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Clinical trial: the effect and timing of food on the pharmacokinetics and pharmacodynamics of dexlansoprazole MR, a novel Dual Delayed Release formulation of a proton pump inhibitor – evidence for dosing flexibility

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SUMMARY

Background
Dexlansoprazole MR is a proton pump inhibitor with a Dual Delayed Release (DDR) formulation designed to prolong the dexlansoprazole plasma concentration–time profile. The presence of food or time of dosing relative to food may affect dexlansoprazole absorption.

Aims
To evaluate the effect of food on the pharmacokinetics (PK) and pharmacodynamics (PD) of dexlansoprazole following oral administration of dexlansoprazole MR.

Methods
In this open-label, single-dose, randomized, 4-way crossover study, 48 healthy subjects received placebo (day 1) and dexlansoprazole MR 90 mg (day 3) after fasting, 5 or 30 min before a high-fat breakfast, or 30 min after a high-fat breakfast. Intragastric pH (days 1 and 3) and PK (day 3) of dexlansoprazole were assessed over a 24-h interval after each dose.

Results
Following administration of dexlansoprazole MR under fasted/fed conditions, mean dexlansoprazole plasma concentration–time profiles generally exhibited two distinct peaks, resulting from the DDR formulation. Increases in dexlansoprazole maximum plasma concentration (12–31%) and area under the plasma concentration–time curve (9–21%) were observed with the fed regimens; however, differences in intragastric pH were not considered clinically relevant.

Conclusion
Dexlansoprazole MR can be administered without regard to food or the timing of food in most patients.

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INTRODUCTION

The efficacy of most proton pump inhibitors (PPIs) is influenced by food and the time of dosing relative to a meal. PPIs achieve maximal efficacy when they are administered before a meal because they only bind to actively secreting proton pumps, which are activated postprandially.[1] The American College of Gastroenterology guidelines recommend that patients administer their PPI prior to breakfast.[2] However, there is evidence to suggest that PPIs are not always administered as recommended. A recent survey of 1046 primary care physicians reported that 36% provide incorrect instructions to their patients on proper PPI dosing.[3] In a separate survey, 66% of patients reported difficulty remembering to take their anti-ulcer medication 30 min before a meal, and 68% stated a preference for taking medications with a meal.[4]

The absorption and bioavailability of some PPIs are diminished when they are administered with a meal. For example, when esomeprazole is administered with food, the area under the plasma concentration-time curve (*AUC*) decreases 43–53% compared with the *AUC* observed under fasted conditions.[5] When esomeprazole is administered 15 min prior to eating a high-fat meal, the *AUC* has been shown to decrease by 44% and the maximal drug concentration (C_{max}) by 66% compared with administration in the fasted state.[6] In a separate study of omeprazole, the C_{max} and *AUC* were also found to decrease significantly (63% and 38% respectively) when the drug was administered with food compared with the fasted state.[7] Similarly, administration of lansoprazole 30 mg with food has been shown to decrease C_{max} by up to 61% and *AUC* by up to 53%.[8, 9] In light of these data, product labelling for lansoprazole, omeprazole, and esomeprazole recommend administering these PPIs before eating (in the case of esomeprazole, 1 h before meals) to avoid the negative food effect.[5, 10, 11]

Dexlansoprazole MR (TAK-390MR, Takeda Global Research & Development Center, Inc., Deerfield, IL, USA) is a novel modified release formulation of dexlansoprazole, an enantiomer of lansoprazole, which employs an innovative delivery system with Dual Delayed Release (DDR) technology designed to prolong the plasma–concentration time profile of dexlansoprazole and extend the duration of acid suppression. Phase 1 data indicate that dexlansoprazole MR 60, 90, and 120 mg produce a dual-peaked pharmacokinetic (PK) profile.[12] The first peak is designed to occur approximately 1–2 h after dosing and the second approximately 4–5 h after dosing, which prolongs the plasma concentration–time profile and provides greater acid suppression than lansoprazole 30 mg.

