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DRUG FOCUS ARTICLE

Dexlansoprazole MR – A review

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Abstract
Dexlansoprazole MR is the R-enantiomer of lansoprazole that is delivered by a novel system, the dual delayed release formulation. The drug has been shown to be efficacious in healing erosive esophagitis as compared with lansoprazole. When compared to placebo, dexlansoprazole provided significantly higher maintenance rates for healed esophageal mucosa in patients with erosive esophagitis and symptom control in patients with non-erosive reflux disease. Dexlansoprazole could be taken without regard to food. Overall, dexlansoprazole is well tolerated and has a comparable side-effect profile to lansoprazole.

Key words: *Dexlansoprazole, dual delayed release formulation, gastroesophageal reflux disease, heartburn, proton pump inhibitor*

Introduction

Gastroesophageal reflux disease (GERD) is the most common out-patient gastroenterology diagnosis in the United States, with a prevalence of 10% to 20% in the Western world and an annual incidence of 0.38% to 0.45% (1). In the United States, 20% of the adult population experiences GERD-related symptoms weekly (2) and 7% daily (3). Erosive esophagitis accounts for up to 30% of the GERD population, while non-erosive reflux disease (NERD) can affect up to 70% of these patients (4). GERD reduces health-related quality of life and imposes a significant economic burden on the health care system (5).

Acid suppression is the mainstay of therapy for GERD. The development of proton pump inhibitors (PPIs), which reduce gastric acid secretion through blockade of the active H^+/K^+ ATPase (proton pump), has revolutionized the treatment of GERD. Generally, PPIs are a safe class of drugs that provide symptomatic relief and achieve healing of esophageal mucosa in the majority patients with erosive esophagitis. Moreover, PPIs have been shown to improve the quality of life of GERD patients (6,7).

Despite the success that PPIs have achieved in treating GERD and GERD-related complications, unmet needs and significant challenges remain. Specifically, approximately 10%–15% of adult patients with erosive esophagitis fail to achieve complete healing after 8 weeks of treatment. This subset of patients usually demonstrate moderate to severe disease (Los Angeles grades C and D) and comprise approximately 25%–30% of all erosive esophagitis patients (8). Moreover, even when continuing the initial healing dose, 15%–23% of adult patients with Los Angeles grades A and B and 24%–41% with grades C and D relapse within 6 months. In addition, up to 40% of non-erosive reflux disease (NERD) adult patients remain symptomatic while on standard dose (once daily) PPI therapy (9). In general, treatment of extraesophageal manifestations of GERD with a PPI has been a very disappointing clinical experience (10). Other unmet needs include faster and more effective control of postprandial heartburn, improved heartburn relief during sleep for both erosive esophagitis and NERD patients, improved acid control in Barrett's esophagus patients,

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Key messages

- Dexlansoprazole is the R-enantiomer of lansoprazole and, unlike the current proton pump inhibitors, it contains a dual delayed release formulation.
- Comparative trials demonstrated superior efficacy against lansoprazole in healing of erosive esophagitis and against placebo in symptom resolution of patients with non-erosive reflux disease.
- The therapeutic potential of dexlansoprazole in areas of unmet needs in gastroesophageal reflux disease remains to be elucidated.

Abbreviations

GERD	gastroesophageal reflux disease
NERD	non-erosive reflux disease
PPI	proton pump inhibitor

and a flexible schedule of treatment with a PPI. Dexlansoprazole MR (modified release) with the Dual Delayed Release™ (DDR) formulation was designed to prolong plasma concentration–time profile in the hope of providing improved symptoms control and esophageal mucosal healing with a once-daily dose. The drug was approved by the FDA on 30 January 2009 for once-daily treatment of heartburn associated with symptomatic non-erosive GERD, acute erosive esophagitis healing, and maintenance of healed erosive esophagitis.

Background

Proton pump inhibitors irreversibly inhibit the final common pathway of acid production in the parietal cell, the H^+,K^+-ATPase enzyme (proton pump) (11). For PPIs to be highly effective, they must be present in high concentration during proton pump activation (12,13).

Not all proton pumps are active at the same time, and approximately 25% of them are regenerated daily (12,13). Since the peak plasma concentration (C_{max}) of PPIs is reached within 2 hours after oral administration and the residence time in the body is limited due to liver metabolism, the capability of once-daily PPI to inhibit proton pumps after administration is progressively diminished. Thus, with once-daily dosing, systemic exposure to PPIs tends to wane until there is no circulating PPI present in the plasma during later times of the 24-hour dosing interval. This may enable recovery of gastric acid secretion by uninhibited, restored, or new proton pumps (14). Consequently, once-daily, standard-dose PPI does not provide complete control of gastric acid secretion over a period of 24 hours (13,15).

