

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Update on Dual Delayed-Release PPI Formulations

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G&H Could you explain how the dual delayed-release proton pump inhibitor formulation works?

CH At the moment, only 1 dual delayed-release formulation of a proton pump inhibitor (PPI) is commercially available: dexlansoprazole (Dexilant, Takeda), which is the R-enantiomer of lansoprazole. The dexlansoprazole capsule contains 2 different sets of enteric-coated granules. The enteric coating on each of these disintegrates at a different pH level. The enteric coating of the first set of granules starts to disintegrate in the proximal small intestine, and dexlansoprazole starts to be absorbed. Close monitoring of the plasma-concentration profile reveals 2 peaks in plasma levels. The first (and smaller) peak in plasma concentration occurs approximately 1–2 hours after dosing. The second (and larger) peak in absorption occurs when the enteric coating of the other set of granules disintegrates. This peak occurs approximately 5–6 hours after dosing because the pH coating is designed to disintegrate at a higher level of pH, which is normally present farther down the intestinal tract.

G&H Given that PPIs are effective in most gastroesophageal reflux disease patients, why was there a need for another formulation?

CH Although PPIs are effective in most gastroesophageal reflux disease (GERD) patients, some patients who take a PPI once daily continue to complain of breakthrough heartburn. In these patients, heartburn usually occurs during the second half of the dosing interval, typically in

the late evening or overnight. This has led some patients to take their PPI twice daily. Although physicians frequently recommend this for selected patients, there is actually very little published evidence to indicate that it is an appropriate treatment decision. Furthermore, twice-daily PPI use is not approved by the US Food and Drug Administration (FDA) for the treatment of GERD.

The new dexlansoprazole formulation offers an approved option for these patients. The formulation is designed to extend the absorption of the drug and maintain higher plasma concentrations for longer periods of time, above a certain critical threshold, so that the drug can still be effective during the second half of the dosing interval. This means that the concentration of drug present in the circulation is sufficiently high enough during the second half of the day to inhibit any molecules of proton pump that become inserted into parietal cell membranes.

G&H Could you further discuss the advantages of this formulation compared to standard PPIs?

CH One potential advantage is that the US FDA has approved this formulation on a once-daily basis, irrespective of the timing of meals. For most of the other PPIs, it is recommended that the drug be taken in a fasting state approximately 30–60 minutes before meals. Due to its dual delayed-release design, dexlansoprazole can be taken regardless of meal times. In addition, this formulation lasts longer and controls intragastric acidity for longer periods of time. The formulation may also help to improve GERD symptoms during the second half of the day.

G&H For which indications has this formulation been approved thus far?

CH Presently, the only approved indications are the healing of all grades of erosive esophagitis (treatment up to 8 weeks), the maintenance of healing of erosive esophagitis (treatment up to 6 months), and heartburn in patients of symptomatic nonerosive GERD (treatment up to 4 weeks). There may be other indications that are being investigated at the moment, but that information is not yet available.

G&H Could you discuss any recent study results, particularly in terms of the drug's short- and long-term efficacies?

CH The most recent studies have been the pivotal clinical trials, all of which have been published in *Alimentary Pharmacology & Therapeutics*. Two 8-week trials were conducted comparing dexlansoprazole with lansoprazole 30 mg for the healing of erosive esophagitis. Both of these trials showed a higher healing rate with dexlansoprazole than with lansoprazole. In one of the trials, the higher healing rate on dexlansoprazole was statistically significant, whereas in the other trial, it did not achieve statistical significance. The US FDA has approved the 60-mg dose of dexlansoprazole to be taken once daily for up to 8 weeks for the healing of all grades of erosive esophagitis.

There have been separate publications looking at the use of the drug for the maintenance of healing of erosive esophagitis. Patients who had participated in the healing studies and who had documentation of healed erosive esophagitis were rerandomized to receive either dexlansoprazole or placebo for up to 6 months. Dexlansoprazole 30 mg once daily was significantly superior to placebo for the maintenance of healing of all grades of erosive esophagitis. The 30-mg dose is FDA-approved for this indication.

One other published study involved patients with nonerosive GERD. This was a 4-week randomized clinical trial in which dexlansoprazole 30 mg was compared to placebo. Dexlansoprazole 30 mg was statistically significantly superior to placebo for relief of heartburn in this study. The advantage of dexlansoprazole 30 mg over placebo was evident as early as 2 days after randomization, and the therapeutic gain was still present at the end of the 4-week treatment period. The US FDA has approved the 30-mg dose for this indication.

G&H Have any studies examined this formulation specifically for treatment of nighttime GERD?

CH I am not aware of any studies that specifically examined the formulation for nighttime GERD. However, the

placebo-controlled trials evaluating patients with healed erosive esophagitis specifically asked those patients about both daytime and nighttime heartburn. The results were very positive, showing very effective control of both daytime and nighttime heartburn in people with healed erosive esophagitis. In one of the trials, dexlansoprazole 30 mg once daily was associated with a median of 99% of nights that were heartburn-free. Having said this, nighttime heartburn is not officially part of dexlansoprazole's US FDA-approved label.

G&H Have studies compared the administration of dexlansoprazole at different meal times or times of day?

CH Yes, this has been studied. The pharmacokinetics and pharmacodynamics of the drug were examined when given in the fasting state or before or after meals. There was no significant change in the pharmacokinetics or pharmacodynamics, whether taken after a prolonged fast or before or after a high-fat meal.

G&H Is this new formulation an option for patients who are still experiencing symptoms with standard PPI therapy, or just as first-line therapy?

CH This dexlansoprazole formulation is approved as a first-line therapy for the indications mentioned above. Some physicians may consider it for patients who have an incomplete or inadequate response to standard doses of another PPI or for patients who are currently taking another PPI twice daily even though it is not specifically approved for such use. As of yet, there have been no specific studies comparing dexlansoprazole to other PPIs apart from lansoprazole and that was only in the short-term healing of erosive esophagitis.

G&H How has patient satisfaction and tolerability been with this formulation?

CH The drug appears to have a tolerability profile similar to that of lansoprazole. In the maintenance studies, there was very little patient dropout, and patient acceptance was good. Published studies have shown a very low incidence of adverse events.

G&H How safe is this drug?

CH There have been a number of concerns raised in the last few years regarding the safety of PPIs in general. In my opinion, PPIs are a safe group of drugs and many of the safety concerns that have been raised about the class have been exaggerated or overestimated. I am not aware of any safety issues specific to dexlansoprazole.

G&H Have the drug's interactions with clopidogrel been analyzed?

CH There is no a priori reason to suspect that this drug would interact with clopidogrel. However, the manufacturers are currently undertaking a large interaction study in healthy volunteers, looking at dexlansoprazole and several other PPIs for any evidence of an interaction with clopidogrel. The results of this ongoing study are not yet known.

G&H Are there any alternate formulations in development?

CH I am not aware of any alternate formulations that are in development. There is currently one additional FDA-approved dosing option for patients who have difficulty swallowing capsules. The dexlansoprazole capsule can be opened and the granules dropped into applesauce, which can then be swallowed. As long as the patient does not chew or disturb the granules, the absorption of the drug is adequate when taken in this form.

Suggested Reading

Sharma P, Shaheen NJ, Perez MC, et al. Clinical trials: healing of erosive oesophagitis with dexlansoprazole MR, a proton pump inhibitor with a novel dual-delayed release formulation – results from two randomized controlled trials. *Aliment Pharmacol Ther.* 2009;29:731-741.

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