The current trial was designed to evaluate the effect of dosing time relative to food intake on the PK and pharmacodynamics (PD) of dexlansoprazole following administration of a single oral dose of dexlansoprazole MR 90 mg (the highest dose under investigation for clinical use) compared with the fasted state. Since food intake alone leads to an increase in intragastric pH,[13] inclusion of a placebo for each regimen on day 1 allowed for the assessment of changes in the 24-h intragastric pH profile in the presence or absence of food. Hence, the determination of pH following administration of a placebo and subsequent dexlansoprazole MR on day 3 can be used to separate the effect of food from the effect of dexlansoprazole on the 24-h intragastric pH profiles.

METHODS

Study population

Healthy male and female subjects, aged 18–55 years, with a body mass index of 18 to 30 kg/m^2 were eligible to participate in the study. Female subjects had to have a negative serum pregnancy test result at screening and agreed to use an acceptable form of contraception.

Subjects were excluded if they had taken any prescription or over-the-counter (OTC) medication (including vitamins and dietary supplements) within 14 days prior to initial administration of study drug, or had taken any herbal OTC medications or any drug or agent known to alter hepatic or renal clearance (e.g. erythromycin, cimetidine, barbiturates, phenothiazines) within 28 days prior to initial administration of study drug. Use of oral contraceptives and hormone replacement therapy was allowed. Occasional use of acetaminophen (up to 2 g/day) was acceptable.

The investigator ensured that the trial was conducted in compliance with Institutional Review Board regulations and within the ethical principles stated in the 1989 Declaration of Helsinki. All subjects voluntarily signed an informed consent form before any study-related procedure was initiated.

Study design

This was a phase 1, open-label, single-dose (placebo and active drug), single centre, 4-way crossover study to evaluate the effect of the timing of food on the PK and PD of dexlansoprazole after administration of a single, oral dose of dexlansoprazole MR 90 mg.

On day −1 of each of the four periods, subjects were confined to the clinical testing facility where they remained until all study procedures were completed on day 4 of each period. All subjects had normal intragastric acidity at baseline with no evidence of hypochlorhydria. During each of the four crossover periods, subjects received a single oral dose of placebo on day 1 and a single oral dose of dexlansoprazole MR 90 mg on day 3. Dosing began at approximately 8:00 AM after a 10-h overnight fast. There was an interval of ≥5 days between the dexlansoprazole MR dose in a period and the placebo dose in the subsequent period. This allowed for a sufficient washout of at least 5 to 7 half-lives between dexlansoprazole MR doses, given the half-life of dexlansoprazole to be approximately 1.5 h. At study completion, a subject was to have received four doses of dexlansoprazole MR 90 mg and four doses of placebo.

Subjects were randomized on the first dosing day, day 1 of Period 1, to one of the four groups that determined the order in which they received study drugs under four different conditions. For reference regimen, subjects received a single dose of placebo or dexlansoprazole MR after fasting on day 1 and day 3 respectively and no food was given until lunch (4 h postdose). Dosing relative to food intake was explored under three different conditions: (1) placebo or dexlansoprazole MR was administered 30 min after the start of a high-fat breakfast (the fed state as defined by the US Food and Drug Administration guidance on food effect bioavailability and fed bioequivalence studies[14]); (2) placebo or dexlansoprazole MR was administered 5 min before a high-fat breakfast; and (3) placebo or dexlansoprazole MR was administered 30 min before a high-fat breakfast.

For the three fed conditions, subjects received an identical standardized high-fat breakfast (2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 oz hash-brown potatoes, and 8 oz whole milk), which was to be consumed entirely within 25 min. Across all four regimens, all subjects received the same lunch, dinner, and snack on day 1 and day 3.

Pharmacokinetic measurements and statistical analyses

A sample size of 48 subjects allowed for a dropout rate of 25% and provided at least a 92% probability of concluding equivalence of dexlansoprazole *AUC* between two regimens, i.e. the 90% confidence interval of the ratio of dexlansoprazole *AUC* between two regimens is within the bioequivalence range of 0.80, 1.25. This assumed that the true difference between dexlansoprazole *AUC* central values from two regimens was ≤5%.

A total of 17 blood samples for the determination of dexlansoprazole plasma concentrations were collected from each subject on day 3 of each period from predose to 24 h postdose. Samples were collected in heparinized tubes and plasma obtained within 1 h of collection by centrifugation. Plasma concentrations of dexlansoprazole were determined using a validated liquid chromatography tandem mass spectrometry assay. The lower limit of quantification (LLOQ) was 5.00 ng/mL using a plasma sample volume of 0.100 mL.

