows for the rapid uptake of circulating OME by activated parietal cells leading to irreversible inhibition of a large proportion of available molecules of H^+,K^+-ATPase. This may help to explain both the rapidity of onset of the antisecretory effect and its prolonged duration. This hypothesis assumes that OME is principally absorbed from the proximal small intestine when ingested as IR-OME, just as with the conventional DR formulation.

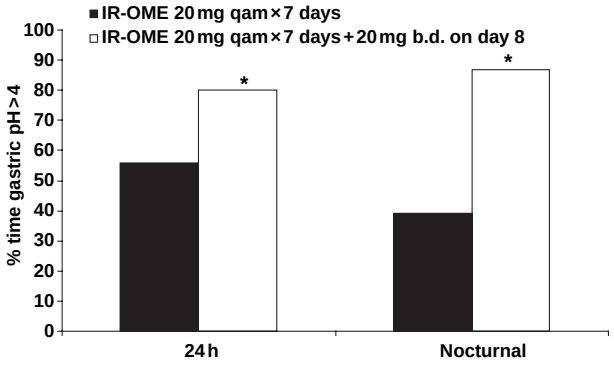

Figure 3. Effect of additional evening dose of immediate-release omeprazole (IR-OME) 20 mg on 24 h and nocturnal intragastric acidity ($n = 17$; *$P < 0.001$; adapted from Goldlust *et al.*[11]).

EFFECTS OF CONCOMITANT ANTACID ON ABSORPTION OF DR-PPIs

Because DR-PPIs do not produce maximal symptom relief in GERD patients with the first dose,[4] patients may combine a DR-PPI with antacid during the first few days of treatment. Therefore, it is important to know whether antacids alter the absorption of DR-PPIs and, in view of the advantages conferred by the sodium bicarbonate in IR-OME, whether co-administration of antacids augments absorption of PPIs from DR formulations.

A study in 12 healthy male volunteers, found that median t_{max}, median C_{max} and *AUC* were not statistically different when a single-dose of OME 20 mg was administered with or without a liquid antacid.[13] When six healthy male volunteers were given single doses of OME 30 mg with or without a liquid antacid, t_{max}, C_{max} and *AUC* were not significantly changed by administration of the antacid.[14] Median $t_{max}$with OME was 3.25 h when given alone and 1.0 h when given with antacid; however, this was not statistically significant due to the small sample size and the marked interindividual variability seen in the rate of absorption. Similarly, the effects of antacids on the pharmacokinetics of rabeprazole were studied in 12 healthy male volunteers, and no significant differences in mean t_{max}, C_{max}, *AUC*, or $t_{1/2}$ were seen when rabeprazole was given alone, with antacid, or after antacid.[15]

Results with lansoprazole 30 mg, when administered with or without an antacid to 12 healthy subjects, showed no significant differences in mean t_{max} or *AUC*.[16] However, mean C_{max} was significantly reduced when lansoprazole was administered with or after the antacid compared with when given alone.

Therefore, current evidence indicates that antacids do not have a major effect on the absorption or disposition of the DR-PPIs. There is no evidence to suggest that antacid co-administration enhances the absorption of DR-PPIs, and it is unlikely that administration of DR-

OME with an antacid would result in the favourable pharmacokinetic and pharmacodynamic profile seen with IR-OME.

SUMMARY AND CONCLUSIONS

IR-OME is unique among PPI formulations in that it has no enteric coating. It is associated with rapid absorption of OME and rapid onset of antisecretory effect. Single daily doses of IR-OME produce prolonged acid suppression, including postprandial periods. IR-OME is different from the earlier OME/sodium bicarbonate combination called SOS. The SOS formulation contains residual enteric coating from the OME granules, and has inferior pharmacokinetic and pharmacodynamic properties when compared with conventional DR-OME. The favourable pharmacokinetic and pharmacodynamic profiles seen with IR-OME do not appear to be achievable by using an antacid with a DR-PPI, because this is not associated with improvement or acceleration of PPI absorption.

DISCUSSION

How does IR-OME differ from a traditional DR-PPI given with antacid?

Currently available studies do not indicate that concomitant antacid improves the absorption of DR-PPIs including OME, lansoprazole and rabeprazole.[13–16] IR-OME is uniquely formulated with no enteric coating and the antacid sodium bicarbonate. It is not anticipated that giving a conventional DR-PPI with an antacid could reproduce the favourable pharmacokinetic and pharmacodynamic profile seen with IR-OME.

Do traditional antacids elevate serum gastrin?

There is limited experimental evidence that serum gastrin concentrations increase following the ingestion of antacids. Feurle[12] found a prompt rise in serum gastrin, which approximately doubled within 1 h, following infusion of sodium bicarbonate into the stomach of healthy volunteers and duodenal ulcer patients. Intragastric instillation of sodium chloride did not produce any measurable effect on serum gastrin levels.[12]

Another study in healthy volunteers and patients with a history of duodenal ulcer showed that the administration of sodium bicarbonate by intragastric infusion raised serum gastrin levels to a greater degree than the same dose administered intravenously.[17] However, serum gastrin concentrations were not significantly elevated above baseline until after 5 h of continuous intragastric infusion of sodium bicarbonate. The rise in serum gastrin was 23–30% of that achieved with the intragastric instillation of a homogenized steak meal.

What is the site of omeprazole absorption when administered as IR-OME?

It is thought that the OME in IR-OME is absorbed from the proximal small intestine, just as it is when given as in a DR formulation. However, because IR-OME is ingested as a liquid, there is rapid transfer to the duodenum where subsequent absorption is more rapid than with DR-OME. However, the site of absorption of IR-OME has not been studied.

Are there any other specific advantages to IR-OME in the management of GERD?

The more rapid absorption of OME and the more rapid onset of acid suppression may offer a clinical benefit. Multiple randomized-controlled trials attest to the efficacy of different DR-PPIs when taken on-demand by patients with endoscopy-negative GERD.[18] The rapid onset of action may make IR-OME the PPI formulation of choice for on-demand treatment of GERD although this has not been investigated clinically.

Theoretically, the liquid formulation of IR-OME would be a more attractive option than a tablet or capsule of a DR-PPI for patients with gastroparesis or delayed gastric emptying. Furthermore, patients with gastroparesis have constant stimulation of gastric acid secretion because of the prolonged dwell-time of food in the stomach. The prolonged antisecretory effect seen with IR-OME may help to counteract this situation.

Other groups of GERD patients who might benefit specifically from IR-OME would be those with swallowing difficulties, those who do not take breakfast regularly or who have difficulty always taking their DR-PPI before food (because there is evidence that IR-OME dosed independently of food still exerts its maximal antisecretory effect), patients who work shifts or who have a demanding travel schedule (because of problems timing their dose of a DR-PPI) and, as already mentioned, patients who wish to take their PPI on-demand for control of GERD symptoms.

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