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Review article: dual delayed release formulation of dexlansoprazole MR, a novel approach to overcome the limitations of conventional single release proton pump inhibitor therapy

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SUMMARY

Background
Proton pump inhibitors (PPIs) provide the most effective pharmacotherapy for treating acid-related disorders. However, PPIs do not completely control acid over 24 h with once-daily dosing.

Aims
To discuss limitations inherent in the pharmacokinetics (PK) and pharmacodynamics of conventional PPI formulations, which provide a single drug release. Also, to consider approaches to extending the duration of acid suppression focusing on dexlansoprazole MR, a PPI with a novel Dual Delayed Release (DDR) formulation.

Method
We reviewed the available literature regarding marketed and investigational PPIs.

Results
Non-standard dosing of currently marketed PPIs has produced incremental advances in acid control. Multiple approaches are being evaluated to enhance acid suppression with PPIs. Dexlansoprazole MR is a DDR formulation of dexlansoprazole, an enantiomer of lansoprazole, with two distinct drug release periods to prolong the plasma dexlansoprazole concentration–time profile and extend duration of acid suppression. Clinical studies show that dexlansoprazole MR produces a dual-peak PK profile that maintains therapeutic plasma drug concentrations longer than lansoprazole, with a single-peak PK profile, and increases the percentage of time that intragastric pH >4.

Conclusions
Novel drug delivery platforms, including the dexlansoprazole MR DDR formulation, may improve acid suppression and offer benefits over conventional single release PPI formulations.

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BACKGROUND

Proton pump inhibitors (PPIs) have radically improved the treatment of gastro-oesophageal reflux disease (GERD) and other acid-related disorders since their introduction nearly two decades ago.[1, 2] Despite the dramatic success of pharmacological acid suppression, PPI treatment failure is an increasing problem.[3–5] Currently, there is no standard definition for PPI treatment failure. However, there is consensus that about 30% of GERD patients fail to obtain complete healing and/or symptom resolution after a standard course of PPI therapy.[4, 6]

Multiple factors are involved in PPI failure and include limitations inherent in the drug release kinetics from conventional PPI formulations, which provide a single drug release. Here we describe the pharmacokinetic and pharmacodynamic limitations of conventional PPIs, discuss different approaches to addressing these limitations and focus on dexlansoprazole MR, a novel modified release formulation of dexlansoprazole (an enantiomer of lansoprazole).

REGULATION OF ACID SECRETION

Suppression of gastric acid secretion by PPIs is the greatest when proton pumps are the most active. In the unstimulated state, gastric acid secretion is low (basal acid output) due to inherent inhibition of gastrin release by somatostatin released from D cells in the body and antrum. Anticipation of food ingestion and mastication lead to an increase in vagal tone and acetylcholine release during the cephalic phase of acid secretion. Once food is swallowed, the gastric phase of acid secretion is characterized by a rise in gastric pH, antral distension and nutrient-induced suppression of somatostatin tone, which, in turn, leads to an increase in release of the hormone gastrin that drives enterochromaffin-like cells to release histamine.[7] (Figure 1).

Histamine and acetylcholine are two major secretagogues that bind to parietal cells and, through second messenger systems, ultimately lead to activation of H^+,K^+-ATPase enzymes (proton pumps), thereby stimulating acid output. The final common pathway is fusion of the H^+,K^+-ATPase enzyme with the secretory canaliculus to promote intracellular H^+ exchange for extracellular K^+. This process, in turn, lowers gastric pH and activates a feedback mechanism resulting in re-establishment of somatostatin tone and restoration of the basal (interprandial) secretion (Figure 1).[7]

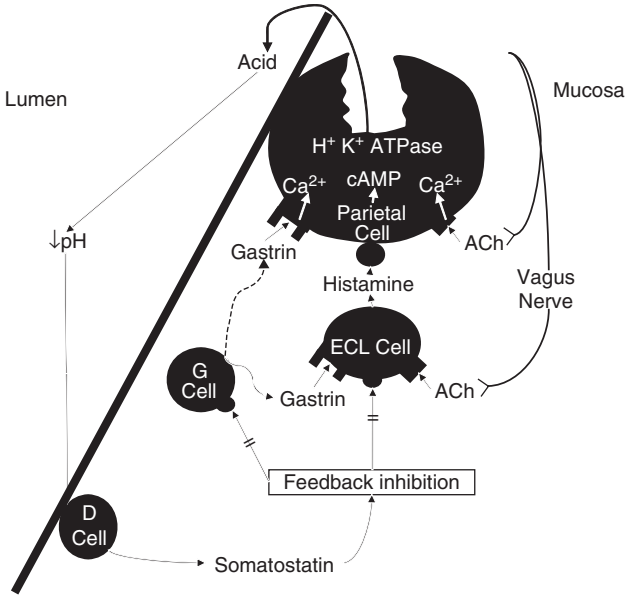

Figure 1. Schematic of regulation of gastric acid secretion. ECL, enterochromaffin-like.