Pharmacokinetic parameters for dexlansoprazole were estimated by standard noncompartmental analysis using WinNonlin version 4.1 (Pharsight Corporation, Mountain View, CA, USA). The C_{max}, t_{lag} (the time delay between drug administration and first observed concentration above the LLOQ) and t_{max} were obtained directly from the plasma concentration-time profile for each subject. The apparent terminal phase elimination rate constant (λ_z) was estimated using least squares regression analysis of the terminal log-linear portion of the plasma concentration-time profiles. The apparent terminal elimination-phase half-life ($t_{1/2z}$) was calculated as $\ln(2)/\lambda_z$. The *AUC* from time zero to the last quantifiable concentration (AUC_t) was calculated using the linear trapezoidal rule. The extrapolated *AUC* from the time of the last quantifiable concentration to infinity ($AUC_{t-\infty}$) was estimated by dividing the last quantifiable concentration by the estimated λ_z. The *AUC* to infinity (AUC_∞) was calculated as the sum of AUC_t and $AUC_{t-\infty}$.

Dexlansoprazole plasma concentrations and PK parameter estimates were tabulated and descriptive statistics were computed by each regimen. The primary assessment was to determine the effect of food and the timing of food on dexlansoprazole systemic exposure measured as C_{max} and *AUC* values. The relative bioavailability and bioequivalence of

dexlansoprazole of the three fed conditions compared with the fasted state were assessed using analysis of variance (ANOVA) for t_{max} and the natural logarithms of C_{max}, AUC_t, and AUC_∞ using a model with factors of sequence, subjects nested within sequence, period and regimen. The factor of subjects-within-sequence was treated as random and all other factors were fixed. Within the framework of the ANOVA model, the relative bioavailability was assessed by point estimates and 90% confidence intervals for the ratios of the central values of C_{max} and AUCs of each fed condition to the fasted state. A conclusion of 'no effect' of food or the timing of food was made, if the 90% CIs for the ratios of C_{max} and AUC values for the three fed conditions relative to the fasted state were within 0.80 and 1.25.

Pharmacodynamic measurement and evaluations

Ambulatory 24-h continuous intragastric pH monitoring with a Medtronic Digitrapper pH recorder (Medtronic, Inc., Minneapolis, MN, USA) was used in this study to measure the PD responses after dosing with placebo and dexlansoprazole MR on day 1 and day 3 of each period respectively. A single-channel, antimony pH probe was inserted in the stomach via the nares to a distance of approximately 10 cm past the lower oesophageal sphincter using standard clinical procedures. For each subject, the length of the probe insertion to the lower oesophageal sphincter was recorded at the time of initial probe placement on the first dosing day to ensure consistency of probe placement during subsequent recordings. Standard clinical procedures were employed including use of a topical anaesthetic to minimize the discomfort of probe insertion; use of topical anaesthetics was documented and recorded.

Intragastric pH was automatically sampled and recorded every 4 s over a 24-h interval after dosing on days 1 and 3. The median of these values over 15-min intervals was determined and used to calculate all PD parameters. The primary PD parameters were the calculated average pH over the entire 24-h postdose interval and the percentage of time that intragastric pH was >4 over the total 24-h postdose interval.

The pH measurements on day 1 provided data for the evaluation of the effect of food intake alone on pH. The pH measurements on day 3 encompass the combined effects of food and drug intake on pH. Therefore, to assess the effects of dexlansoprazole exposure alone on pH, pH parameters on day 1 were subtracted from the corresponding measurements on day 3. The PD parameters on day 1 or 3, as well as the change from day 1 to day 3, were analysed using ANOVA models. The models included factors of sequence, subjects nested within sequence, period and regimen. The factor of subjects-within-sequence was treated as random and all other factors were fixed. The primary assessments were comparisons of each of the three fed conditions to the fasted state. Differences were deemed statistically significant, if the P value was ≤ 0.05.