Overall, the differences in pharmacokinetics and oral bioavailability among the PPIs have not translated in pharmacodynamic studies to large differences in antisecretory effect (16). Consequently, further improvement in acid inhibition could be achieved by increasing the residence time of PPIs in the systemic circulation, resulting in much more prolonged acid suppression (17). Regardless, complete suppression of acid secretion over a period of 24 hours is likely an unachievable and undesirable goal.

Dexlansoprazole is the R-enantiomer of lansoprazole, which constitutes more than 80% of the circulating drug after administration of oral lansoprazole (18). The drug has a lower clearance time and a 5-fold greater systemic exposure than the S-enantiomer of lansoprazole (19).

Dexlansoprazole MR (Dexilant™, TAK-390MR, Takeda Global Research & Development Center, Inc., Deerfield, IL, USA) is a modified release formulation of dexlansoprazole that employs a novel Dual Delayed Release (DDR) formulation to deliver the drug in two discrete phases. This technology is based on a mixture of two types of granules with different pH-dependent dissolution profiles. One type of granules is designed to release 25% of the drug immediately after the granules reach the proximal duodenum (at pH 5.5), while the second type of granules is designed to release the remaining 75% of the drug farther down in the distal portion of the small bowel (at pH 6.8). As a result, administration of dexlansoprazole MR results in a dual-peak time–concentration profile as opposed to the single peak seen with conventional delayed release PPIs (Figure 1). As a result, plasma exposure is markedly extended following oral administration of dexlansoprazole MR, which potentially allows inhibition of newly activated proton pumps that turn on following initial PPI effect.

Overall, dexlansoprazole MR provides an improved pharmacodynamic profile as compared with lansoprazole, which contains a conventional single-release drug delivery system (20,21).

Pharmacokinetics

In two phase I randomized, open-label, cross-over studies , the authors evaluated the pharmacokinetics and pharmacodynamics of four different doses of dexlansoprazole MR (30 mg, 60 mg, 90 mg, and 120 mg) as compared with lansoprazole 15 mg and 30 mg (20). Forty patients received each dose daily for five consecutive days in a random sequence. The

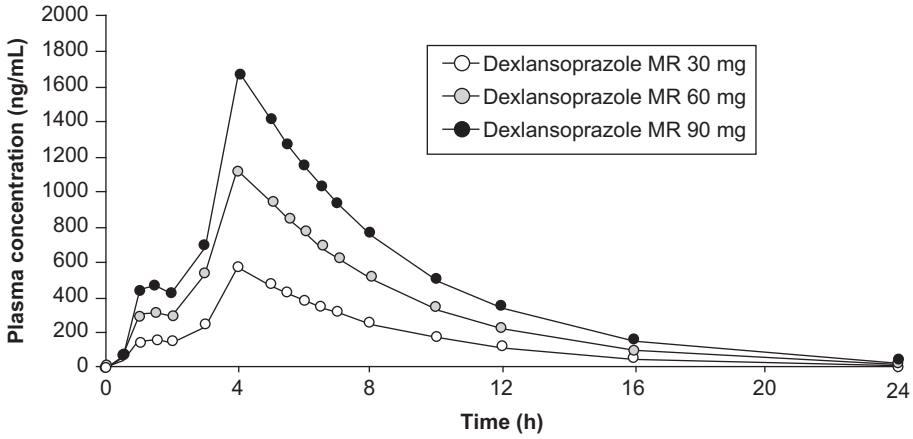

Figure 1. Mean time-concentration profiles of different doses of dexlansoprazole MR. Reproduced from Metz DC, Vakily M, Dixit T, Mulford D. Review article: dual delayed release formulation of dexlansoprazole MR, a novel approach to overcome the limitations of conventional single release proton pump inhibitor therapy. Aliment Pharmacol Ther. 2009;29:928 – 37 (18), with permission from John Wiley.

first peak in the plasma concentration–time profile of dexlansoprazole MR occurred approximately 1–2 hours after oral administration, as was observed after oral administration of the conventional delayed release capsules of lansoprazole. However, a second peak occurred approximately 4–5 hours after oral administration, prolonging the plasma concentration–time profile (Figure 1). The results of the C_{max}, AUC_t, and AUC_{24} of the aforementioned regimens are presented in Table I. All dexlansoprazole MR doses achieved greater area under the curve (AUC) without an equivalent increase in C_{max} as compared with lansoprazole.

