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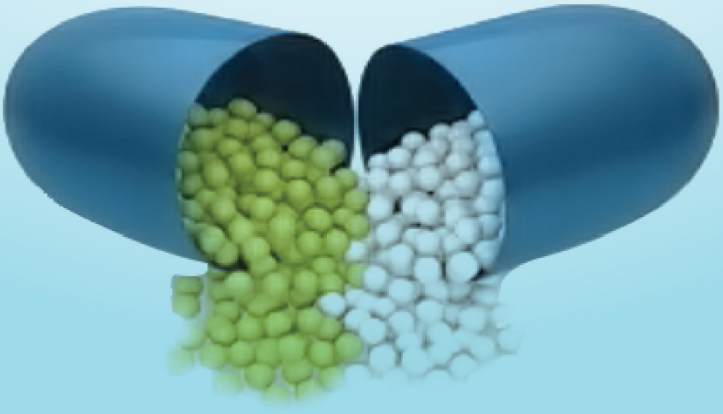

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TOPIC HIGHLIGHT

Michele Cicala, Professor, MD, *Series Editor*

Proton pump inhibitor resistance, the real challenge in gastro-esophageal reflux disease

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Abstract

Gastro-esophageal reflux disease (GERD) is one of the most prevalent chronic diseases. Although proton pump inhibitors (PPIs) represent the mainstay of treatment both for healing erosive esophagitis and for symptom relief, several studies have shown that up to 40% of GERD patients reported either partial or complete lack of response of their symptoms to a standard PPI dose once daily. Several mechanisms have been proposed as involved in PPIs resistance, including ineffective control of gastric acid secretion, esophageal hypersensitivity, ultrastructural and functional changes in the esophageal epithelium. The diagnostic evaluation of a refractory GERD patients should include an accurate clinical evaluation, upper endoscopy, esophageal manometry and ambulatory pH-impedance monitoring, which allows to discriminate non-erosive reflux disease patients from those presenting esophageal hypersensitivity or functional heartburn. Treatment has been primarily based on doubling the PPI dose or switching to another PPI. Patients with proven disease, not responding to PPI twice daily, are eligible for anti-reflux surgery.

Key words: Gastro-esophageal reflux disease; Proton pump inhibitor; Ambulatory pH-impedance monitoring; Esophageal hypersensitivity; Gastro-esophageal reflux disease treatment

Core tip: The present review focuses on the subgroup of patients in whom proton pump inhibitor refractoriness more frequently occurs, on the mechanisms possibly involved in the lack of response, the diagnostic work-up and the therapeutic strategies in these patients. Various mechanisms and factors have been demonstrated and some mechanisms have also been proposed, although not yet supported by strong evidence. In the management of these patients, a careful clinical interview might conduct the diagnostic evaluation and the therapeutic approaches.

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INTRODUCTION

Gastro-esophageal reflux disease (GERD) is one of the most prevalent chronic diseases in Western countries, affecting approximately 20% of the United States adult population weekly, and 7% daily[1,2]. Although the acid-suppressive drugs have improved in efficacy over the last few decades, and proton pump inhibitors (PPIs) represent the mainstay of treatment both for healing erosive esophagitis and for symptom relief as well as for preventing complications, several studies have shown that up to 40% of GERD patients reported either partial or complete lack of response of their symptoms to a

standard PPI dose once daily[3-5]. Therefore, particularly in third referral Gastrointestinal Units, the management of refractory GERD patients is a very common, as well as a very challenging, task. Indeed, chronic heartburn is associated not only with a significant decrease in all the physical and mental domains of health-related quality of life questionnaires but, also, with a significant increase in healthcare costs, due to repeated diagnostic procedures, physician examinations and drug prescriptions[6]. The present review focuses on the subgroup of patients in whom PPI refractoriness more frequently occurs, on the mechanisms possibly involved in the lack of response, the diagnostic work-up and the therapeutic strategies adopted in these patients.

MOST DIFFICULT PATIENTS

The clinical suspicion that the symptomatic response to PPIs is less frequent in those patients affected by the most common presentation of GERD, *i.e.*, non-erosive reflux disease (NERD), than in those presenting erosive esophagitis (ERD) has been confirmed several years ago. In one of the first reports focusing on NERD patients, treatment with omeprazole 20 mg for 4 wk resulted in complete symptom relief in only 46% of patients, in even fewer of them on 10 mg and in those receiving placebo, and symptom improvement (satisfaction) in 66%[7]. The main messages of the study were the better results obtained with higher doses, which do not support the concept of NERD as a milder form of GERD and, more important, the concept that symptom relief proves to be directly correlated with esophageal acid exposure time, that is to say, the greater the acid exposure, the higher the PPI response. So far, only a few trials have compared the outcome of PPI treatment in NERD *vs* ERD patients. Almost all of these trials were carried out using a double blind, parallel group design with a short (4 wk) follow-up period. In a study performed by Bate *et al*[8], relief of heartburn was achieved in 47% of NERD, and in 53% of ERD patients (the difference not being significant). Of interest, as far as concerns the non-responders, 67% became heartburn-free after an additional 4 wk of treatment[8].

Better results, both in NERD and ERD patients, have been reported in a multicenter study by Venables *et al*[9]: heartburn relief, was achieved after 4 wk of omeprazole, in more than 60% of NERD and in 79% of ERD patients. Galmiche *et al*[10], besides heartburn remission, reported semi-quantitative measures of symptom severity and their impact on quality of life: At 4 wk, heartburn was resolved in 62% of NERD and 71% of the ERD patients, even higher values being observed after an additional 4-wk treatment with omeprazole. Of interest, quality of life improved in all treatment groups, but the improvement was higher in those on full PPI dose (*vs* half-dose) group[10]. Armstrong *et al*[11], in a randomized, Canadian multicenter study, confirmed complete relief in a larger proportion (although not significant) of ERD, than NERD, patients receiving pantoprazole. Although some data were not stratified for the presence/absence of esophagitis, a modified intention-to-treat analysis demonstrated, in the PPI group, a trend of increased therapeutic gain throughout the 4 wk[11]. More recently, a multicenter trial performed in Japan, has shown that, following 4-wk rabeprazole 40 mg/die, complete relief of symptoms was achieved in only 36% of the NERD and in approximately 55% of the erosive group, a response rate similar to that observed in Western countries. Here, patients were stratified according to a modified Los Angeles classification and, of interest, the more severe the esophageal mucosal injury, the more effective the therapy. The design of the study and symptom assessment could also demonstrate that the median time to the first 24- and 48-h heartburn-free intervals was significantly shorter for erosive than for non-erosive patients[12]. Before concluding the issue regarding the response to PPI treatment in non-erosive *vs* erosive reflux disease, it may be useful to re-consider a major dilemma concerning NERD, namely the lack of a standard definition, which is likely to affect the results of clinical trials, and makes interpretation of data, challenging. It is generally agreed that NERD is the most common presentation (up to 75%) of GERD, with the same symptom severity and quality of life impairment as ERD, but, at the same time, there is still lack of agreement concerning the definition of NERD: should all symptomatic patients with endoscopy-negative findings be considered to be suffering from NERD? The 24-h pH test does, indeed, distinguish patients with and without pathological esophageal acid exposure, and, more important, patients with and without significant symptom-reflux association, which can reveal hypersensitivity to non-pathological acid exposure.