PROTON PUMP INHIBITOR PHARMACOLOGY

Proton pump inhibitors are potent inhibitors of gastric acid secretion because they irreversibly block the final common path of acid production, the activated proton pumps.[8] However, to be most effective, PPIs must be present in high concentrations when the pumps are stimulated.[9] Once-daily oral dosing with conventional PPIs does not completely control acid secretion over 24 h.[2, 10] It is estimated that conventional PPIs inhibit 70% of active pumps at steady state with once-daily dosing.[3, 8, 11] Not all proton pumps are active at the same time and approximately 25% of pumps are regenerated every day.[8] Furthermore, all conventional PPIs have a relatively short plasma half-life (1–2 h) and limited residence time in the systemic circulation.[11, 12] Thus, with once-daily dosing, systemic exposure to PPIs tends to wane until there is no circulating PPI present in plasma during the later stages of the 24-h interval.[9, 13] This enables resumption of gastric acid secretion by uninhibited, restored or new pumps.[9] Additionally, pump turnover time varies greatly within and between individuals.[14] Gastric acid secretion is likely to be more difficult to inhibit in patients whose proton pumps turn over more rapidly compared with those whose pumps turn over more slowly.

Conventional PPIs typically require 3 days to achieve maximal acid suppression, thereby delaying the onset

of acid control.[9] Although there are differences in pharmacokinetics and oral bioavailability of PPIs, the differences in the antisecretory effects among these drugs when administered chronically at standard doses are small.[15] For patients with chronic acid-related disorders, including GERD, increasing the duration of acid suppression is likely to be more beneficial than shortening the time to the onset of acid suppression. As the differences in per-milligram potency of PPIs are only minimal,[16, 17] improved efficacy would probably result from an increased residence time of a PPI in the systemic circulation relative to other PPIs. A number of different approaches have been employed to extend the duration of acid control with PPIs (Table 1).[4]

One approach has been to increase the daily dose and administer it once daily. The recommended dosages of all currently available PPIs produce systemic exposure sufficient to achieve a nearly maximal effect; therefore, increasing the dose would not be expected to produce a difference in duration of acid control despite the fact that the higher dose leads to a slightly longer serum concentration above the threshold required for proton pump inhibition. The few studies that have evaluated the effect of doubling the dose have shown only marginal benefit and no consensus exists on the value of this approach.[18–20]

Another alternative has been to increase the dosing frequency of the conventional PPI by administering it twice daily (either by splitting a standard dose or adding a second dose). This approach has been shown to enhance acid control.[21] Twice-daily dosing may be an option for patients who do not respond to a standard course of PPI therapy. However, increasing dosing frequency has been shown to reduce adherence to treatment regimens.[22–24] Once-daily dosing is the preferred mode of administration, supporting the need for a once-daily PPI with a better pharmacokinetic/pharmacodynamic profile.[5]

Table 1. Methods for improving intragastric pH control

Mechanism	Comments
Increasing daily dosage	Marginal effect
Increasing dosing frequency	Limits adherence
Purified PPI enantiomer	Limited effect (esomeprazole)
PPIs with longer half-life	In development (ilaprazole, tenatoprazole)
Co-administration with pump activators	In development (VB101) Available but unproven (Omeprazole IR)
Potassium-competitive acid blockers	Unavailable
Prolonged intestinal delivery	In development (CMA omeprazole) Approved (Dexlansoprazole MR)

CMA, chemically metered absorption.

Esomeprazole, the *S*-isomer of omeprazole, was the first enantiomer PPI. It is metabolized more slowly than *R*-omeprazole,[25] which results in higher plasma concentration. In a 5-way crossover study, esomeprazole 40 mg was shown to provide a significantly greater acid control than omeprazole 20 mg, lansoprazole 30 mg, rabeprazole 20 mg or pantoprazole 40 mg.[26] Still, esomeprazole maintained intragastric pH > 4 for only 58.43% of the day. Furthermore, the plasma half-life of esomeprazole is similar to that of other PPIs.[11] This suggests that an enantiomer PPI alone may not be sufficient to provide the extended duration of acid control required for optimal efficacy.

