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# The effect of time-of-day dosing on the pharmacokinetics and pharmacodynamics of dexlansoprazole MR: evidence for dosing flexibility with a Dual Delayed Release proton pump inhibitor

R. D. LEE, D. MULFORD, J. WU & S. N. ATKINSON

Research & Development, Takeda Global Research & Development Center, Inc., Deerfield, IL USA

Correspondence to:
Dr R. D. Lee, Clinical Pharmacology, Takeda Global Research & Development Center, Inc., One Takeda Parkway, Deerfield, IL 60015, USA.
E-mail: ronald.lee@tgrd.com

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## SUMMARY

### Background
Dexlansoprazole MR is a Dual Delayed Release proton pump inhibitor formulated to extend the duration of acid suppression.

### Aim
To evaluate the pharmacokinetics and pharmacodynamics of dexlansoprazole MR dosed before 4 different meal times.

### Methods
In this randomized, open-label, four-way crossover study, 48 healthy subjects received dexlansoprazole MR 60 mg once daily 30 min before breakfast, lunch, dinner or an evening snack. Pharmacokinetics of dexlansoprazole MR and intragastric pH were assessed over a 24-h postdose interval on day 5 for each regimen.

### Results
Absorption was delayed when dexlansoprazole MR was administered before each regimen relative to breakfast; however, systemic exposures of dexlansoprazole at all regimens were bioequivalent. There were no statistically significant differences in mean 24-h intragastric pH between dosing before dinner or an evening snack vs. breakfast; however, there was a small (0.2), but statistically significant difference between lunch and breakfast. There was a statistically significant difference of 7 percentage points in the percentage of time intragastric pH was >4 for the snack regimen relative to the breakfast regimen, but there were no statistically significant differences between lunch or dinner compared with breakfast.

### Conclusion
Dexlansoprazole MR provides comparable acid control when administered at different times of the day.




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## INTRODUCTION

Proton pump inhibitors (PPIs) only inhibit actively secreting proton pumps ($H^+$,$K^+$-ATPase molecular targets within the gastric parietal cell); therefore, antisecretory therapy is optimal when proton pumps are activated at the same time that the parietal cell is maximally stimulated, as occurs postprandially.[1] As the absorption and bioavailability of omeprazole, esomeprazole and lansoprazole have been shown to diminish when they are administered with food,[2–5] dosing guidelines generally recommend that PPIs be administered before meals to optimize antisecretory effects and minimize the possibility of a negative pharmacokinetic food interaction.[6, 7] However, a survey of 100 patients with poorly controlled gastro-oesophageal reflux disease reported that 54% of patients administered their PPIs suboptimally (defined as >60 min before a meal, after meals, as needed or at bedtime).[8] In a separate survey, 64% of primary care physicians instructed patients to administer their PPI before a meal, while 36% instructed patients to administer their PPI with or after a meal or did not specify timing of administration.[9]

As to the preferred time of day, morning dosing is generally recommended so that the highest concentration of drug is present when the greatest number of $H^+$,$K^+$-ATPase molecules have accumulated in the parietal cells, which occurs overnight after a prolonged fast.[7, 10] However, not all proton pumps are activated after a meal. This poses a potential issue for conventional single-release PPIs, which have a short half-life of 1–2 h and limited mean residence time in the systemic circulation. In theory, it would be possible to improve acid control with a PPI by extending its mean residence time so that drug is still available to inhibit new, restored or uninhibited pumps after initial PPI inactivation.[11]

Dexlansoprazole MR is a novel modified-release formulation of dexlansoprazole, an enantiomer of lansoprazole, which employs an innovative Dual Delayed Release™ (DDR) delivery system designed to prolong plasma concentration of dexlansoprazole and provide extended duration of acid suppression.[12] The DDR technology is designed to deliver the drug in two discrete phases of release, thereby prolonging the mean residence time of the dexlansoprazole in plasma.[13] Dexlansoprazole MR has been demonstrated to be effective in symptom relief and healing in patients with moderate-to-severe erosive oesophagitis[14] and non-erosive reflux disease[15] and to prevent relapse and maintain symptom relief in patients with healed erosive oesophagitis for up to 6 months.[16] The safety profile of dexlansoprazole MR is similar to that of lansoprazole.[17]

The goal of the current study was to characterize the steady-state pharmacokinetics and pharmacodynamics of dexlansoprazole MR taken once daily at four different times of day, 30 min before one of three meals or an evening snack.