Safety assessments

Safety was monitored through adverse event (AE) reporting, concomitant medication use, physical examinations and laboratory evaluations. A complete physical examination (including vital signs and laboratory evaluations) was performed at the Screening Visit, on day −1 of each period, and day 4 of Period 4. Electrocardiograms were obtained at the Screening Visit and prior to discharge. Adverse events and serious AEs were reported from receipt of informed consent through 30 days after the last dose of study drug. Treatment-emergent AEs were defined as AEs with an onset or a worsening in severity after the first dose of study drug. All AEs were collected, whether observed by the investigator or spontaneously reported by the subject. Investigators evaluated event severity and determined whether the AE(s) was related to study drug administration.

RESULTS

Study population

Forty-six of 48 subjects who were randomized to the four sequence groups completed all dosing regimens and were included in the PK and PD analyses; two subjects prematurely discontinued the study (1 withdrew consent and 1 discontinued because of an AE). Subjects were mostly men (60%) and ranged in age from 19 to 53 years (mean ± s.d., 32 ± 11 y); 77% were white and 23% were African American, and respective mean ± s.d. height and weight were 172 ± 10 cm and 76 ± 12 kg. All 48 subjects were included in the safety analyses.

Table 1. Summary of the effect of timing of food on dexlansoprazole pharmacokinetic parameter estimates following a single oral dose of dexlansoprazole MR 90 mg

Regimen	Measure	t_{lag} h	t_{max} h	C_{max} ng/mL	AUC_t ng·h/mL	AUC_∞ ng·h/mL	$t_{1/2z}$ h
Dosed in the fasted state	*n*	46	46	46	46	37	37
	Mean	0.87	5.38	1486	6996	7058	1.82
	s.d.	0.61	1.94	808	3739	3749	1.09
Dosed 30 min after the start of a high-fat breakfast	*n*	46	46	46	46	37	37
	Mean	1.91	7.63	1825	7999	8157	1.54
	s.d.	0.87	1.84	659	3856	3992	0.76
Dosed 5 min before a high-fat breakfast	*n*	46	46	46	46	37	37
	Mean	0.49	5.94	1653	7975	8198	1.40
	s.d.	0.66	2.45	718	3751	3910	0.68
Dosed 30 min before a high-fat breakfast	*n*	46	46	46	46	37	37
	Mean	0.53	4.73	1597	7448	7970	1.71
	s.d.	0.49	2.84	761	3843	4015	1.05

AUC_t, area under the plasma concentration-time curve (*AUC*) from time zero to last quantifiable concentration; AUC_∞, *AUC* from time zero 0 to infinity; C_{max}, observed maximum plasma concentration; s.d., standard deviation; t_{lag}, the time delay between drug administration and first observed concentration above the lower limit of quantification; t_{max}, time to reach the observed maximum plasma concentration; $t_{1/2z}$, the apparent terminal elimination-phase half-life.

Pharmacokinetics

A summary of the PK parameter estimates for dexlansoprazole is presented in Table 1. Oral administration of dexlansoprazole MR 30 min after a high-fat breakfast delayed the absorption of dexlansoprazole. When dexlansoprazole MR was administered 5 min and 30 min before a high-fat meal, mean dexlansoprazole t_{lag} values were similar to that of the fasted regimen; however, the mean t_{lag} was approximately 1 h longer when administered 30 min after a high-fat breakfast. The increase in t_{max} (approximately 2 h) was statistically significant ($P < 0.001$ for those receiving dexlansoprazole MR 30 min after a meal compared with the other regimens). The mean of the $t_{1/2z}$ values did not appear to be affected, indicating that a high-fat breakfast did not alter the systemic clearance of dexlansoprazole.

The mean dexlansoprazole plasma concentration–time profiles for the regimens are shown Figure 1a. The two distinct peaks characteristic of the DDR formulation are evident for 3 of the 4 regimens; however, the dual peaks in the mean concentration-time profile for those receiving dexlansoprazole MR 30 min after a high-fat meal were obscured probably because of the delayed absorption induced by variability in GI transit time and/or pH under the fed state. Intersubject variability in dexlansoprazole C_{max} and *AUC*s was generally similar between regimens (Figure 1b,c). The point estimates of the relative bioavailability for dexlansoprazole (Table 2) indicated that the central values for C_{max} and *AUC* increased (12–31% and 9–21% for C_{max} and *AUC*, respectively) following administration of dexlansoprazole MR under the various fed conditions compared with the fasted state. The 90% CIs for the relative bioavailability when dexlansoprazole MR was administered 30 min before food relative to the fasted state were within the 'no effect' range. The 90% CIs for the ratios of the central values when dexlansoprazole MR was administered 30 min after a meal or 5 min before a meal relative to the fasted state extended above the upper 'no effect' range of 1.25 for C_{max} and *AUC*s. These results indicate that the bioavailability of dexlansoprazole relative to the fasted state increased when dexlansoprazole MR was administered 30 min after the start of a meal or 5 min before a meal, but was bioequivalent when the drug was administered 30 min before a meal.