New PPI therapies that have greater potency and longer half-lives compared with conventional PPIs are being investigated. For example, preclinical and clinical studies of tenatoprazole in healthy subjects have shown that this nonbenzimidazole compound exhibits more potent inhibitory activity on H^+,K^+-ATPase and a much longer half-life (approximately 8 and 14 h after single and multiple 20 mg doses, respectively), resulting in approximately 20-fold greater area under the plasma concentration curve (AUC), which represents tissue exposure, compared with currently available PPIs.[27, 28] Another PPI, the benzimidazole derivative ilaprazole, is reported to have a half-life of 3.6 h in healthy volunteers[29] and produces a significantly greater and more prolonged suppression of gastric pH than omeprazole in GERD patients.[30] Ilaprazole is currently approved in China.

Strategies to increase the effectiveness of currently available PPIs have also been developed. Vecam (VB101) is an oral agent with pentagastrin-like activity that stimulates proton pumps without the need for food ingestion and can be administered with any PPI.[31] VB101 is reported to be in phase 3 trials[32] and is being tested in combination with omeprazole given 1 h before VB101.[31] Immediate-release omeprazole (Zegerid, Santarus, San Diego, CA, USA), a currently available product, is a combination of non-enterically coated omeprazole powder with sodium bicarbonate, which theoretically shields the uncoated drug from

gastric acid degradation. It possibly provides a more rapid onset of action that may result from the activation of proton pumps caused by neutralization of intragastric pH by sodium bicarbonate.[33]

Potassium-competitive acid blockers (PCABs), which target the K^+-binding region of the H^+,K^+-ATPase, are another class of drug that has been investigated.[27] PCABs garnered interest because they achieve peak plasma concentrations rapidly after oral delivery and produce a fast onset of acid inhibition. On the downside, they require twice-daily administration. The prototype, SCH298080 (Schering-Plough Corporation, Kenilworth, NJ, USA), was developed two decades ago. Development was halted because of hepatic toxicity. Others PCABs have been synthesized and studied; however, AZD0865 (AstraZeneca LP, Wilmington, DE, USA) was the only one to reach large scale trials, where it was shown to be no more effective than standard PPIs. The clinical trial programme for AZD0865 was suspended in 2005.[27]

Alternative delivery systems for some existing PPIs are being developed to prolong the duration of drug exposure and subsequently, acid suppression. Chemically metered absorption (CMA) formulations provide a novel mechanism for delivery that may be combined with any PPI to provide more sustained drug exposure.[10] In healthy subjects, CMA-omeprazole, administered as a 600 mg capsule [delivering approximately a 50 mg molar equivalent of an acid-labile sodium salt of a sulfonamide of omeprazole (Allergan, Inc., Irvine, CA, USA)], maintained intragastric pH > 4 significantly longer than esomeprazole 40 mg in healthy subjects.[34] Half-life and *AUC* values were approximately double those of esomeprazole.[35] Extended plasma concentration can also be achieved with the use of modified-release formulations of a PPI.[11] A modified-release formulation of dexlansoprazole, an enantiomer of lansoprazole, is described in the sections that follow.

THE DESIGN PRINCIPLE

Proton pump inhibitors are prodrugs that are absorbed primarily in the proximal small intestine. Peak plasma concentration (C_{max}) is attained within 2 h, and the residence time in the body is limited, reducing the ability of the PPI to deactivate proton pumps later in the dosing interval (over 24 h) with once-daily dosing. A PPI that prolongs acid suppression with once-daily dosing may improve clinical efficacy.[34]

Lansoprazole and its enantiomers are equipotent at inhibiting proton pumps. However, the *R*-enantiomer, dexlansoprazole, constitutes >80% of circulating drug after oral administration of lansoprazole, provides lower clearance and 5-fold greater systemic exposure than the *S*-enantiomer following oral administration of lansoprazole.[36] Based on these pharmacokinetic advantages, dexlansoprazole was chosen for further clinical development in a manner similar to the development of esomeprazole from omeprazole.[37, 38]