Dexlansoprazole MR (30–120 mg qd for 5 days) has demonstrated a longer mean residence time (MRT) than lansoprazole following oral administration (5.5–6.4 hours versus 2.8– 3 hours, respectively). This is primarily attributable to the prolongation of the mean absorption time (MAT), the result of the dual delayed release formulation (20). However, there was no evidence of significant systemic drug accumulation after once-daily administration (22). The pharmacokinetic profile of dexlansoprazole MR, as was determined in healthy persons, was subsequently confirmed in GERD patients (23).

Pharmacodynamics

Dexlansoprazole MR (60 mg, 90 mg, and 120 mg) achieved significantly higher mean 24-hour intragastric pH values and percentage of time intragastric pH $>$ 4 as compared with lansoprazole 30 mg (Table II) (22). Mean intragastric pH values increased by more than 0.5, and percent of time intragastric pH $>$ 4 by more than 10% during the 16–24-hour interval for all the studied regimens as compared with standard dose of lansoprazole (24).

In a retrospective *post-hoc* analysis and modeling, which was performed using data from three open-label, multiple-dose, phase I studies, the authors determined that a plasma dexlansoprazole MR concentration of 125 ng/mL corresponds to the longest time intragastric pH is greater than 4 over a 24-hour period (25). After daily administration of dexlansoprazole MR (60 to 120 mg/day) for 5 days, the drug concentration in the plasma was maintained above the aforementioned threshold level for a period that was 2–3 times longer than after administration of lansoprazole 30 mg. Thus, dexlansoprazole MR at the dose range used in these studies improved the concentration–time profile and provided extended acid suppression as compared with lansoprazole 30 mg/day.

Effects of food intake and time of administration

The effects of dosing time relative to food intake on the pharmacokinetics and pharmacodynamics of dexlansoprazole MR were evaluated after administration of a single 90 mg dose (26). Mean plasma concentrations–time profile, C_{max}, and AUC following administration of dexlansoprazole MR under fasted and various fed conditions are presented in Figure 2. Plasma drug level increased (12%–31% for C_{max} and 9%–21% for AUCs) following dexlansoprazole MR administration in the fed state (30 minutes after a high-fat breakfast) as compared with a fasting state (5 or 30 minutes before a high-fat breakfast). This is in contrast to the decrease in C_{max} and AUC values that are expected after oral administration of a conventional delayed release PPI in the fed state. However, there was no significant difference in the mean 24-hour intragastric pH between the fed and the fasting state (Table III). Although the exact underlying mechanism for the increase in

Table I. Plasma pharmacokinetic estimates for dexlansoprazole MR 30, 60, 90, and 120 mg and lansoprazole 30 mg administered once daily for 5 days. Results presented are from treatment day 5 (data presented as mean ± SD). Adapted from (20).

	C_{max}	AUC_t	AUC_{24}
Dexlansoprazole 120 mg	2517 ± 1158	13220 ± 9386	135749 ± 366
Dexlansoprazole 90 mg	2197 ± 923	9751 ± 6728	9938 ± 6758
Dexlansoprazole 60 mg	1434 ± 703	6373 ± 4780	6720 ± 4906
Dexlansoprazole 30 mg	658 ± 263	3182 ± 1559	3275 ± 1539
Lansoprazole 30 mg	845 ± 380	1886 ± 1547	1949 ± 1540

C_{max} = maximum plasma concentration; AUC_t = area under the plasma concentration–time curve (AUC) from time zero to last measurable concentration (ng.h/mL); AUC_{24} = AUC from time zero to 24 h (ng.h/mL).

bioavailability of dexlansoprazole following administration in a fed state remains to be elucidated, this study provides strong support for its administration without regard to meals. This is in contrast with the current recommendation for the conventional delayed release PPIs that have to be taken before a meal and not during a meal because of a significant decrease in drug absorption.

The relative effect of administering dexlansoprazole MR 60 mg at different times of the day was assessed in 44 healthy subjects in a randomized, open-label, cross-over study (27). No other doses of dexlansoprazole MR were evaluated. The drug was administered daily for 5 days, at four different times of the day (before breakfast, lunch, dinner, and bedtime snack). Absorption of the drug was delayed when dexlansoprazole MR was administered before each meal as compared with breakfast. However, this delay did not translate to any difference in pharmacokinetics. The C_{max}, AUC, and plasma half-life were similar among the different times of drug administration. There was a significant decrease in intragastric pH when the drug was administered before an evening snack as compared with the other time periods. Overall, dexlansoprazole MR provides comparable pH intragastric control across a 24-hour period regardless of the meal except before an evening snack.