Endoscopy-negative patients not presenting pathological acid exposure, with negative symptom-reflux association and without a satisfactory response to the PPI test are, indeed, affected by functional heartburn, according to the Rome Ⅲ criteria, and thus do not belong to the NERD population. These "functional" patients, in whom symptoms are, by definition, not related to reflux, might be a minority but they frequently attend the outpatients units and are, often, enrolled in clinical trials. The low response to PPIs reported in NERD may be affected by including this functional subgroup in a "too heterogeneous" NERD population. Another common risk of mis-classification of NERD is due to the healing of esophagitis at the time of upper endoscopy, and, thus, a recent consensus underlines the importance not only of an appropriate pharmacological washout before endoscopy but, also, of checking for previous endoscopic findings in the same patient, if available[13]. In the attempt to better evaluate the response rate in NERD patients according to the different criteria of the participants enrolled in clinical trials, a recent meta-analysis of the literature has demonstrated that lower rates of partial or complete response are reported in the large majority of studies with a poor characterization of the patients, lacking pH-test findings

Table 1 Principal mechanisms and factors involved in proton pump inhibitor resistance

Adherence to PPI therapy
Compliance
Dosing, time
Reflux pattern
Weakly acidic reflux
Proximal reflux
Mixed reflux
Residual acid refluxes
Esophageal hypersensitivity
Other mechanisms
Reduced PPI bioavailability
Increased PPI metabolism
Mutations cyt. p450

PPI: Proton pump inhibitor.

and, therefore, likely including patients with functional heartburn and functional dyspepsia[14]. Future studies, enrolling well-defined NERD patients and, hopefully, with a longer follow-up, might offer more precise data on PPI efficacy.

MECHANISMS AND FACTORS INVOLVED IN PPI RESISTANCE

In patients with reflux symptoms refractory to medical therapy, namely those with typical GERD symptoms - heartburn and regurgitation - not responding to a standard or double dose of PPI given for at least 8 wk, various causes have been demonstrated and some mechanisms have also been proposed, although not yet supported by strong evidence. Principal mechanisms and factors involved in PPI resistance are summarized in Table 1.

Ineffective control of gastric acid secretion, in terms of excessive residual acid reflux despite adequate PPI treatment, can be due to lack of compliance, rapid PPI metabolism - due to CYP2C19 polymorphism - or hypersecretory syndromes such as Zollinger Ellison. While these two latter conditions are uncommon, non-compliance to treatment, in terms of incorrect medication dose or timing, is reported to frequently occur. Two recent meta-analyses have clearly shown that lack or non-compliance to therapy is particularly frequent in GERD patients, in whom adherence to the prescribed PPI is acceptable in only 55% of patients, at one month, and in 30% at 6 mo after prescription.

The lowest levels of compliance, in terms of daily or dose administration, were observed in NERD patients, and, of the various factors, the most frequently reported were: lack of knowledge about the treated disorder, desire for personal control, side-effects and additional medications[15]. In a study focusing on patients with persistent GERD symptoms despite prolonged PPI treatment, it was reported that in less than 46% of these patients the drug was administered in the fasting state, before breakfast[16].

In the new era of combined pH and impedance 24-h monitoring, it is possible to detect reflux episodes with more accuracy compared to the pH-monitoring alone, following the movement of refluxate along the esophageal body and to distinguish air/liquid component as well as acidic composition of each episode. Over the last decade, several pH-impedance investigations have been conducted on patients with NERD and, particularly, on those patients with a poor symptomatic response to PPIs. Results emerging from those studies have confirmed a condition already observed with pH-tests, namely esophageal hypersensitivity in terms of perception of not-abnormal reflux, and this enhanced sensitivity involves not only acidic reflux but, also, weakly acidic reflux and gas-containing (mixed) reflux episodes. Either cohort studies analyzing the reflux pattern and reflux-symptom association[17] or pathophysiologic investigations, looking at the perception of each reflux episode[18] have clearly shown that, in NERD patients, besides acidic reflux, weakly acidic reflux and gas-containing episodes (both of them probably associated with increased reflux volume and esophageal distension) are responsible for a significant proportion of symptoms (approximately 20%), much higher when compared to those in ERD patients. These studies have demonstrated both a possible mechanism explaining symptom persistence despite acid suppression and the higher diagnostic yield of the pH-impedance test in these patients.

Recent pathophysiological investigations have also shown that a dynamic characteristic, such as the proximal migration of reflux, an indicator of high volume refluxate, represents a major determinant of reflux perception, particularly in NERD patients. Interestingly, in large multicenter studies, these three characteristics, namely weakly acidic reflux, mixed (liquid-gas) reflux and the higher proximal extent, have also been recognized as the main mechanisms underlying failure of PPI treatment in patients with reflux-related symptoms[19-21]. Finally, experimental studies suggest that some of the NERD patients presenting PPI-resistance may also present a more generalized condition of visceral hyperalgesia[22].

The research field focusing on the ultrastructural and functional changes in the esophageal epithelium has contributed to a better understanding of NERD and of PPI-resistance pathophysiology. In those conditions not associated with severe mucosal inflammation and/or epithelial erosions, it is not clear how severe and recurrent symptoms can occur in an apparently normal mucosa (NERD). A well studied ultra-structural alteration, *i.e.*, dilated intercellular spaces (DIS), has been demonstrated by means of Transmission Electron Microscopy both in ERD and NERD patients[23,24], and this would explain the genesis of symptoms triggered by the activation of intramucosal chemo-sensitive pain-receptors. The increased para-cellular permeability, associated with the presence of DIS, and the resulting breakdown in the epithelial barrier, do not necessarily result from excessive acid exposure, as shown in NERD patients presenting a normal acid contact time at pH-monitoring, can be induced, in ex-

perimental models, by weakly acidic and acidified bile solutions and even occurs during acute stress situations[25]. Interestingly, the feature of DIS has been observed in patients with PPI-resistant symptoms, during treatment, but not in patients affected by functional heartburn[26], returns to normal following PPIs, together with symptoms[27], and, therefore, the impaired mucosal integrity would now appear to be the mechanism that best explains the enhanced sensitivity to chemical and mechanical stimulation in NERD and PPI-resistant patients. Indeed, peripheral sensory pathways, in terms of up-regulated pain receptors, central sensitization of sensory neurons and processing of ascending stimula are now under intense investigation and may be involved in the conditions of esophageal and visceral hypersensitivity.

Several conditions not, or not directly, related to gastro-esophageal reflux, should also be considered when assessing PPI refractoriness. Infectious esophagitis, eosinophilic esophagitis and pill esophagitis may be other, not frequent, causes of refractory heartburn. Anxiety and depression, demonstrated to increase reflux perception, may also be involved.