Dexlansoprazole MR (TAK-390MR, Takeda Global Research & Development Center, Inc., Deerfield, IL, USA) is a modified release formulation of dexlansoprazole, which employs a novel Dual Delayed Release (DDR) technology that delivers the drug in two discrete phases of release, thereby inhibiting newly activated proton pumps that turn over following initial PPI inactivation of H^+,K^+-ATPase. Early development of dexlansoprazole MR involved the generation of multiple prototypes of pH-dependent delivery formulations. The dexlansoprazole MR formulation used in clinical development was selected from those early prototypes based on its favourable drug concentration-time profile. The DDR technology provides two distinct drug release periods in the GI tract, thus extending plasma concentrations following oral administration. Dexlansoprazole MR capsules contain a mixture of two types of granules, each providing a different pH-dependent dissolution profile. One type of granule is designed to release drug quickly after the granules reach the proximal duodenum, while the second is designed to release the remaining dose farther along the GI tract at the distal portion of the small intestine. As a result, dexlansoprazole MR produces a dual-peak PK profile, as opposed to the single peak seen with conventional PPIs. To maintain prolonged plasma concentrations, dexlansoprazole MR releases drug over a longer period than conventional delayed release PPIs and thereby requires higher daily doses. Compared with lansoprazole, dexlansoprazole MR achieves higher *AUC*s without a commensurate increase in C_{max}. The amount of drug released is sufficient to achieve therapeutic blood levels, as evidenced by elevated intragastric pH and the percentage of time intragastric pH > 4 over 24 h.[39] Thus, dexlansoprazole MR provides an improved pharmacodynamic profile as compared with the conventional single-release drug delivery systems commonly used in the formulation of PPIs.

Dual Delayed Release also prolongs the mean residence time (MRT; the average time a drug molecule spends in the systemic circulation) of dexlansoprazole. The MRT values for dexlansoprazole MR are 5.6 to 6.4 h compared with 2.8 to 3.2 h for conventional

single release lansoprazole, demonstrating that the DDR formulation extends the duration of drug exposure by prolonging mean absorption time (MAT).[40] This extended dwell time for the drug in plasma occurs without any significant change in mean terminal elimination half-life.

DEXLANSOPRAZOLE PHARMACOKINETICS AFTER ORAL DOSING OF DEXLANSOPRAZOLE MR

The pharmacokinetics of dexlansoprazole were evaluated following oral administration of dexlansoprazole MR in a phase 1 randomized, open-label, multidose, crossover study designed to assess three different doses of dexlansoprazole MR compared with those of lansoprazole 30 mg.[39] Absorption of dexlansoprazole was rapid. The first peak in the dexlansoprazole plasma concentration-time profile occurred approximately 1–2 h after dosing, similar to the t_{max} observed for lansoprazole after oral administration of the conventional delayed release capsules (Prevacid, Takeda Pharmaceuticals America, Inc., Deerfield, IL, USA). A second peak occurred approximately 4–5 h after dosing, prolonging the plasma concentration–time profile. Consequently, dexlansoprazole MR has a longer apparent MRT than lansoprazole following oral administration.[40] This is mainly attributable to the prolongation of the MAT due to drug release in both the proximal and more distal small intestine.

Approximate dose proportionality was observed for mean C_{max} and *AUC* values for dexlansoprazole following single and multiple daily doses of dexlansoprazole MR. The exposure of dexlansoprazole on day 5 was similar to that on day 1 for all dexlansoprazole MR regimens, indicating that dexlansoprazole exhibits time-independent pharmacokinetics following oral administration of dexlansoprazole MR (Table 2).

Table 2. Mean plasma pharmacokinetic parameter estimates for dexlansoprazole MR or lansoprazole (days 1 and 5)[39]