## METHODS

### Study population

Healthy male and female subjects, aged 18–55 years, with a body mass index of 18–30 kg/m$^2$ were eligible to participate in this study. All subjects were required to have a negative breath test for *Helicobacter pylori* at screening. Female subjects were required to have a negative serum pregnancy test at the screening visit and day −1 of period 1 and agree to use an acceptable form of contraception.

Subjects were not enrolled if they had taken any prescription or over-the-counter medication within 14 days before initial administration of study drug or any herbal medication or any drug known to alter hepatic or renal clearance within 28 days before administration of study drug. Occasional use of acetaminophen was acceptable (≤2 g/day).

This study was approved by an Institutional Review Board (RCRC IRB, Austin, TX, USA) and conducted according to the ethical principles stated in the Declaration of Helsinki. All subjects voluntarily provided informed consent before any study-related procedure was initiated.

### Study design

This was a phase 1, randomized, open-label, multiple-dose, single-centre (Jasper Clinic, Inc., Kalamazoo, MI, USA), four-way crossover study to assess the steady-state pharmacokinetics and pharmacodynamics of dexlansoprazole after administration of dexlansoprazole MR 60 mg orally once daily for 5 days at one of the four different times of day: 30 min before (i) breakfast (reference regimen), (ii) lunch, (iii) dinner or (iv) an evening snack (Table 1). Dexlansoprazole MR 60-mg capsules were manufactured and supplied by Takeda Pharmaceutical Company Limited (Osaka, Japan). The

**Table 1.** Dexlansoprazole MR treatment periods, sequence and dosing regimens

| Sequence | Subjects (*n*) | Regimen | | | |
|---|---|---|---|---|---|
| | | Period 1 | Period 2 | Period 3 | Period 4 |
| 1 | 12 | Breakfast | Lunch | Dinner | Evening snack |
| 2 | 12 | Lunch | Evening snack | Breakfast | Dinner |
| 3 | 12 | Dinner | Breakfast | Evening snack | Lunch |
| 4 | 12 | Evening snack | Dinner | Lunch | Breakfast |

Breakfast regimen: Dexlansoprazole MR 60 mg q.d. administered orally 30 min before breakfast for 5 days at approximately 8:00 h.
Lunch regimen: Dexlansoprazole MR 60 mg q.d. administered orally 30 min before lunch for 5 days at approximately 11:30 h.
Dinner regimen: Dexlansoprazole MR 60 mg q.d. administered orally 30 min before dinner for 5 days at approximately 16:30 h.
Evening snack regimen: Dexlansoprazole MR 60 mg q.d. administered orally 30 min before an evening snack for 5 days at approximately 20:30 h.

**Table 2.** Nutritional analysis of standardized meals

| Meal | Calories | Protein (g) | Carbohydrates (g) | Fat (g) |
|---|---|---|---|---|
| Breakfast | 811 | 35 | 91 | 27 |
| Lunch | 714 | 31 | 86 | 28 |
| Dinner | 658 | 29 | 83 | 23 |
| Evening snack | 344 | 15 | 32 | 17 |

60-mg dose is the highest dose approved for healing erosive oesophagitis.

Subjects underwent a screening evaluation of at least 28 days before being randomized and receiving the first dose of dexlansoprazole MR. Eligible subjects were randomly assigned (1:1:1:1) to one of four regimen sequence groups; each subject received all four regimens in a crossover fashion (Table 1). During each period, subjects were confined to the research unit beginning on day −1 and ending on day 6 or 7, depending on when the last dose of study drug was administered. On day −1, subjects received a standard evening snack; lunch and dinner were optional. Beginning on day 1, standard meals were given each day that simulated meals that patients would be expected to consume and that are typical for each time of day (Table 2). Meals were served at the same time for each period: breakfast, 8:30 AM; lunch, 12:00 PM; dinner, 5:00 PM; and snack, 9:00 PM, and were to be consumed within 25 min. Subjects received the same standard meals on days 5 and 6 of each period. On days 1 through 5, subjects received dexlansoprazole MR 60 mg at the time stipulated by their assigned regimen sequence. As the half-life of dexlansoprazole is approximately 1.5 h, a washout interval of at least 5 days between the last dose in the preceding period and the first dose in the subsequent period was considered sufficient to avoid any carryover effect. Subjects were discharged from the research unit during washout periods.