DIAGNOSTIC EVALUATION

Clinical evaluation

As previously pointed out, lack of compliance - in terms of adherence to treatment, timing and dosing - and the presence of functional heartburn are the main findings in patients referred for refractory heartburn, therefore a careful interview, also looking at the confounding presence/co-existence of atypical - ENT and respiratory - symptoms and at their possible relation with GER, is crucial. The presence of functional disorders, such as functional dyspepsia and irritable bowel syndrome, as well as of psychological disorders, should also be assessed as these are associated with visceral hyperalgesia as well as a with reduced response to acid-suppressive drugs.

Endoscopy

Although the sensitivity of upper endoscopy is very low - most patients have NERD - it might be helpful for ruling out pill and infectious esophagitis, eosinophilic esophagitis (4%-6% in PPI-refractory patients, multiple biopsies should be obtained) and the rare cases of Zollinger Ellison syndrome.

Esophageal manometry

Conventional or high-resolution manometry should be performed in order to rule out severe motor disorders, to better locate LES for pH-sensor positioning, and, furthermore can provide useful information when a surgical anti-reflux approach is indicated.

Ambulatory pH [impedance] monitoring

The only test which provides quantitative information on the esophageal exposure to reflux, also assessing its relationship with symptoms, remains 24-h ambulatory pH-monitoring. Prolonged (48 to 96 h) wireless pH-monitoring improves the diagnostic yield of the test by improving the likelihood of a positive reflux-symptom association[28]. We have previously discussed the advantages of the combined ambulatory pH-impedance test, as well as its greater accuracy in discriminating NERD patients from those presenting esophageal hypersensitivity or functional heartburn. Indeed, typical and atypical symptoms not responding to PPIs represent the main indication for performing ambulatory pH-impedance monitoring. The test performed "off" therapy can confirm or exclude a pathological gastro-esophageal reflux and, according to a recent investigation[29] offers the best chances to detect a positive association between symptoms and reflux episodes. Recent studies have shown that refractory patients studied "off" and "on" therapy are, indeed, characterized by an abnormal number of reflux events and a higher sensitivity to all types of reflux - acidic, weakly acidic, mixed and propagated[30,31]. On the other hand, performing the test "on" PPIs, provides useful information regarding the efficacy of acid-suppressive treatment and may detect a positive association between symptoms and weakly acidic reflux episodes - the large majority of episodes during acid suppressive drug -, which is a possible indication for anti-reflux surgery[32].

MANAGEMENT OF PATIENTS

Proton pump inhibitors

The large majority of patients with reflux symptoms receive PPI therapy once daily. If symptoms are not relieved, and after the presence of functional heartburn and CYP2C19 polymorphism have been excluded, several therapeutic strategies can be proposed. These include doubling the current PPI dosage or switching to another PPI.

Indeed, treatment failure may result from an insufficient dose of PPI. Doubling the PPI dose, giving PPI before breakfast and before dinner, is one of the most common therapeutic strategies adopted by practicing physicians having also been recommended in the 2008 American Gastroenterological Association guidelines for GERD, and confirmed by the Cochrane review[33,34]. However, is still not clear the dose-response relationship for heartburn resolution in either erosive esophagitis or non-erosive reflux disease patients[35]. Even if doubling the PPI dose has become one of the standard strategies, escalation of the PPI administration beyond the twice daily dosage, both for symptom control or for healing of erosive esophagitis, is not supported by strong clinical data. In the attempt to identify the patients who would benefit from dose escalation, Becker *et al*[36] performed pH-impedance monitoring in patients presenting persistent symptoms despite one month of standard PPI therapy. According to the pH-impedance data, two groups, one with and one without pathological findings, received high dose PPI (or fundoplication in a few cases). Imped-

ance was pathological in 40% of the non-responders, in whom escalating therapy was significantly more successful (90% relief) than in patients with normal findings.

Switching to another PPI is a very common, cost-effective, therapeutic strategy adopted in the management of patients who failed with the PPI once daily approach. In several studies, switching those patients who had failed with a PPI to esomeprazole, resulted in significant symptom improvement[37,38].

Antireflux surgery

Although it is well established that patients with symptoms not responding to PPIs have a less favorable post-operative clinical outcome compared to those patients responding to treatment, refractory GERD represents the most common (88%) indication for anti-reflux surgery. In a recent long-term follow-up study, 82% of the PPI-refractory patients reported that the preoperative reflux symptoms were completely resolved, and 94% were satisfied with the results of the surgery[39]. Several studies have suggested that a positive symptom-reflux association[40,41] and/or pathological AET[42,43], observed by impedance-pH monitoring in patients off PPI, predict a favorable response to surgery. It has been recently demonstrated that ranitidine 300 mg twice daily has a comparable efficacy respect to rabeprazole 20 mg twice daily when given on-demand for the treatment of NERD and both medications are associated with improvement of the quality of life[44].

It should be taken into consideration that the large majority of PPI-resistant patients do not present an erosive disease, therefore, given the possible adverse events associated with surgery and the recognized benign course of NERD, anti-reflux surgery should only be considered in selected patients, in whom objective evidence of reflux is revealed upon investigation. In summary, although surgery appears to be valid therapeutic option in GERD patients with typical symptoms who failed to respond to PPIs, further outcome and controlled studies, on a larger series of patients, using combined impedance-pH monitoring are warranted in order to draw definite conclusions.

Lifestyle modifications

It has been recently suggested that weight loss and elevation of head of the bed are effective in improving GERD symptoms in refractory patients, whilst no sufficient data support any other lifestyle modifications[45]. It has been recently reported that shorter dinner-to-bed time interval (less than 3 h) is significantly associated with persistence of GERD symptoms[46].

However, the relevance of lifestyle modifications in GERD patients who failed PPI treatment still remains to be fully elucidated.

Visceral pain modulators, psychological treatment

The therapeutic option represented by visceral pain modulators is highly attractive but, at present, studies specifically evaluating their efficacy in refractory GERD patients are still lacking. Tricyclic anti-depressants and selective serotonin reuptake inhibitors have been shown to relief esophageal pain in patients with non-cardiac chest pain[46-48]. Unfortunately, side effects of these drugs appear to be not uncommon and may hamper their usage.

It has been shown that refractory patients are more likely to have a psychosocial comorbidity[49], therefore it is conceivable that refractory GERD patients would benefit of psychological evaluation and treatment.