Regimen	Day	Measure	t_{max}, h	C_{max}, ng/mL	AUC_t, ng·h/mL	$AUC_{\infty \text{ or } 24}$*, ng·h/mL	*AUC*/Dose*†	$t_{1/2z}$‡, h	MRT, h
Dexlansoprazole MR 60 mg	1	*n*	34	34	34	30		30	30
		Mean	5.03	1290.18	5995.01	6533.50	109	1.49	6.41
		CV%	44	57	74	77		77	33
	5	*n*	34	34	34	30		30	30
		Mean	4.51	1433.65	6372.74	6720.34	112	1.39	5.10
		CV%	51	49	75	73		46	32
Dexlansoprazole MR 90 mg	1	*n*	35	35	35	30		30	30
		Mean	5.01	1774.89	8564.47	9375.69	104	1.57	6.12
		CV%	51	54	74	72		61	31
	5	*n*	34	34	34	33		33	33
		Mean	4.93	2196.71	9751.12	9938.42	110	1.28	5.63
		CV%	38	42	69	68		51	31
Dexlansoprazole MR 120 mg	1	*n*	32	32	32	28		28	28
		Mean	5.53	2427.81	12,446.74	11,677.40	97	1.36	6.39
		CV%	46	42	75	57		94	30
	5	*n*	30	30	30	29		29	29
		Mean	4.22	2516.60	13,220.13	13,574.32	113	1.44	5.89
		CV%	46	46	71	69		69	30
Lansoprazole 30 mg	1	*n*	31	31	31	27		27	27
		Mean	1.71	839.77	2040.85	2179.12	73	1.23	2.99
		CV%	29	40	82	82		52	38
	5	*n*	31	31	31	30		30	30
		Mean	1.54	844.65	1885.85	1949.17	65	1.11	2.84
		CV%	22	45	82	79		54	33

* AUC_∞ for day 1, AUC_{24} for day 5; † Dose-normalized *AUC* (ng·h/mL/mg); ‡ Harmonic mean.
AUC_{24}, area under the plasma concentration-time curve from time 0 to 24 h; AUC_∞, *AUC* from time 0 to infinity; AUC_t, *AUC* from time 0 to last measurable concentration; C_{max}, maximum observed plasma concentration; CV%, coefficient of variation; MRT, mean residence time; t_{max}, time to reach the observed maximum plasma concentration; $t_{1/2z}$, apparent terminal elimination half-life.

For dexlansoprazole MR (60, 90, and 120 mg), mean *AUC* values were 3–7 times higher, and mean C_{max} values were 1.5–3 times higher than for lansoprazole 30 mg. Dexlansoprazole MR 60, 90, and 120 mg extended the duration of drug exposure compared with lansoprazole 30 mg as evidenced by a delayed t_{max} and substantially higher plasma concentrations 3–8 h postdose.

The presence of the characteristic 2-peak, prolonged PK profile following administration of dexlansoprazole MR in phase 1 studies in healthy subjects was subsequently confirmed by population pharmacokinetic analysis of combined data from two studies:[41]a phase 1 pharmacokinetic study in GERD patients who received dexlansoprazole MR 30, 60, or 90 mg and from a small number of symptomatic non-erosive GERD patients who participated in a long-term (12-month) safety study that assessed dexlansoprazole MR 60 and 90 mg. The predicted population concentration-time profiles following oral administration of dexlansoprazole MR 30, 60, and 90 mg in patients from these studies are shown in Figure 2. The 2-peak prolonged profile, as well as the estimated systemic exposure results, was consistent with the findings in healthy subjects in phase 1 studies.

The concept underlying dexlansoprazole MR is that it is not simply a higher dose of an enantiomer of lansoprazole; the modified release technology alters the time course of the plasma time-concentration profile, delaying the t_{max} and overcoming the pharmacokinetic limitation of the drug's short half life. A retrospective analysis of dexlansoprazole MR 60 mg and lansoprazole 60 mg using data from two separate but similarly designed (randomized, double-blind, dose-ranging) phase 1 studies was performed to evaluate the pharmacokinetics of these two doses.[42] These data are representative of results from other studies. The plasma concentration–time profile for dexlansoprazole MR 60 mg was characterized by two distinct peaks (Figure 3). The first peak occurred 1–2 h after dosing, similar to the t_{max} observed for lansoprazole 60 mg. The second peak occurred 4–5 h after dosing. The average MRT value for dexlansoprazole (5.5 h) was nearly twice that for lansoprazole (2.9 h), demonstrating the extended duration of drug exposure following the administration of dexlansoprazole MR. The longer MRT values for dexlansoprazole MR are attributable to the release characteristics of the DDR formulation leading to a prolongation of the MAT. Dexlansoprazole MR 60 mg maintained plasma drug concentrations for a longer period of time than lansoprazole 60 mg. However, the relative contributions of the enantiomeric and the MR approaches in the development of dexlansoprazole MR cannot be defined precisely in the absence of additional multiarmed studies comparing dexlansoprazole with and without MR technology with standard lansoprazole with and without MR technology.