Table II. Mean 24-hour intragastric pH and percentage of time intragastric pH > 4 achieved by dexlansoprazole MR (60 mg, 90 mg, and 120 mg) compared with lansoprazole 30 mg (during steady state after 5 days of treatment). Adapted from (22).

	16–24 hours	Total 24 hours
Mean intragastric pH		
Dexlansoprazole MR 60 mg	4.79[c]	4.55[c]
Dexlansoprazole MR 90 mg	4.06[c]	4.51[b]
Dexlansoprazole MR 120 mg	4.79[c]	4.57[c]
Lansoprazole 30 mg	3.85	4.13
Percent time intragastric pH > 4		
Dexlansoprazole MR 60 mg	71.24%	70.99%[b]
Dexlansoprazole MR 90 mg	54.51%	69.81%[a]
Dexlansoprazole MR 120 mg	67.27%	70.71%[b]
Lansoprazole 30 mg	42.34%	60.15%

[a]$P < 0.05$; [b]$P < 0.01$; [c]$P < 0.001$, respectively (P values from test of difference between a given dexlansoprazole regimen and lansoprazole 30 mg/day).

The results of the aforementioned studies demonstrate that dexlansoprazole MR offers a greater dosing flexibility as compared with other delayed release PPIs for the treatment of GERD. This feature may improve compliance to treatment.

Drug interaction

Drug interaction studies demonstrated that dexlansoprazole MR and lansoprazole have the potential to inhibit the activity of CYP3A, CYP2C19, and, in the case of dexlansoprazole MR, also the potential to induce the human hepatic CYP1A. Presently, there is no evidence that concomitant administration of dexlansoprazole MR with diazepam, phenytoin, warfarin, or theophylline affects the pharmacokinetics of these drugs (26). Therefore, it is unlikely that dexlansoprazole MR alters the pharmacokinetic profile of other drugs that are metabolized by CYP2C19, CYP2C9, CYP1A2, and CYP3A (28).

In the package insert, it is recommended that dexlansoprazole MR should not be co-administered with the HIV drug atazanavir because of significant decrease in systemic concentration of the latter medication. Furthermore, patients who require warfarin in addition to dexlansoprazole should have their international normalized ratio (INR) prothrombin time (PT) followed closely. This is more a cautionary recommendation that is not based on any evidence in the literature. Co-administration of dexlansoprazole MR and tacrolimus may increase tacrolimus blood concentration. Like any other PPI, dexlansoprazole MR may interfere with absorption of drugs that require acidic intragastric pH for bioavailability (e.g. digoxin, ketoconazole, iron, and ampicillin).

Use in specific populations

Age (18–40 years versus 65–80 years) and gender did not have a clinically important effect on the