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Alimentary Pharmacology & Therapeutics

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]

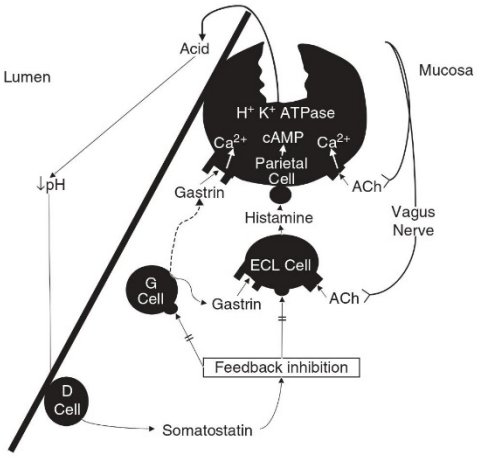

Figure 1. Schematic of regulation of gastric acid secretion. ECL, enterochromaffin-like.

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_{∞} 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.

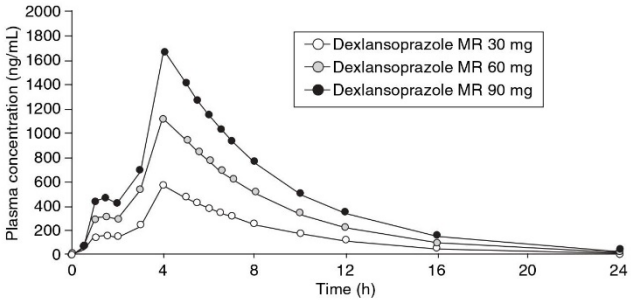

Figure 2. Predicted dexlansoprazole population pharmacokinetic profiles following oral administration of dexlansoprazole MR 30, 60, and 90 mg in patients.

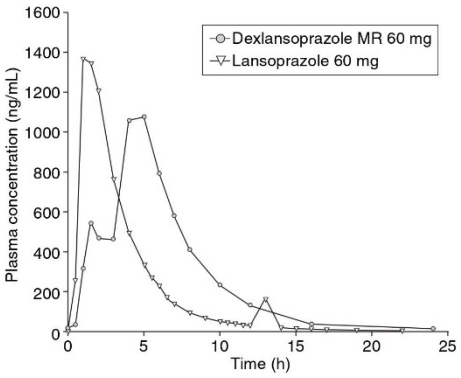

Figure 3. Mean plasma concentration-time profiles from two separate trials evaluating dexlansoprazole MR 60 mg or lansoprazole 60 mg on day 5 in healthy subjects. Note that first peak occurring with dexlansoprazole corresponds with that of lansoprazole and that the t_{max} has been shifted by approximately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

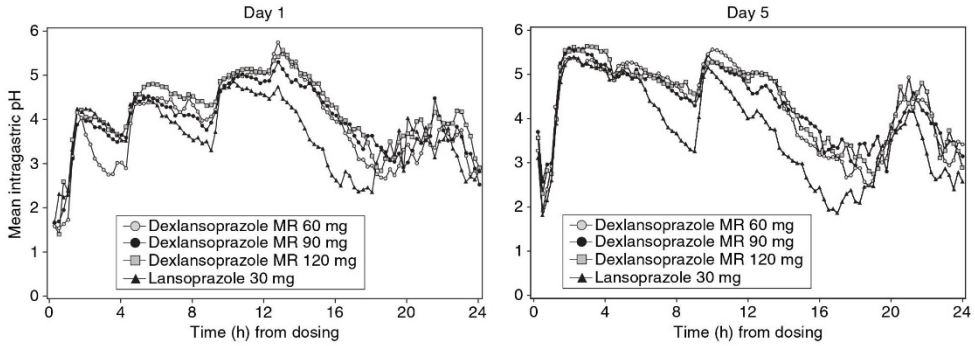

Figure 4. Mean intragastric pH measurements for dexlansoprazole MR 60, 90, and 120 mg and lansoprazole 30 mg in healthy subjects.

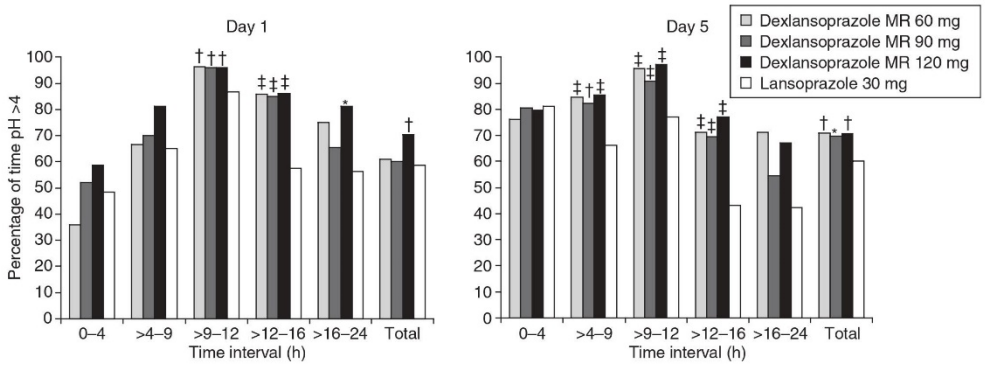

Figure 5. Mean percentage of time pH was >4 for dexlansoprazole MR 60, 90, and 120 mg and lansoprazole 30 mg in healthy subjects. $^{*}P < 0.05$; $^{\dagger}P < 0.01$; $^{\ddagger}P < 0.001$.

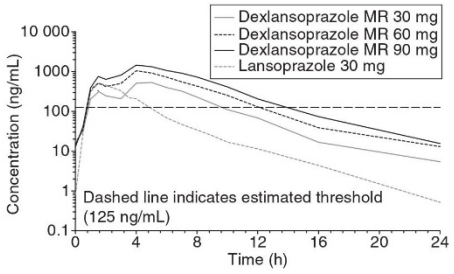

Figure 6. Mean concentration-time profiles for dexlansoprazole MR 30, 60, and 90 mg and lansoprazole 30 mg based on an empirical modeling analysis.

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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ORIGINAL RESEARCH

Comparator pH study to evaluate the single-dose pharmacodynamics of dual delayed-release dexlansoprazole 60 mg and delayed-release esomeprazole 40 mg

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Background: This paper describes a Phase 1, single-center, randomized, open-label, two-period crossover study which compared the pharmacodynamic effects of single doses of dexlansoprazole modified-release 60 mg and esomeprazole 40 mg on 24-hour intragastric pH in healthy adult subjects.

Methods: Forty-four subjects aged 20–54 years were randomized in a 1:1 ratio to two sequence groups defining the order in which they received dexlansoprazole and esomeprazole in periods 1 and 2. Primary pharmacodynamic end points over 24 hours postdose were percentage of time with intragastric pH $>$ 4 and mean pH, and secondary pharmacodynamic end points were percentage of time intragastric pH $>$ 4, and mean pH at 0–12 hours, and at $>$12–24 hours postdose. Each drug was given after an overnight fast and one hour before breakfast. Continuous pH recording began immediately before dosing through to 24 hours postdose.