POTENTIAL LIMITATIONS OF MR TECHNOLOGY

The MR formulation technology may be limited in that the time interval separating the two drug releases cannot be increased. Further separation of the second plasma dexlansoprazole peak from the first peak may result in the drug release beyond the ileocecal junction in the colon, where dexlansoprazole absorption is expected to be limited. Nevertheless, the dexlansoprazole MR design principle is adequate to prolong the plasma concentration–time profile and extend the duration of acid suppression with a single daily dose. Consequently, dexlansoprazole MR optimizes the capabilities of the currently available technology and may provide many of the benefits of twice-daily dosing in a QD regimen.

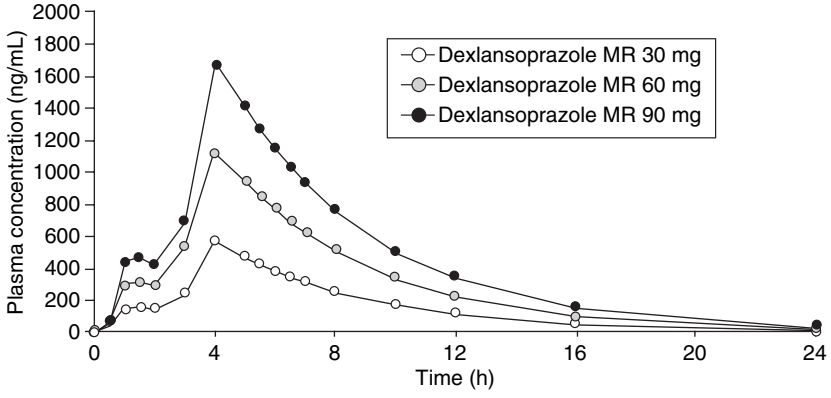

Figure 2. Predicted dexlansoprazole population pharmacokinetic profiles following oral administration of dexlansoprazole MR 30, 60, and 90 mg in patients.

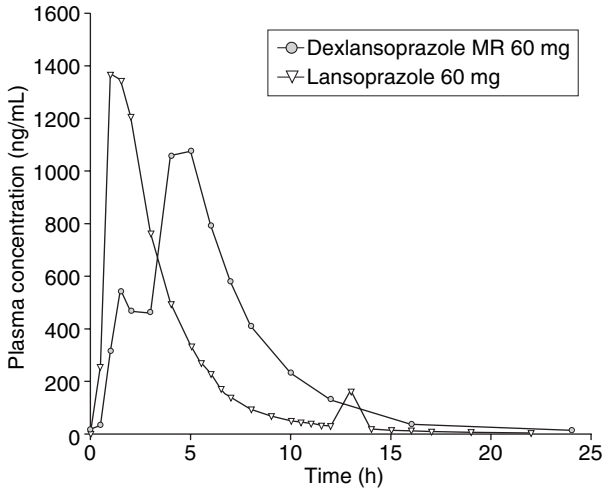

Figure 3. Mean plasma concentration-time profiles from two separate trials evaluating dexlansoprazole MR 60 mg or lansoprazole 60 mg on day 5 in healthy subjects. Note that first peak occurring with dexlansoprazole corresponds with that of lansoprazole and that the t_{max} has been shifted by approximately 3 h.

A higher dose of dexlansoprazole MR is used compared with the conventional PPIs to achieve the prolonged concentration–time profile produced by releasing the drug over a longer period of time. Hence, a higher dexlansoprazole *AUC* without a commensurate increase in C_{max} was achieved.[40] Potential concerns about a high drug load in the formulation of dexlansoprazole MR have not been observed after oral administration of dexlansoprazole MR 30–120 mg doses in the clinical trials because the drug release occurs at two distinct time intervals within GI tract.[39] In addition, no issue with drug dumping has been observed during the development of dexlansoprazole MR. Furthermore, the terminal elimination $t_{1/2}$ of dexlansoprazole was not altered due to the prolonged drug absorption and there was no evidence of meaningful systemic drug accumulation after once-daily administration of dexlansoprazole MR.[39] As would be expected in drugs of this class, increases in fasting serum gastrin have been observed in patients receiving dexlansoprazole MR 60 and 90 mg for up to 12 months.[43] These increases in gastrin levels were not dose-related and gastrin concentrations remained stable after the 3 months of dosing. Further, no clinically concerning findings have been observed in mean change from baseline in laboratory values, vital signs or gastric biopsy results.[43–46]