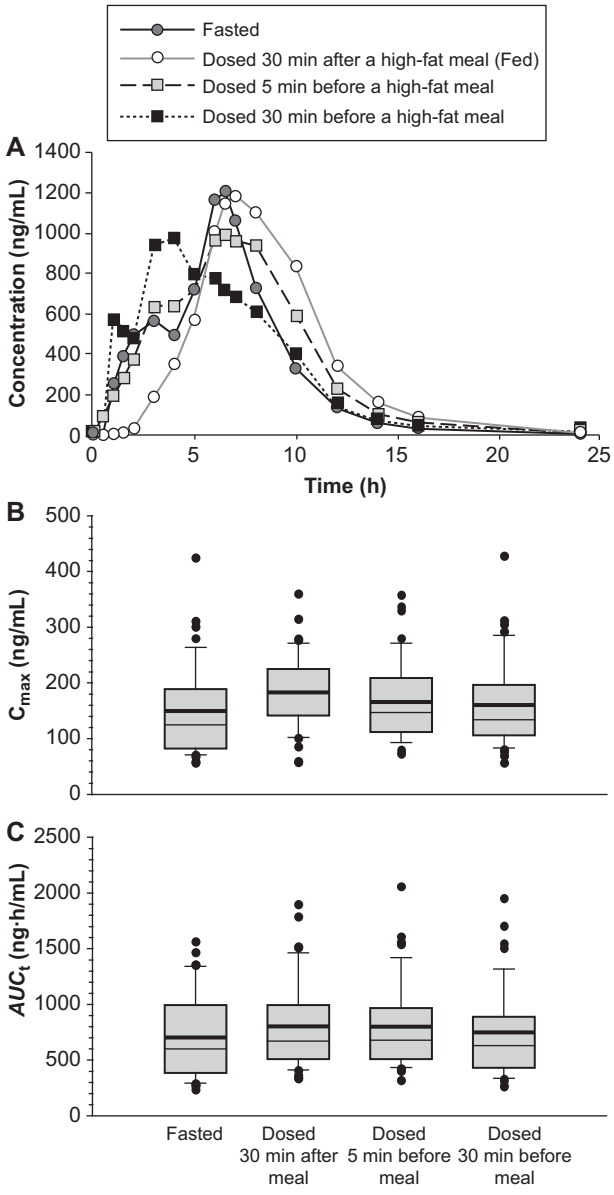

Figure 2. Mean dexlansoprazole plasma concentrations–time profiles (A), C_{max} (B), and AUC_t (C) values following administration of a single oral dose of dexlansoprazole MR 90 mg under fasted and various fed conditions. The boundary of the box closest to zero indicates the 25th percentile, the thinner line within the box marks the median, the thicker line within the box marks the mean, and the boundary of the box farthest from zero indicates the 75th percentile. Error bars above and below the box indicate the 90th and 10th percentiles, respectively. Solid circles indicate all data points outside the 90th and 10th percentiles. Reproduced from Lee RD, Vakily M, Mulford D, Wu J, Atkinson SN. Clinical trial: the effect and timing of food on the pharmacokinetics and pharmacodynamics of dexlansoprazole MR, a novel dual delayed release formulation of a proton pump inhibitor - evidence for dosing flexibility. Aliment Pharmacol Ther. 2009;29:824–33 (26), with permission from John Wiley and Sons.

pharmacokinetic profile of dexlansoprazole MR following a single dose of 60 mg in a phase I, open-label, parallel-group study (29).

Dexlansoprazole MR is completely metabolized by the liver to inactive metabolites. Consequently, dexlansoprazole MR is not expected to accumulate in the presence of renal insufficiency, and thus dose adjustment is not required in patients with renal impairment. In subjects with moderate hepatic impairment (Child–Pugh class B), accumulation of dexlansoprazole MR (demonstrated by increased C_{max} and AUC) occurred after a single 60 mg dose as compared with healthy subjects (30). However, these differences were not considered clinically significant. Regardless, the package insert recommends the use of dexlansoprazole MR 30 mg in patients with moderate hepatic dysfunction. No studies were conducted in patients with severe hepatic impairment. In addition, no studies were conducted in pregnant women, and thus dexlansoprazole MR is considered pregnancy category B.

Healing of erosive esophagitis

Two identically designed trials evaluated the efficacy and safety of dexlansoprazole MR versus lansoprazole in healing erosive esophagitis (31). Both trials were designed to test for non-inferiority; the doses shown to be non-inferior were then tested for superiority as compared with lansoprazole. A total of 4,092 patients with erosive esophagitis were randomized to receive placebo, dexlansoprazole MR 60 mg, dexlansoprazole MR 90 mg, or lansoprazole 30 mg once daily. Of those with erosive esophagitis, 30% demonstrated moderate to severe disease (Los Angeles grades C and D). Healing of esophageal mucosa was assessed by an upper endoscopy after 4 and 8 weeks of treatment. The primary end-point of both studies was the percentage of patients with healed erosive esophagitis at weeks 4 and 8. The secondary end-points included symptoms control and the percentage of subjects with healed moderate-to-severe erosive esophagitis at 4 and 8 weeks. For the primary end-point in both trials, dexlansoprazole MR (both doses) was non-inferior to lansoprazole. Dexlansoprazole MR 60 mg was superior to lansoprazole 30 mg in one trial (85% versus 79% healing rates after 8 weeks of treatment, respectively; $P < 0.05$), and dexlansoprazole MR 90 mg was superior to lansoprazole 30 mg in healing rates after 8 weeks of treatment in both trials (86% versus 79% and 90% versus 85%; $P < 0.05$). Integrated data from these two trials demonstrated that dexlansoprazole MR 90 mg was significantly more effective than lansoprazole 30 mg in patients with moderate-to-severe erosive esophagitis, which resulted in a therapeutic gain of 8% (Figure 3). This therapeutic gain suggests that an additional 25%–30% of patients with moderate-to-severe erosive esophagitis who

Table III. Mean intragastric pH during the total 24-h post-dose time interval on dexlansoprazole MR versus placebo. Reproduced from Lee RD, Vakily M, Mulford D, Wu J, Atkinson SN. Clinical trial: the effect and timing of food on the pharmacokinetics and pharmacodynamics of dexlansoprazole MR, a novel dual delayed release formulation of a proton pump inhibitor - evidence for dosing flexibility. Aliment Pharmacol Ther. 2009;29:824–33 (26), with permission from John Wiley and Sons.