Results: At 0–24 hours postdose, the mean percentage of time with pH $>$ 4 for dexlansoprazole and esomeprazole was 58% and 48%, respectively; the difference was statistically significant ($P = 0.003$). The average of mean pH values at 0–24 hours postdose for dexlansoprazole and esomeprazole were 4.3 and 3.7, respectively; the difference was statistically significant ($P < 0.001$). At $>$12–24 hours postdose, mean percentage of time with pH $>$ 4 and average of mean pH were greater for dexlansoprazole (60% and 4.5, respectively) compared with esomeprazole (42% and 3.5, respectively); the difference was statistically significant ($P < 0.001$ for both intervals). At 0–12 hours postdose, the difference in dexlansoprazole and esomeprazole values for the pharmacodynamic end points was not statistically significant.

Conclusion: For the entire 24-hour postdose period, predominantly resulting from the $>$12–24-hour postdose interval, the average intragastric pH following a single dose of dexlansoprazole 60 mg was higher compared with that observed following a single dose of esomeprazole 40 mg, and the difference was statistically significant.

Keywords: proton pump inhibitor, TAK-390MR, esomeprazole, intragastric pH, single dose, pharmacokinetics

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for healing of and maintenance of healed erosive esophagitis and treatment of heartburn associated with symptomatic, nonerosive gastroesophageal reflux disease.

One of the limitations to the use of proton pump inhibitors on a once-daily basis has been incomplete acid suppression over the 24-hour postdose interval.[1] Dexlansoprazole modified-release is a formulation that uses an innovative dual delayed-release (DDR™) delivery system. DDR technology is designed to provide an initial drug release in the proximal small intestine followed by another drug release at more distal regions of the small intestine several hours later.[2] As a result, dexlansoprazole modified-release produces a plasma concentration-time profile with two distinct peaks, whereby the first peak occurs 1–2 hours after administration, followed by a second peak at 4–5 hours postdose.[2–4] Esomeprazole is a delayed-release formulation with single-release characteristics that produces maximum plasma concentrations at approximately 1.6 hours postdose.[5] Dexlansoprazole modified-release may be taken without regard to meals.[4,6] In comparison, esomeprazole is recommended to be taken at least one hour before a meal to achieve maximal efficacy.[5]

The pharmacodynamic, pharmacokinetic, and safety profiles of various proton pump inhibitors following administration in humans have been extensively studied.[2,3,7–11] However, this is the first clinical study reported in the literature as a head-to-head comparison of the pharmacodynamics of dexlansoprazole modified-release and esomeprazole after a single dose. Because the study population consisted of healthy adult subjects, no efficacy endpoints were evaluated in this study. Comparison of the single-dose pharmacodynamics of dexlansoprazole modified-release and esomeprazole in a well controlled crossover study adds to the knowledge base for proton pump inhibitors without having to compare across studies. It is known from the literature that these two proton pump inhibitors have pharmacokinetic differences. Esomeprazole exhibits a dose-dependent and time-dependent pharmacokinetic profile that results in an approximate 2.5-fold increase in bioavailability at steady state and increased pharmacodynamic effects after five days of once-daily dosing.[12] The pharmacokinetics of dexlansoprazole modified-release are time-independent and the pharmacokinetic and pharmacodynamic profiles after five days of once-daily dosing are similar (less than 10% difference) to those observed after a single dose.[2,4]

The objective of the current trial was to evaluate the pharmacodynamic effects of single doses of dexlansoprazole modified-release 60 mg and esomeprazole 40 mg on 24-hour intragastric pH in healthy subjects. The dosage strengths chosen for this study were the highest approved for healing of erosive esophagitis (60 mg for dexlansoprazole modified-release and 40 mg for esomeprazole).

Materials and methods

Ethics

The institutional review board (IntegReview, Austin, TX) reviewed and approved the study protocol, protocol amendment 1, and the informed consent form prior to enrollment of subjects; all subjects were enrolled under amendment 1. This study was conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice, the ethical principles of the World Medical Association Declaration of Helsinki, and local regulations.

Study population

Eligible subjects were adult men or women, aged 18–55 years inclusive, and in good health. Women of childbearing potential were required to have negative urine pregnancy tests at screening and at day -1 of period 1. Sexually active women and men agreed to use acceptable contraception for a period of time starting from signing of the informed consent throughout the duration of the study and for 30 days following the last dose of study drug.

Women who were pregnant or lactating, and any subjects with an uncontrolled, clinically significant disorder or abnormality which may have impacted the ability of a subject to participate in the study or potentially confound the study results were excluded as per the study exclusion criteria. In addition, subjects were excluded if they had a hypersensitivity to any component of dexlansoprazole modified-release, esomeprazole, or related compounds, had any significant findings from physical examination or clinical laboratory test results, had positive test results on urine screens for alcohol and drugs of abuse, a positive serum caffeine screen, a positive breath test for *Helicobacter pylori* at screening, or consumed any medication or foods contraindicated by the protocol.

Medication or dietary products including grapefruit or Seville oranges, nicotine-containing products, prescription medication (except for hormonal contraceptives and hormone replacement therapy, if on a stable dose for at least 90 days prior to day 1 of period 1), hepatic or renal clearance altering agents, over the counter medications, vitamin supplements, and alcohol or caffeine-containing products were excluded

during the screening and treatment periods. Occasional use of acetaminophen (≤2 g/day) was allowed, except on day 1 of each period.

Study design

This open-label, randomized, two-period crossover study was conducted at a single study site. During each period, subjects were confined to the study site from day -1 until all study procedures were completed on day 2. A washout interval of at least seven days separated doses of study drugs in periods 1 and 2. This washout interval was considered sufficient because the half-lives are 1–2 hours[4] and approximately 1.6 hours[5] for dexlansoprazole and esomeprazole, respectively, and it allowed intragastric pH to return to baseline levels between doses of study drugs.

On day 1 of each period, study drug was administered at approximately 8 am after an overnight fast of at least eight hours and followed by a 60-minute postdose fast. Breakfast, lunch, dinner, and an evening snack were served at hours 1, 4, 9, and 12 postdose, respectively. During confinement in period 2, subjects received meals identical to those received by the confined subjects in period 1. Each meal was standardized to contain approximately 25% fat. Blood samples were collected at scheduled time points up to 24 hours postdose to quantify dexlansoprazole and esomeprazole plasma concentrations. Intragastric pH recording was performed for 24 hours beginning immediately prior to study drug administration on day 1 of each period. Subjects fasted overnight for at least eight hours prior to collection of blood and urine samples for safety laboratory tests on day 2 of each period.

Pharmacodynamic assessments

On day -1 of period 1, a single-channel antimony probe attached to a Digitrapper® data recorder (Sierra Scientific Instruments, Los Angeles, CA) was inserted intranasally into the stomach to a distance of approximately 10 cm past the lower esophageal sphincter. This procedure verified that the subject could tolerate probe insertion and obtained the length of the probe insertion that was used on day 1 of periods 1 and 2. The unit for measurement of intragastric pH was calibrated with standard buffers (pH approximately 1 and 7) before each use. On day 1 of periods 1 and 2, intragastric pH was recorded every four seconds over the 24-hour postdose interval; however, median intragastric pH values over 15-minute intervals were determined and used for the calculation of pharmacodynamic parameters.