DEXLANSOPRAZOLE PHARMACODYNAMICS AFTER ORAL DOSING OF DEXLANSOPRAZOLE MR

The percentage of time that intragastric pH is maintained >4 over a 24-h period postdose has become the benchmark for predicting clinical efficacy of PPIs in the treatment of acid-related disorders.[47] The pharmacodynamic profile of dexlansoprazole was evaluated following oral administration of dexlansoprazole MR or a standard dose of lansoprazole.[39] After oral administration of dexlansoprazole MR 60–120 mg, the pharmacodynamics of dexlansoprazole compared with lansoprazole 30 mg were characterized by significantly higher 24-h mean intragastric pH values and percentage of time that pH was >4 (Figures 4 and 5). Pairwise comparisons of values for mean 24-h intragastric pH and the mean percentage of time pH was >4 were significantly greater for each dexlansoprazole MR regimen compared with lansoprazole 30 mg during >9- to 12-h and >12- to 16-h intervals. Potentially clinically meaningful increases in mean pH (>0.5 as noted previously by Bell and colleagues)[47] and percent of time pH was >4 (greater than 10% during the >16- to 24-h interval) were observed on day 5 for dexlansoprazole MR doses. Dexlansoprazole MR extended the exposure and prolonged pH control across all dose levels compared with lansoprazole 30 mg.[39]

Establishing a threshold PPI concentration and dose to achieve the percentage of time that intragastric pH is maintained >4 over a 24-h period would provide a useful marker to assess and compare the effects of various drug delivery systems on the pharmacokinetic and pharmacodynamic profiles of a drug in this class. During the clinical development of dexlansoprazole MR, empirical models were selected based on the Akaike Information Criteria (AIC) and used to understand better the relationship between the percentage of time that plasma concentration remains higher than a threshold concentration and the percentage of time that intragastric pH was >4 after administration of multiple oral doses of dexlansoprazole MR or lansoprazole.[48] Based on this empirical modeling analysis, 125 ng/mL was determined to be the threshold concentration that provides the best relationship between the percentage of time that concentration is higher than this level and the percentage of time that pH was >4.[49] From doses of 30 mg to 120 mg, dexlansoprazole MR was found to maintain plasma drug concentration higher than the 125 ng/mL-threshold, 2 to 3 times longer than lansoprazole 30 mg at all doses (Figure 6).

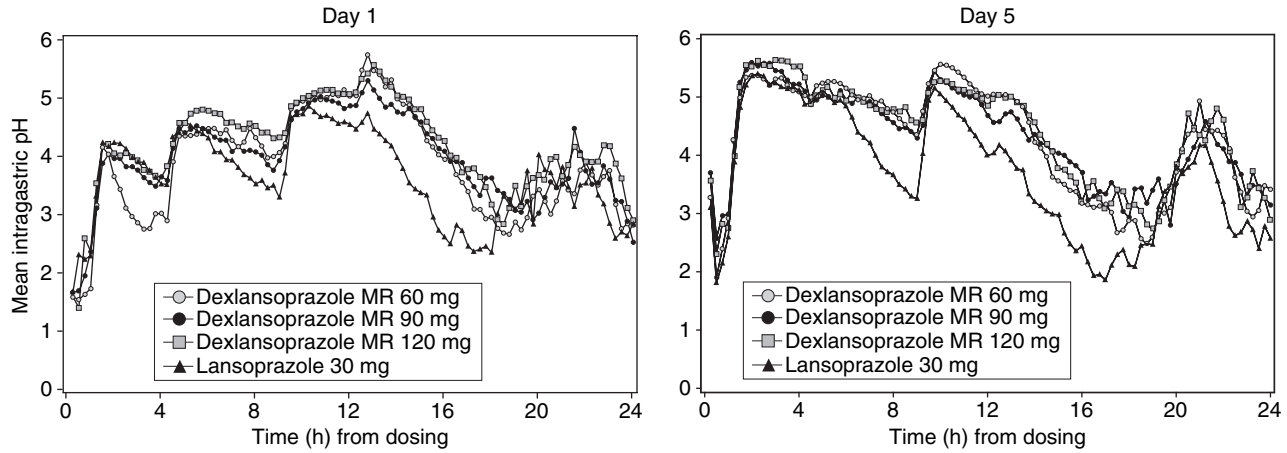

Figure 4. Mean intragastric pH measurements for dexlansoprazole MR 60, 90, and 120 mg and lansoprazole 30 mg in healthy subjects.