		Relative time of dosing			
	Analysis	Fasting	30 min after breakfast	5 min before breakfast	30 min before breakfast
Mean intragastric pH over 24 hours	Day 1 (placebo)	2.28	2.27	2.19	2.14
	Day 3 (dexlansoprazole MR)	4.46	4.25	4.43	4.53
	Day 3 minus day 1	2.18	1.97	2.24	2.13

were not healed with lansoprazole at week 8 may be healed with dexlansoprazole MR 90 mg. The number needed to treat in order to prevent 1 treatment failure was 13 for patients with moderate-to-severe erosive esophagitis and 17 for patients with all grades of erosive esophagitis. In addition, both doses of dexlansoprazole MR resulted in a high rate of symptoms relief, although not statistically different from those achieved by patients receiving lansoprazole 30 mg/day. More than 80% of the participants in all three treatment groups reported sustained resolution of heartburn (i.e. 7 consecutive heartburn-free days). Both dexlansoprazole MR doses were well tolerated with no dose-dependent adverse events and with a side-effect profile similar to that of lansoprazole 30 mg once daily.

In summary, dexlansoprazole MR-improved healing rates in patients with erosive esophagitis appear to be related to better healing of moderate-to-severe erosive disease. However, there are no studies comparing equivalent doses of dexlansoprazole MR and lansoprazole in healing and controlling symptoms in patients with erosive esophagitis.

Maintenance of erosive esophagitis healing

Subjects with healed erosive esophagitis in either of the two aforementioned trials were eligible for enrollment into one of two trials designed to evaluate the maintenance of healing over a 6-month period. Both studies were randomized, double-blind, and placebo-controlled. Healing was evaluated by an upper endoscopy at 1, 3, and 6 months after initiating treatment.

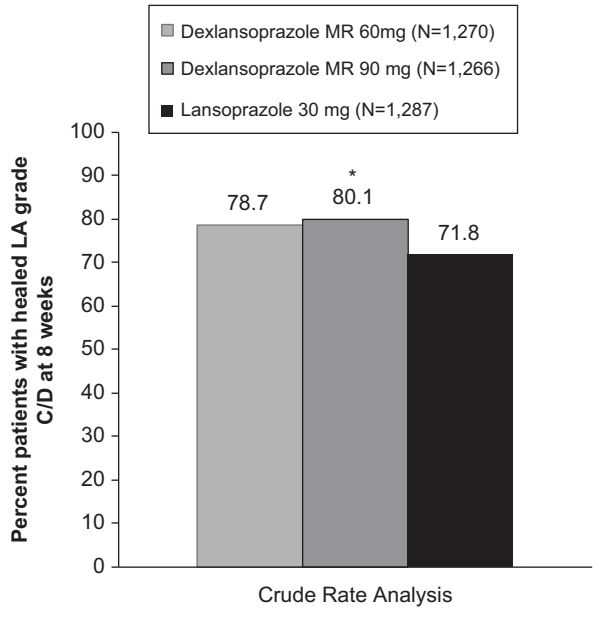

Figure 3. Integrated healing rates of erosive esophagitis at week 8 in patients with base-line Los Angeles grading C or D (*$P < 0.05$ versus lansoprazole). Reproduced from Sharma P, Shaheen NJ, Perez MC, Pilmer BL, Lee M, Atkinson SN, et al. Clinical trials: healing of erosive oesophagitis with dexlansoprazole MR, a proton pump inhibitor with a novel dual delayed-release formulation - results from two randomized controlled studies. Aliment Pharmacol Ther. 2009;29:731–41 (31), with permission from John Wiley and Sons.