Pharmacodynamics

Statistical analysis on the PD parameters showed that there were no statistically significant differences in

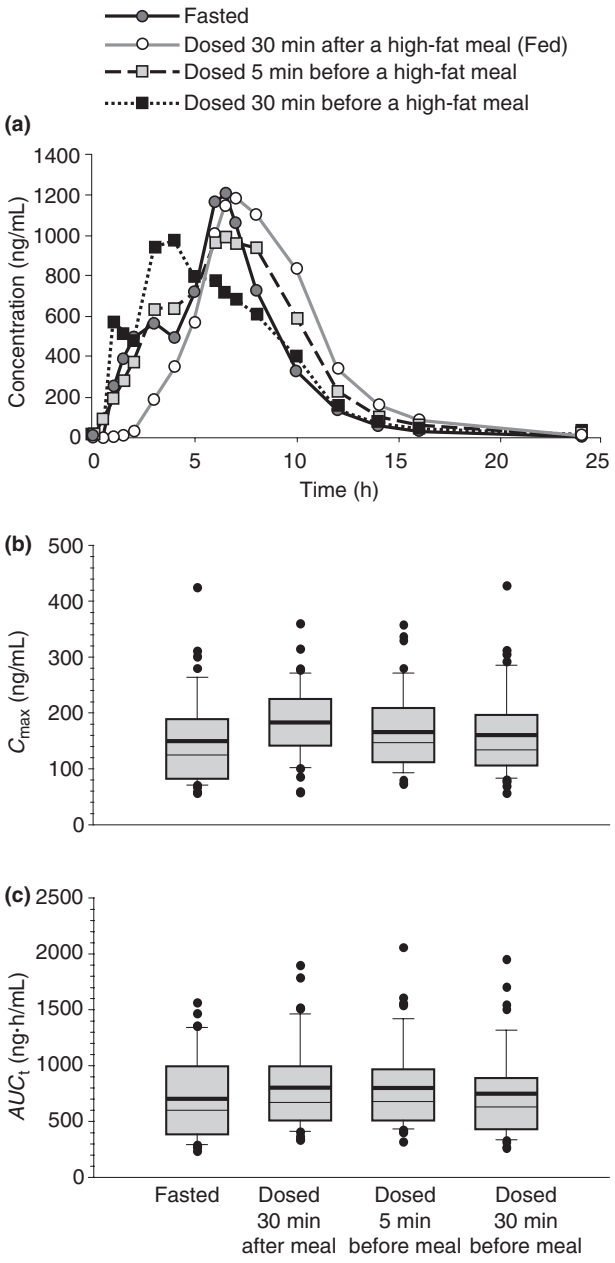

Figure 1. Mean dexlansoprazole plasma concentrations-time profiles (a), C_{max} (b), and AUC_t (c) values following administration of a single oral dose of dexlansoprazole MR 90 mg under fasted and various fed conditions. The boundary of the box closest to zero indicates the 25th percentile, the thinner line within the box marks the median, the thicker line within the box marks the mean, and the boundary of the box farthest from zero indicates the 75th percentile. Error bars above and below the box indicate the 90th and 10th percentiles respectively. Solid circles indicate all data points outside the 90th and 10th percentiles.

mean 24-h intragastric pH among any of the pairwise comparisons of the various fed conditions compared with the fasted state for day 1, day 3 or the change from day 1 to day 3 (Table 3). Furthermore, there were no statistically significant differences between the fasted and fed conditions for the percentage of time with intragastric pH >4 over the total 24-h postdose interval except for the change from day 1 to day 3, as well as the actual values on day 3 for the comparison between dexlansoprazole MR administered while fasting and 30 min after breakfast. However, the absolute difference in the change from day 1 to day 3, as well as on day 3, was not greater than 8 percentage points between those two regimens.