## Pharmacokinetic measurements

Venous blood samples were collected in heparinized tubes from each subject on day 5 of each period before administration of dexlansoprazole MR (0 h) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h post-dose. Plasma concentrations of dexlansoprazole were determined using a validated liquid chromatography tandem mass spectrometry assay at MDS Pharma Services (Lincoln, NE, USA). The lower limit of quantification (LLOQ) was 5.00 ng/mL using a 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). Pharmacokinetic parameters included observed maximum plasma concentration ($C_{max}$), area under the plasma concentration–time curve ($AUC$), $AUC$ from time 0 to the last quantifiable concentration ($AUC_t$), $AUC$ within a dosing interval ($AUC_\tau$), time delay between drug administration and first

observed concentration above the LLOQ ($t_{lag}$), time to maximum plasma concentration ($t_{max}$) and the apparent terminal elimination rate constant ($\lambda_z$).

### Pharmacodynamic measurements

Intragastric pH was monitored with a Medtronic Digitrapper pH recorder (Medtronic, Inc., Minneapolis, MN, USA) for 24 h beginning immediately before administration of dexlansoprazole MR for all four regimens on day 5. On day −1 of period 1, a probe was inserted into the subject's stomach via the nares to a distance of approximately 10 cm past the lower oesophageal sphincter. The length of the probe was recorded to ensure consistent placement on subsequent days. On day 5 of each period, intragastric pH was sampled and measured every 4 seconds beginning just before dosing through 24 h postdose. Median intragastric pH values over 15-min intervals were used to estimate the pharmacodynamic parameters evaluated: the percentage of time intragastric pH > 4 and the mean intragastric pH for the 24-h period after administration.

### Safety assessments

Safety was monitored via adverse event reporting, concomitant medication use, physical examinations and laboratory tests. A complete physical examination was performed during the screening visit, on day −1 of each period and at the end of period visit for each period. Electrocardiograms were obtained at the screening visit, on day −1 of each period and at the end of period 4.

An adverse event was defined as any untoward medical occurrence including an abnormal laboratory finding. All treatment-emergent adverse events, defined as adverse events that happened or worsened after the first dose of study drug, were recorded whether reported spontaneously by the subject or in response to a query or observed by site personnel. The investigator evaluated the severity of each adverse event and determined the relationship to study drug administration. Adverse events were classified by system organ class according to the Medical Dictionary of Regulatory Activities version 10.0 (MedDRA MSSO, Chantilly, VA, USA) and were tabulated by regimen and event severity. A serious adverse event was defined as an adverse event that resulted in death, inpatient hospitalization, persistent or significant disability or incapacity or a congenital anomaly (birth defect).

### Statistical analyses

A sample size of 48 subjects allowed for a dropout rate of 16.7% and provided >93% probability at 0.05 level of significance to detect a 0.5-unit difference in mean 24-h pH between two treatment regimens. The power to detect a 10% difference in the percentage of time pH > 4 over 24 h was ≥88%. The SAS System Version 8.2 (SAS Institute Inc., Cary, NC, USA) for the UNIX operating system was used to perform all statistical analyses. All statistical tests were two-tailed at $\alpha = 0.05$ level of significance; values were considered significantly different, if the *P*-value was <0.050 after rounding to three decimal places.

For each regimen, plasma dexlansoprazole concentrations and pharmacokinetic and pharmacodynamic parameter estimates were tabulated. Descriptive statistics were computed for subjects who had valid parameter estimates for at least two regimens, including dosing before breakfast (reference regimen). Pairwise comparisons were performed for the lunch, dinner and snack regimens relative to dosing before breakfast. An analysis of variance (ANOVA) was performed for pharmacokinetic and pharmacodynamic parameters using a model with factors of sequence, subjects nested with sequence, period and regimen. The factor of subjects within sequence was treated as random; all other factors were fixed. For pharmacokinetic parameters, the natural logarithm of $C_{max}$ and *AUC*s were used in the ANOVA models. Relative bioavailability was assessed by point estimates and 90% CIs for the ratios of the central values of $C_{max}$ and *AUC*s between two regimens from the pairwise comparison of $C_{max}$ and *AUC*s on the log scale within the ANOVA framework. It was concluded that there was no difference between the two regimens if the 90% CIs of the ratios were between 0.80 and 1.25 for $C_{max}$ and *AUC*s. For pharmacodynamic parameters, the original scale was used in the ANOVA models. Pairwise comparisons between regimens were conducted in the ANOVA model framework.

## RESULTS

### Study population

Forty-eight subjects were enrolled and randomly assigned to one of the four sequence groups. Subjects were mostly men (71%) and white (81%). Mean height ± s.d. was 174 ± 9 cm, and mean weight was 77 ± 11 kg. All subjects tested negative for *H pylori*.