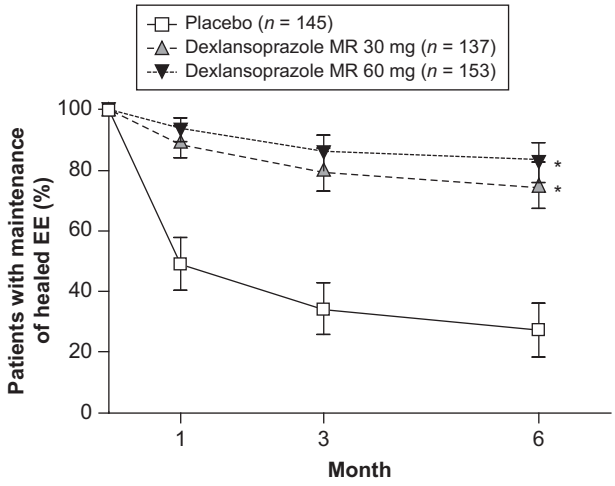

Figure 4. Cumulative life-table rates of maintenance of healed erosive esophagitis (*$P < 0.0025$ versus placebo). Reproduced from Metz DC, Howden CW, Perez MC, Larsen L, O'Neil J, Atkinson SN. Clinical trial: dexlansoprazole MR, a proton pump inhibitor with dual delayed-release technology, effectively controls symptoms and prevents relapse in patients with healed erosive oesophagitis. Aliment Pharmacol Ther. 2009;29:742–54 (21), with permission from John Wiley and Sons.

In the first trial (445 patients), dexlansoprazole MR 30 mg and 60 mg were significantly better than placebo in maintaining healed erosive esophagitis and relieving heartburn (Figure 4) (21). There was no statistically significant difference in the maintenance rate between dexlansoprazole MR 30 mg and 60 mg. However, numerically more patients with moderate-to severe erosive esophagitis maintained healing with the 60 mg dose as compared with the 30 mg dose. Both dexlansoprazole MR doses were highly effective in relieving day-time and night-time heartburn (Figure 5). The median percentages of 24-hour heartburn-free days were 96% and 91% for dexlansoprazole MR 30 mg and 60 mg, respectively, as compared with 29% for placebo. Both dexlansoprazole MR doses were well tolerated over the study period.

In a second study, 451 patients with healed erosive esophagitis were randomized to dexlansoprazole MR 60 mg, 90 mg, or placebo once daily (32). Both doses were superior to placebo in maintaining healed erosive esophagitis, controlling day-time and night-time symptoms, and maintaining quality of life. The 90 mg dose of dexlansoprazole provided no additional clinical benefit over the 60 mg dose.

Treatment of non-erosive reflux disease (NERD)

The efficacy and safety of dexlansoprazole MR in controlling GERD-related symptoms in patients with NERD was evaluated in a 4-week, double-blind, placebo-controlled trial (33). A total of 947 NERD patients were randomized to dexlansoprazole MR 30 mg, 60 mg, or placebo once daily. Diagnosis of NERD was determined based on the presence of heartburn for at least 6 months and normal esophageal mucosa on upper endoscopy. Patients had to have at least 4 days with heartburn symptoms during the 7-day run-in period. The percentage of 24-hour heartburn-free days was significantly higher in patients receiving dexlansoprazole MR 60 and 30 mg once daily versus placebo (54.9% and 50.0% versus 17%, respectively; $P < 0.00001$) (Figure 6). The percentage of nights without heartburn was also significantly higher in patients receiving dexlansoprazole MR 60 and 30 mg versus placebo (80.8% and 76.9% versus 51.7%, respectively; $P < 0.00001$) (Figure 6). Heartburn relief occurred as early as day 3 of treatment with dexlansoprazole MR and was maintained throughout the 4-week treatment period. Dexlansoprazole MR also reduced symptom severity and improved quality of life. There were no statistically significant differences between