Figure 2a displays mean 24-h intragastric pH profiles over 24 h at day 1 (baseline) after placebo under various fed conditions compared with the fasted state. It includes the effect of food and timing of the first meal of the day relative to dosing on the mean intragastric pH profile. For each of the four regimens, the pH level increased soon after each meal. For the fasting regimen, the pH profile remained relatively flat until lunch. For the three fed conditions, the locations of the first peaks in the pH profiles were staggered, depending on the timing of breakfast, which corresponded well with the meal. There were no apparent differences in the mean pH profiles among these regimens after lunch.

Figure 2b presents the mean 24-h intragastric pH profiles after a single dose of dexlansoprazole MR 90 mg on day 3 under fasting and various fed conditions. It includes the effect of food and timing of the first meal of the day relative to dosing with dexlansoprazole MR, as well as the effect of dexlansoprazole MR on the 24-h intragastric pH profile. The pH profiles for all four regimens on day 3 were higher than those on day 1, confirming the effect of dexlansoprazole MR to increase intragastric pH. The differences in the pH profiles among these four regimens were more pronounced before lunch and started to diminish thereafter. The pH profiles for all four regimens after dinner were similar.

Figure 2c depicts the change in the 24-h intragastric pH profile from day 1 to day 3. It is constructed by subtracting the effect of food and timing of food on the 24-h intragastric pH profile and represents the effect of dexlansoprazole on the intragastric pH profile when dexlansoprazole MR was administered under fasting and various fed conditions. The curves appeared to be similar for all four regimens for most

Table 2. Bioavailability of dexlansoprazole following a single oral dose of dexlansoprazole MR 90 mg administered under various fed conditions relative to the fasted state

Relative time of dosing	Pharmacokinetic parameter	Point estimate	90% Confidence interval
30 min after the start of a high-fat breakfast	C_{max}	1.31	1.174–1.455
	AUC_t	1.19	1.125–1.259
	AUC_∞	1.21	1.145–1.268
5 min before a high-fat breakfast	C_{max}	1.17	1.049–1.301
	AUC_t	1.19	1.126–1.260
	AUC_∞	1.21	1.148–1.274
30 min before a high-fat breakfast	C_{max}	1.12	1.003–1.243
	AUC_t	1.09	1.031–1.154
	AUC_∞	1.15	1.089–1.211

AUC_t, area under the plasma concentration vs. time curve (AUC) from time zero to last quantifiable concentration; AUC_∞, AUC from time zero to infinity; C_{max}, observed maximum plasma concentration.

Table 3. Analysis of mean intragastric pH and percentage of time intragastric pH > 4 during the total 24-h postdose time interval on day 1 (placebo) and on day 3 (dexlansoprazole MR) and of the change from day 1 to day 3

		Relative time of dosing			
PD Parameters	Analysis	Fasting	30 min after breakfast	5 min before breakfast	30 min before breakfast
Mean intragastric pH over 24 h	Day 1 (Placebo)	2.28	2.27	2.19	2.41
	Day 3 (Dexlansoprazole MR)	4.46	4.25	4.43	4.53
	Day 3 minus day 1	2.18	1.97	2.24	2.13
% Time intragastric pH > 4 over 24 h	Day 1 (Placebo)	17	18	16	19
	Day 3 (Dexlansoprazole MR)	64	57*	62	66
	Day 3 minus day 1	47	39*	46	47

* $P < 0.05$ vs. fasted state from an analysis of variance with effects for regimen, sequence, period and subject nested within sequence.

of the 24 h after dosing, except for the differences between the regimen dosed 30 min after the start of breakfast and the other three regimens during the early hours before dinner; this was probably because of the delayed absorption of dexlansoprazole observed for this treatment regimen.