The primary pharmacodynamic parameters calculated for each treatment regimen over 24 hours postdose were percentage of time with intragastric pH $>$ 4 (ie, percentage of time that the medians over 15-minute intervals had pH values $>$ 4) and mean intragastric pH (ie, the average of the medians over 15-minute intervals). Secondary pharmacodynamic parameters were percentage of time with pH $>$ 4 and mean intragastric pH calculated for the time intervals 0–12 hours postdose and $>$12–24 hours postdose.

Pharmacokinetic assessments

Blood samples for the determination of dexlansoprazole and esomeprazole concentrations in plasma were collected into chilled Vacutainers® containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) according to the following schedule: baseline (within 30 minutes prior to day 1 dosing) and at hours 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 postdose. Plasma concentrations of dexlansoprazole and esomeprazole were determined by liquid chromatography and tandem mass spectrometry at PPD Development (Middleton, WI), with validated concentration ranges of 2.00–2000 ng/mL for dexlansoprazole and 1.00–1000 ng/mL for esomeprazole. Plasma concentrations below the lower limit of quantification were set to zero for calculation of mean plasma concentrations and derivation of individual subject pharmacokinetic parameters.

The following pharmacokinetic parameters were calculated for dexlansoprazole and esomeprazole plasma concentration data: area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_t) and to infinity (AUC_∞); maximum observed plasma concentration (C_{max}); time to reach C_{max} (T_{max}); elimination half-life; oral clearance; and apparent volume of distribution. Pharmacokinetic parameters were derived using noncompartmental methods with WinNonlin® Enterprise, Version 5.2 (Pharsight Corporation, Mountain View, CA). Actual sample times, rather than scheduled sampling times, were used in all pharmacokinetic computations involving sampling times.

Assessment of CYP2C19 metabolizer status

The cytochrome P450 (CYP) 2C19 isozyme is a polymorphic enzyme that is involved in the metabolism of dexlansoprazole[4] and esomeprazole.[5] One blood sample for DNA isolation was collected before dosing on day 1 of period 1 from each subject in the study into plastic K_2EDTA spray-coated tubes and stored under frozen conditions. A portion of the DNA sample was analyzed for the presence of CYP2C19 allelic variants (Covance Central Laboratory,

Indianapolis, IN). Genotyping and phenotyping analysis for CYP2C19 was performed for all subjects to determine CYP2C19 metabolizer status.

Statistical analysis

A sample size of 44 subjects, 22 subjects per sequence group, allowed for up to four dropouts (an approximate 9% dropout rate) and still provided at least 93% power to detect a 10% difference in the percentage of time with intragastric pH > 4 over 24 hours between the two treatment regimens. The sample size was calculated using 159.13 as the intrasubject variance for the percentage of time with intragastric pH > 4, which was estimated from a previous dexlansoprazole modified-release study.[6] The power for detecting a difference of 0.5 in mean 24-hour pH between the two treatment regimens was expected to be greater than 95%. Differences were deemed statistically significant if P was ≤0.05.

An analysis of variance model that included fixed effects of sequence, period, and regimen, as well as a random effect of subject nested within sequence was fitted to the pharmacodynamic parameters. Pairwise comparisons between treatment regimens were conducted. Intragastric pH values > 0 but ≤8 were included in the median calculations. Only subjects who had valid pharmacodynamic parameters estimated for both periods were included in the pharmacodynamic analyses for that parameter. The effect of CYP2C19 metabolizer status on the pharmacodynamics of dexlansoprazole and esomeprazole was assessed by performing an additional analysis of variance that excluded the subjects identified as CYP2C19 poor metabolizers.

Descriptive statistics were used to summarize the plasma concentrations of dexlansoprazole and esomeprazole and their single-dose pharmacokinetic parameters from time of dose (0 hour) to 24 hours postdose for all subjects who completed at least one treatment period.

All data analyses were performed using SAS® Version 9.1 (SAS Institute, Cary, NC). There was no imputation of incomplete or missing data.

Safety analysis

All subjects who received at least one dose of study drug were included in the safety analysis. All safety assessments, including adverse events, clinical laboratory evaluations, 12-lead electrocardiogram results, vital sign measurements, and physical examination findings were summarized by treatment regimen with descriptive statistics, where deemed appropriate. A treatment-emergent adverse event was defined as an adverse event or serious adverse event that started or worsened after receiving the first dose of study drug and within 30 days after the last dose of study drug. Adverse event verbatim reported terms were coded to system organ class and then to the first listed preferred term using the Medical Dictionary for Regulatory Activities, Version 13.1.

Results

Study population

This study was conducted between September 2010 and October 2010. Forty-four subjects, comprising 21 (47.7%) men and 23 (52.3%) women were enrolled, of whom 43 completed the study in accordance with the protocol and had complete pharmacodynamic and pharmacokinetic data for both treatment periods. Ten of the 44 subjects (22.7%) were black or African American, while the race of the remaining 34 subjects (77.3%) was Caucasian. The mean age was 36.7 (range 20–54) years, weight 73.1 kg, height 170.4 cm, and body mass index 25.1 kg/m^2. One subject voluntarily withdrew consent for personal reasons after receiving esomeprazole in period 1, but prior to administration of dexlansoprazole modified-release in period 2. Pharmacokinetic and safety data for this subject from period 1 were included in the summaries. However, because the analysis of variance required pharmacodynamic data from both treatment regimens, this subject was not included in the pharmacodynamic analysis. Forty-two of 44 subjects (95.5%) were extensive CYP2C19 metabolizers and two subjects (4.5%) were poor CYP2C19 metabolizers. Data from all subjects, regardless of CYP2C19 metabolizer status, were included in the pharmacodynamic analyses and pharmacokinetic summary because this was a crossover study where subjects received both treatment regimens and the subjects acted as their own control.

Pharmacodynamics

Mean intragastric pH over 24 hours after single doses of dexlansoprazole modified-release and esomeprazole are presented in Figure 1. Period and sequence effects were not found to be statistically significant. The pharmacodynamic profiles at 0–24 hours after a single dose of dexlansoprazole modified-release or esomeprazole were generally similar to that reported in the literature.[2,3,9,10,12]

Over the 24-hour postdose period, the mean percentage of time with intragastric pH > 4 was 58% for dexlansoprazole compared with 48% for esomeprazole; the difference was statistically significant (P = 0.003, Figure 2). Similarly, >12–24 hours postdose, the mean percentage of time with intragastric pH > 4 was 60% for dexlansoprazole