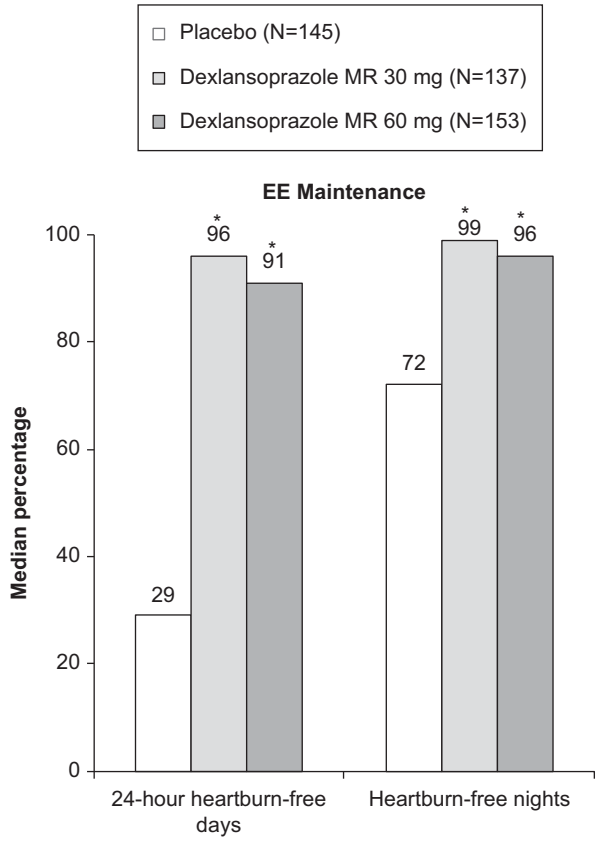

Figure 5. Median percentage of 24-hour heartburn-free days and median percentage of heartburn-free nights during maintenance treatment of healed of erosive esophagitis (*$P < 0.0025$ versus placebo). Reproduced from Metz DC, Howden CW, Perez MC, Larsen L, O'Neil J, Atkinson SN. Clinical trial: dexlansoprazole MR, a proton pump inhibitor with dual delayed-release technology, effectively controls symptoms and prevents relapse in patients with healed erosive oesophagitis. Aliment Pharmacol Ther. 2009;29: 742–54 (21), with permission from John Wiley and Sons.

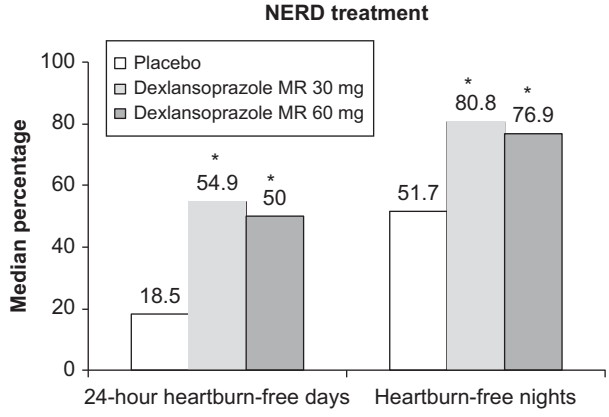

Figure 6. Median percentage of 24-hour heartburn-free days and median percentage of heartburn-free nights during treatment with dexlansoprazole MR for NERD (*$P < 0.00001$). Reproduced from Fass R, Chey WD, Zakko SF, Andhivarothai N, Palmer RN, Perez MC, et al. Clinical trial: the effects of the proton pump inhibitor dexlansoprazole MR on daytime and nighttime heartburn in patients with non-erosive reflux disease. Aliment Pharmacol Ther. 2009;29:1261–72 (33), with permission from John Wiley and Sons.

dexlansoprazole MR 30 mg and 60 mg in any of the clinical end-points. Both dexlansoprazole MR 30 mg and 60 mg were well tolerated by patients, and no dose-related trends were observed for treatment-emergent adverse events.

Side-effects

The safety and tolerability of dexlansoprazole MR were evaluated in more than 4,500 patients in seven trials of the phase III clinical development program. Overall, dexlansoprazole MR in all studied doses was well tolerated and demonstrated a side-effect profile comparable to lansoprazole. The most commonly reported treatment-emergent adverse events (with a frequency of $\geq$ 2%) were diarrhea, abdominal pain, nausea, vomiting, flatulence, and upper respiratory tract infections. Diarrhea was the most common adverse event leading to discontinuation of dexlansoprazole therapy in 0.7% of the patients (34). No changes in the cardiac rhythm or in QT interval were detected in healthy volunteers who received a single dose of dexlansoprazole MR 90 mg or 300 mg (35).

Conclusions

Dexlansoprazole MR is the R-enantiomer of lansoprazole with a unique dual delayed release delivery system that results in a plasma concentration–time profile that is characterized by two distinct peaks 3–4 hours apart. The DDR formulation provides longer duration of therapeutic level of plasma drug concentration as compared with the conventional delayed release lansoprazole. Dexlansoprazole MR is currently approved for three clinical indications: healing of erosive esophagitis at a dose of 60 mg orally once daily for up to 8 weeks, maintenance of erosive esophagitis healing at a dose of 30 mg orally once daily for up to 6 months, and relief of symptoms in NERD patients at a dose of 30 mg once daily for 4 weeks. The safety profile of dexlansoprazole MR is similar to that of lansoprazole. The pharmacokinetic profile of dexlansoprazole MR is not influenced by food.

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