Safety

No consistent clinically important changes were observed in any of the study safety parameters when dexlansoprazole MR was administered under the fasted or various fed regimens. Nineteen subjects (40%) experienced at least 1 treatment-emergent AE; the most common AE was headache (19% of subjects) across all regimens. The one subject who discontinued because of an AE experienced a moderate elevation of liver enzymes attributed to administration of study drug; this subject's serology test was positive for Epstein-Barr nuclear antigen and Epstein-Barr viral capsid antigen IgG. One subject experienced a severe AE (epididymitis), which was not related to study drug, and 13 experienced an AE that was moderate in severity; all other AEs were mild. No deaths or other serious AEs occurred. No other clinically important changes in laboratory

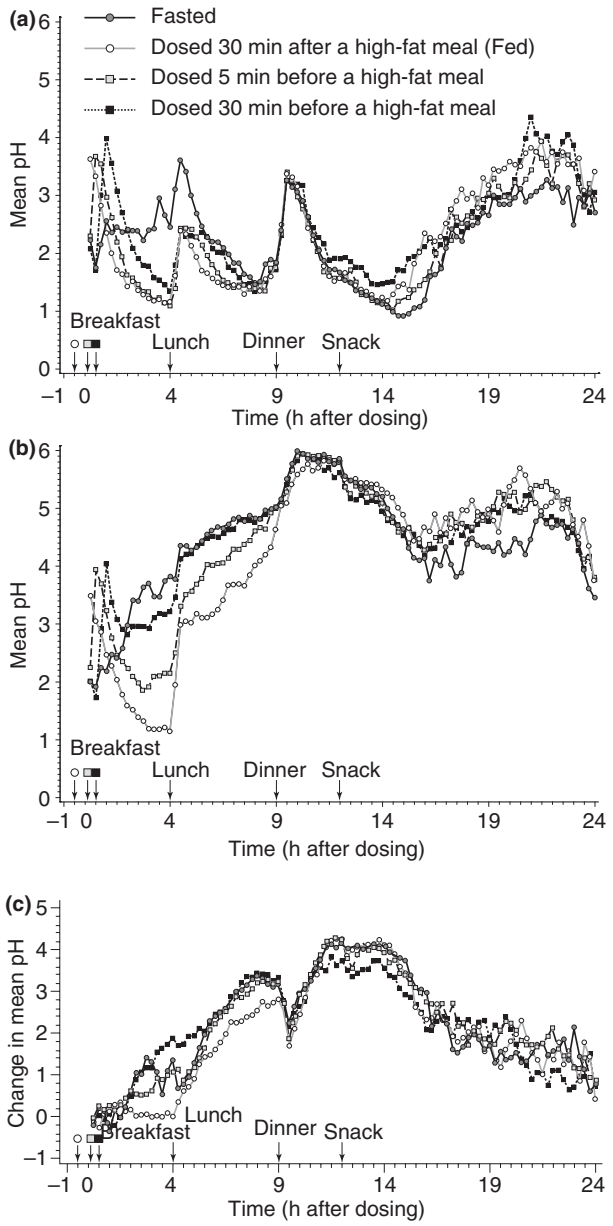

Figure 2. Mean 24-h intragastric pH* over time on (a) day 1 after receiving placebo (effect of food alone), (b) day 3 after receiving dexlansoprazole MR (effect of food + dexlansoprazole), and (c) Change from day 1 to day 3 (effects due to dexlansoprazole exposure alone), by regimen. * Mean pH was calculated based on median values obtained every 4 s over 15-min intervals. Symbols above arrows indicate the timing of breakfast relative to dosing at time 0 and correspond to each fed group.

test results, vital signs, ECGs, or physical examinations were associated with the administration of four doses of dexlansoprazole MR 90 mg to healthy subjects in this study.

DISCUSSION

Food effect studies are routinely performed during drug development according to well defined standards to explore the potential for a food-drug interaction. In the current trial evaluating dexlansoprazole MR, the primary PK assessment showed that plasma dexlansoprazole exposure increased following administration of dexlansoprazole MR under fed conditions compared with the fasted state (a 12–31% increase in C_{max} and a 9–21% increase in the *AUC*s). In separate trials evaluating esomeprazole, omeprazole, and lansoprazole, the oral administration of these PPIs in the fed state decreased C_{max} and *AUC* values by 61–63% and 43–53% respectively.[6, 8, 9] Consequently, the labelling for esomeprazole, omeprazole and lansoprazole recommend that these PPIs be administered before eating.