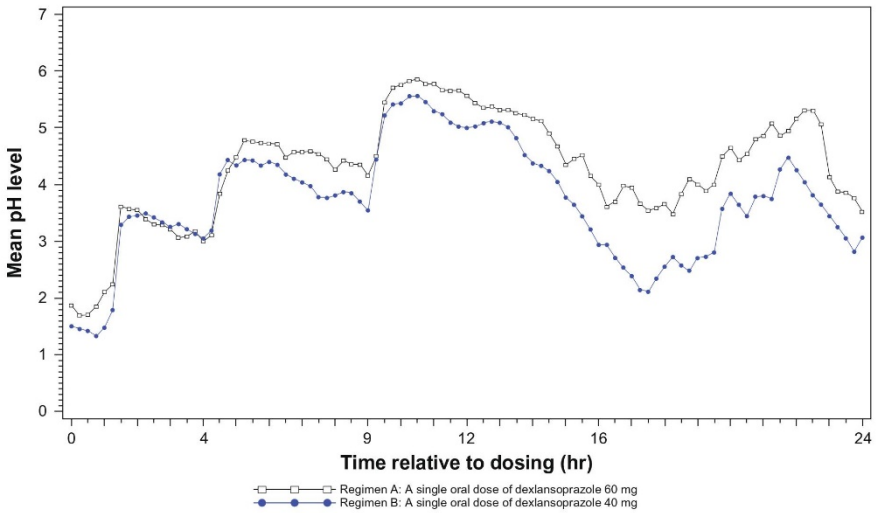

Figure 1 Mean intragastric pH from 0 to 24 hours postdose after single oral doses of dexlansoprazole modified-release 60 mg (n = 43) and esomeprazole 40 mg (n = 44) delayed-release capsules.

relative to 42% with esomeprazole, a difference that was statistically significant ($P < 0.001$). At 0–12 hours postdose, the mean percentage of time with pH > 4 for dexlansoprazole and esomeprazole was 56% and 53%, respectively, and the difference was not statistically significant.

Over the 24-hour postdose period, the average of mean intragastric pH for dexlansoprazole was 4.3 compared with 3.7 for esomeprazole and the difference was statistically significant ($P < 0.001$, Figure 3). Likewise, >12–24 hours postdose, the average of mean intragastric pH was 4.5 for dexlansoprazole compared with 3.5 for esomeprazole and the difference was statistically significant ($P < 0.001$). At 0–12 hours postdose, the average of mean intragastric pH for dexlansoprazole was 4.2 compared with 3.9 for esomeprazole, and the difference was not statistically significant.

Pharmacokinetics

The mean plasma concentration-time curves for dexlansoprazole and esomeprazole in our study were generally similar to that reported in the literature.[2,13–15] Following administration

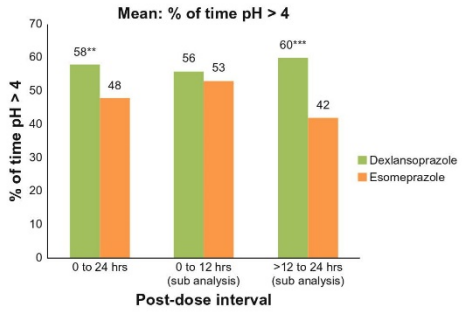

Figure 2 Mean percentage of time with intragastric pH > 4.0 at 0–24 hours, 0–12 hours, and >12–24 hours after single oral doses of dexlansoprazole modified-release 60 mg and esomeprazole 40 mg delayed-release capsules (n = 43). Only subjects who had valid pharmacodynamic parameters estimated for both periods were included in the pharmacodynamic analyses for that parameter.
Notes: *$P \leq 0.05$; **$P < 0.01$; ***$P < 0.001$.

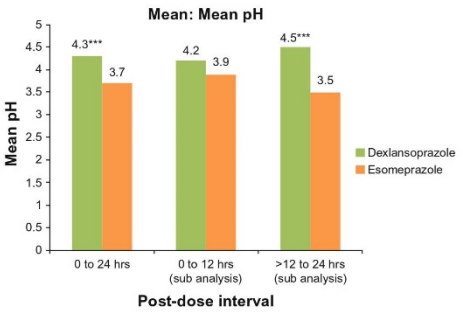

Figure 3 Mean intragastric pH at 0–24 hours, 0–12 hours, and >12–24 hours after single oral doses of dexlansoprazole modified-release 60 mg and esomeprazole 40 mg delayed-release capsules (n = 43). Only subjects who had valid pharmacodynamic parameters estimated for both periods were included in the pharmacodynamic analyses for that parameter.
Notes: *$P \leq 0.05$; **$P < 0.01$; ***$P < 0.001$.

of a single dose of dexlansoprazole modified-release 60 mg, the mean plasma concentration-time curve displayed two peaks at approximately 2 and 5 hours postdose, which are representative of the dual delayed-release characteristics of the dexlansoprazole modified-release capsule; in addition, plasma concentrations were generally detectable throughout the 24-hour postdose interval. For esomeprazole, the median T_{max} occurred at approximately two hours after dosing, and plasma concentrations rapidly decreased thereafter (Figure 4). Concentrations of dexlansoprazole were detectable in the plasma of all subjects (100%) at 12 hours postdose, in 38 of 43 subjects (88%) at 16 hours postdose, and 27 of 43 subjects (63%) at 24 hours postdose. In contrast, esomeprazole was detected in the plasma of 35 of 44 subjects (80%) at 12 hours postdose, 17 of 44 subjects (39%) at 16 hours postdose, and four of 44 subjects (9%) at 24 hours postdose. Plasma pharmacokinetic parameters for dexlansoprazole and esomeprazole are shown in Table 1.

Table 1 Summary of plasma pharmacokinetic parameters for dexlansoprazole and esomeprazole after single oral doses of dexlansoprazole MR 60 mg and esomeprazole 40 mg

Pharmacokinetic parameter (unit)	Treatment mean ± SD			
	Dexlansoprazole MR 60 mg		Esomeprazole 40 mg	
	n	(N = 43)	n	(N = 44)
AUC_t (ng · hour/mL)	43	5666 ± 4763.3	44	1877 ± 1265.8
AUC_∞ (ng · hour/mL)	32	6841 ± 5787.7	41	1984 ± 1254.3
C_{max} (ng/mL)	43	1078 ± 581.5	44	748 ± 444.6
T_{max} (hour)[a]	43	5.00 (1.0, 12.0)	44	2.00 (1.0, 10.0)
$T_{1/2}$ (hour)	32	2.83 ± 2.174	41	1.35 ± 0.437
CL/F (L/hour)	32	13.83 ± 9.433	41	28.68 ± 17.364
V_z/F (L)	32	52.70 ± 59.859	41	51.29 ± 31.140

Note: [a]T_{max} values presented are median (minimum, maximum).
Abbreviations: AUC_t, area under the plasma concentration-time curve from time 0 to the time of last quantifiable concentration; AUC_∞, area under the plasma concentration-time curve from time 0 to infinity; CL/F, oral clearance; C_{max}, maximum observed plasma concentration; MR, modified-release; N, number of subjects; n, number of subjects for whom parameter could be calculated; $T_{1/2}$, half-life; T_{max}, time to reach C_{max}; V_z/F, apparent volume of distribution.