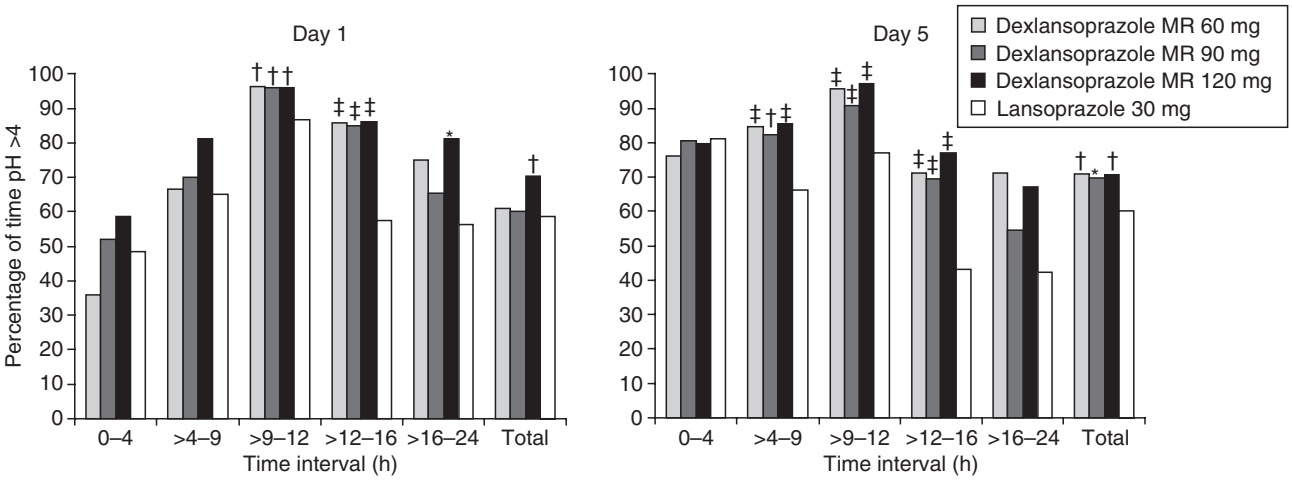

Figure 5. Mean percentage of time pH was >4 for dexlansoprazole MR 60, 90, and 120 mg and lansoprazole 30 mg in healthy subjects. $^{*}P < 0.05$; $^{\dagger}P < 0.01$; $^{\ddagger}P < 0.001$.

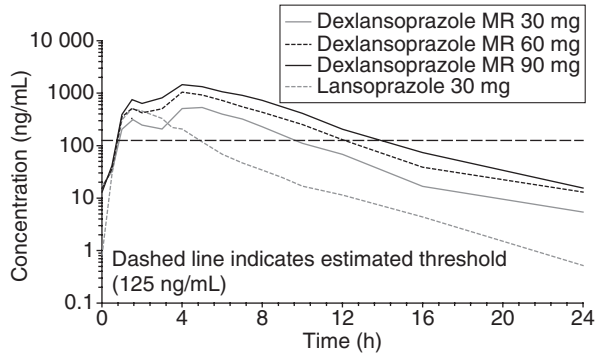

Figure 6. Mean concentration-time profiles for dexlansoprazole MR 30, 60, and 90 mg and lansoprazole 30 mg based on an empirical modeling analysis.

CONCLUSIONS

Conventional PPIs have advanced the standard of care in patients with acid-related disorders since they were first marketed in the 1980s. Despite the efficacy of PPIs, overcoming PPI failure has become an important challenge in the management of GERD.[4] Knowledge of key underlying mechanisms for PPI treatment failure has provided researchers with direction for discovering alternative therapeutic options to address unmet needs of patients on PPI therapy.

Emerging data on dexlansoprazole MR suggest that novel drug delivery platforms may help address some of the underlying shortcomings of PPIs delivered

using currently available conventional formulations and have the potential to improve clinical efficacy.[34] The DDR formulation technology of dexlansoprazole MR results in a plasma concentration-time profile characterized by two distinct peaks, leading to an extended duration of therapeutic plasma drug concentrations compared with conventional delayed release lansoprazole. Furthermore, dexlansoprazole MR maintains plasma drug concentrations above the threshold level longer than lansoprazole at all doses, resulting in an optimized drug exposure-intragastric pH relationship. Finally, dexlansoprazole MR, utilizing DDR technology, increases the percentage of time intragastric pH is >4 vs. lansoprazole on Day 5, suggesting that it may be associated with improved clinical outcomes.[47, 50]

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