In the current study, for the food effect assessments, the 90% CIs for the relative bioavailability under fed conditions were compared with those obtained under the fasted state. The 90% CIs for the ratio of C_{max} and *AUC* central values when dexlansoprazole MR was administered 30 min before breakfast were within the 'no effect' range of 0.80 and 1.25. However, the upper limits of the 90% CIs for the ratio of C_{max} and *AUC* central values for the fed conditions, including 30 min after the start of breakfast, were beyond the 'no effect' range. When the PK data from a food effect study fail to meet the 'no effect' bioequivalency range, the US Food and Drug Administration recommends that investigators provide specific recommendations on the clinical significance of the data on the basis of what is known from the total clinical database and/or the PK/PD relationships of the drug under study.

In this study, mean intragastric pH results over the 24-h postdose interval showed no statistically significant differences for any of the pairwise comparisons of the fed conditions with the fasted state on day 1, day 3, or after subtracting for the effect of food (day 3 minus day 1). Likewise, there were no statistically significant differences between the fasted and fed conditions over the 24-h postdose interval except for the change from day 1 to day 3 for the comparison between dexlansoprazole MR administered 30 min after the start of a high-fat breakfast and under fasting conditions. However, the difference between the two regimens was not greater than 8 percentage points.

Although no firm target has been established, investigators have suggested there is a clinically relevant relationship between time of sustaining a 24-h intragastric

pH > 4 and erosive oesophagitis healing rates.[15–17] As there were no statistically significant differences in the PD comparisons except for a difference of ≤8 percentage points in mean intragastric pH between dexlansoprazole MR administered while fasting and 30 min after breakfast, it is reasonable to assume that most patients receiving dexlansoprazole MR can administer it without regard to meals. However, some patients may benefit from administering the dose prior to a meal if post-meal symptoms do not resolve under post-fed conditions.

The increased bioavailability of dexlansoprazole observed in this study following administration of dexlansoprazole MR for the fed conditions relative to the fasted state could be caused by a variety of factors, including a favourable physicochemical interaction of dexlansoprazole with food, resulting in improved release and dissolution profiles of dexlansoprazole; optimized interaction of the dissolved drug with the gastrointestinal membrane; and/or enhanced transfer of the enteric-coated granules to the more distal segments of the small intestine with more optimal conditions for dexlansoprazole release and absorption. Although the exact mechanism is not known, this observed increase in dexlansoprazole bioavailability following the administration of dexlansoprazole MR with food may also be attributed to the DDR technology employed in the MR formulation of dexlansoprazole.

Increased drug exposure under fed conditions may also be viewed as a potential safety issue. However, the extent of dexlansoprazole exposure under the various fed conditions observed in this study was well within the exposure range seen in clinical studies[18] at doses that were well tolerated in patients.[19] Also in this study, no consistent, clinically important changes were observed in any of the safety parameters when dexlansoprazole MR 90 mg was administered to healthy subjects under fasting or various fed conditions.

One of the main strengths of this trial was the inclusion of pH measurements after administration of a placebo under the various fasting and fed regimens. PD testing is not required by existing guidelines, but is helpful in the current trial in placing the PK data into a context that could be meaningful to practicing clinicians. These measurements allowed for the evaluation of the influence of food alone on intragastric pH, as changes in pH due to food could confound assessment of the results when food was given with dexlansoprazole MR. Thus, the analysis of the intragastric pH profiles on day 1 allowed for a more selective assessment of drug effect on the 24-h intragastric pH.

The ability to dose dexlansoprazole MR with or without food would offer benefits over conventional PPIs that exhibit a food effect. For instance, if patients do not adhere to labelling instructions and take lansoprazole, omeprazole, or esomeprazole with a meal,[5, 10, 11] the effect of that PPI may be diminished because of a food-drug interaction. As is the case with many diseases, poor compliance is a leading cause of treatment failure in acid-related disorders and is a growing problem in clinical practice.[13] The dosing flexibility afforded by dexlansoprazole MR should help address some of the PPI compliance issues prevalent in clinical practice, as well as some of the special problems faced in institutional settings (e.g. hospitals, long-term care facilities), where it may not always be possible to optimize the time of dosing relative to a meal.

In conclusion, this study provides a strong support to recommend that dexlansoprazole MR can be administered without regard to meals or the timing of meals in most patients. PPI dosing flexibility may enhance patient convenience and compliance. This dosing flexibility, combined with the extended duration of therapeutic plasma drug concentrations and prolonged acid suppression following administration of dexlansoprazole MR, suggests that this PPI offers additional benefits to patients with acid-related disorders.

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