Effect of CYP2C19 status on pharmacodynamics and pharmacokinetics

Administration of a proton pump inhibitor with CYP2C19-dependent metabolism may result in higher plasma concentrations in subjects who are CYP2C19 poor metabolizers. Two of the 44 enrolled subjects were determined to be CYP2C19 poor metabolizers. Both subjects had AUC values that were substantially higher than the overall means for dexlansoprazole and esomeprazole. Data for these subjects were included in the pharmacodynamic analyses and pharmacokinetic summary because this was a crossover study where subjects received both treatment regimens, and subject metabolizer status was not expected to affect the overall conclusions of the study. To confirm this assumption, an analysis of variance model that was similar to the analysis for the complete data was fitted to the pharmacodynamic data, excluding the data from the two poor metabolizer subjects. Exclusion of the pharmacodynamic data from the poor metabolizers did not alter the statistical results obtained from the complete data set. Additional descriptive statistics were calculated for the pharmacodynamic and pharmacokinetic parameter data, excluding the data from the poor metabolizers, and indicated that inclusion of data from the poor metabolizers did not affect the overall pharmacodynamic or pharmacokinetic conclusions of the study (data on file at Takeda).

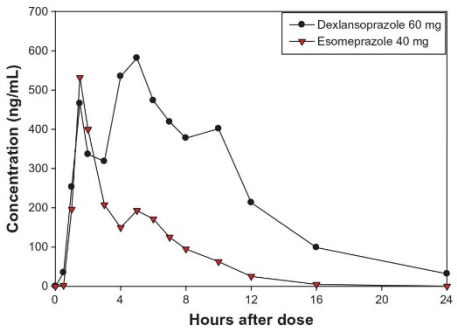

Figure 4 Mean plasma concentration-time curves of dexlansoprazole and esomeprazole after single oral doses of dexlansoprazole modified-release 60 mg (n = 43) and esomeprazole 40 mg (n = 44) delayed-release capsules in healthy subjects, linear scale.

Safety

The incidence of treatment-emergent adverse events was 21% (nine of 43 subjects) and 14% (six of 44 subjects) after single-dose administration of dexlansoprazole modified-release and esomeprazole, respectively. All of the adverse events were rated mild or moderate in severity and only one adverse event (nausea) was considered related to the study drug (dexlansoprazole modified-release) by the investigator. The most common adverse events reported by at least two subjects with dexlansoprazole modified-release were headache (four of 43 subjects, 9%), flatulence (two of 43 subjects, 5%), and joint injury (two of 43 subjects, 5%). No adverse event was reported by two or more subjects with esomeprazole. There were no serious adverse events, deaths, or premature study discontinuations as a result of an adverse event. No clinically meaningful changes in clinical laboratory

values, physical examination findings, vital signs, or 12-lead electrocardiograms were reported over the course of study.

Discussion

Proton pump inhibitors are the drugs of choice for the healing of erosive esophagitis, maintenance of healed erosive esophagitis, and sustained resolution of symptomatic, nonerosive reflux disease. Limitations to the use of proton pump inhibitors on a once-daily basis have been a delayed onset of action, incomplete acid suppression over the 24-hour postdose interval, and the need for ingestion before a meal to achieve maximal efficacy.[1,3] To date, attempts to overcome these issues have included the development of isomeric proton pump inhibitors with stereoselective metabolism (ie, dexlansoprazole [the *R*-enantiomer of lansoprazole] and esomeprazole [the *S*-enantiomer of omeprazole]) and alterations in drug delivery to prolong the inhibition of gastric acid secretion.[3] The dexlansoprazole DDR technology is designed to provide an initial drug release in the proximal small intestine followed by another drug release at more distal regions of the small intestine several hours later. As a result, dexlansoprazole modified-release produces a dual-peaked pharmacokinetic profile that prolongs the plasma concentration-time profile of dexlansoprazole.[2] Unlike esomeprazole, which should be taken one hour prior to a meal,[5] dexlansoprazole modified-release can be taken without regard to food.[4] The aim of this study was to evaluate the pharmacodynamic effects of single doses of dexlansoprazole modified-release 60 mg and esomeprazole 40 mg on 24-hour intragastric pH in healthy subjects. The dosage strengths chosen for this study were the highest approved for healing of erosive esophagitis (60 mg for dexlansoprazole modified-release and 40 mg for esomeprazole).

The measurement of intragastric pH is a well accepted method for the assessment of the pharmacodynamic effects of a proton pump inhibitor.[16–18] The present study is the first head-to-head comparison of the pharmacodynamic effects for a 24-hour period following single doses of dexlansoprazole modified-release and esomeprazole in healthy subjects, utilizing doses that are recommended for healing of erosive esophagitis.

The results of this study indicate that the DDR formulation technology of dexlansoprazole modified-release leads to an extended duration of gastric acid control on day 1 compared with the delayed-release formulation of esomeprazole. After a morning dose of each study drug, the extended duration in pharmacodynamic activity after dexlansoprazole modified-release was demonstrated 0–24 hours postdose, mainly due to the significant differences observed during the >12–24 hours postdose interval relative to esomeprazole. The two proton pump inhibitors had comparable pharmacodynamic activity 0–12 hours postdose.

Overall, the pharmacodynamic profiles in our study were similar to those observed in other published reports.[2,9] The primary pharmacodynamic parameter, mean percentage of time with intragastric pH > 4 from time 0–24 hours postdose, was 58% for dexlansoprazole versus 48% for esomeprazole (Figure 2). The literature reported that percentage of time with intragastric pH > 4 from time 0–24 hours after the same doses were approximately 60% for dexlansoprazole modified-release[2] and 54% and 52% for esomeprazole.[10,12]

A strength of this study is its randomized, crossover design, with each subject acting as his/her own control. A limitation is the single-dose design, preventing extrapolation of the results to a multiple-dose regimen. The study population of healthy volunteers does not allow for assessment of clinical efficacy, and no clinical significance is intended or implied. Nevertheless, the comparison of two proton pump inhibitor enantiomers with different formulation characteristics is of pharmacological interest. Although there are extensive data available detailing the multiple-dose pharmacodynamics and pharmacokinetics of proton pump inhibitors, this is the first clinical study reported in the literature to provide a comparison of the pharmacodynamics of dexlansoprazole modified-release and esomeprazole after a single dose in a well controlled crossover study.

In conclusion, a single dose of dexlansoprazole modified-release 60 mg provided statistically significantly greater pH control for the entire 24-hour postdose interval when compared with a single dose of esomeprazole 40 mg. This observed difference was mainly due to the statistically significant greater pH control from dexlansoprazole modified-release over the >12–24-hour postdose interval as compared with esomeprazole. The two proton pump inhibitors had comparable pharmacodynamic activity at 0–12 hours postdose.

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Disclosure

MK, CE, and SN are employees of Takeda Global Research & Development Center Inc, Deerfield, IL. Writing assistance was funded by Takeda Pharmaceuticals North America Inc. This study was sponsored by Takeda Global Research and Development Center Inc.

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