**Table 3.** Summary of the effect of dosing time on the pharmacokinetics of dexlansoprazole on day 5: subjects with breakfast regimen and at least one of lunch, dinner or evening snack regimens

| Regimen | *n* | $t_{lag}$ (h) | $t_{max}$ (h) | $C_{max}$ (ng/mL) | $AUC_\tau$ (ng·h/mL) | $AUC_\tau$ (ng·h/mL) |
|---|---|---|---|---|---|---|
| Breakfast | 46 | 0.42 (0.43) | 4.66 (2.53) | 1107 (537) | 5376 (2751) | 5432 (2761) |
| Lunch | 45 | 0.95 (1.10) | 6.45 (2.29) | 1055 (530) | 5378 (3058) | 5488 (3029) |
| Dinner | 45 | 0.81 (1.31) | 6.67 (3.10) | 999 (499) | 5474 (3226) | 5587 (3188) |
| Evening snack | 44 | 1.39 (0.95) | 7.60 (1.53) | 1112 (495) | 5319 (3007) | 5431 (3013) |

Values represent mean (s.d.).
$t_{lag}$: Time delay between drug administration and first observed concentration above the lower limit of quantification.
$t_{max}$: Time to maximum (peak) drug concentration.
$C_{max}$: Maximum (peak) plasma drug concentration.
$AUC_\tau$: Area under the plasma drug concentration–time curve (*AUC*) from time zero to the time of the last quantifiable concentration.
$AUC_\tau$: Area under the plasma drug concentration–time curve within a dosing interval.

Four subjects discontinued treatment prematurely: two withdrew consent, one became pregnant and one withdrew because of an adverse event. Forty-six subjects had valid results for more than two regimens (including breakfast) and were included in the pharmacokinetic and pharmacodynamic analyses. All 48 subjects were included in the safety analysis.

## Pharmacokinetics

A summary of the noncompartmental pharmacokinetic parameter estimates for dexlansoprazole on day 5 is presented in Table 3. Absorption of dexlansoprazole was delayed approximately two- to threefold and, as a result, $t_{max}$ values occurred approximately 2–3 h later when dexlansoprazole MR was administered before lunch, dinner or an evening snack compared with administration before breakfast (Table 3 and Figure 1). The two distinct peaks (Figure 1) characteristic of the DDR formulation were evident in two of the four regimens; however, the dual peaks in the mean concentration–time profiles for those receiving dexlansoprazole MR before dinner or an evening snack were not apparent. Figure 1, representing the mean $t_{max}$ and $C_{max}$ values, gives the impression that the first peak was absent; however, when looking at individual data, two distinct $t_{max}$ values were seen for most subjects. The reason for some subjects not having two distinct peaks may be attributed in part to the plasma sampling scheme: fewer samples were taken after 2 h postdose and therefore the second $t_{max}$ may have been missed. While the differences in $t_{lag}$ and $t_{max}$ were statistically

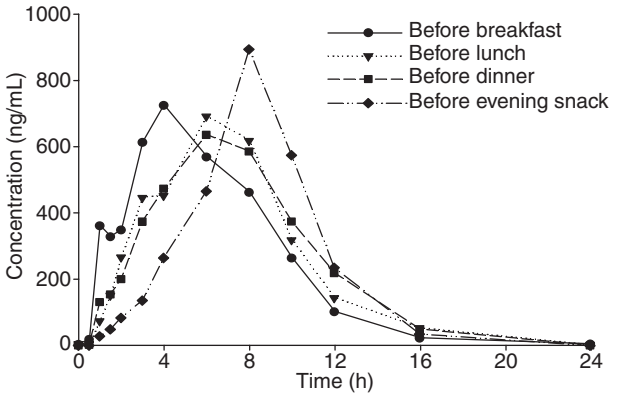


**Figure 1.** Mean dexlansoprazole linear plasma concentration–time profiles on day 5 after daily oral doses of dexlansoprazole MR 60 mg given 30 min before meals or an evening snack.

significant ($P < 0.05$), there were no apparent differences in plasma mean dexlansoprazole $C_{max}$ or *AUC* values when dexlansoprazole MR was administered at different times of the day (Table 3 and Figure 2). Despite the delay in absorption, mean $C_{max}$ was 1055, 999 and 1112 ng/mL when dexlansoprazole MR was administered before lunch, dinner or an evening snack respectively compared with 1107 ng/mL after administration before breakfast. Mean $AUC_t$ was 5378, 5474, and 5319 ng·h/mL when dexlansoprazole MR was administered before lunch, dinner or an evening snack, respectively, compared with 5376 ng·h/mL after administration before breakfast. Mean oral clearance was similar among regimens. The 90% CIs for the

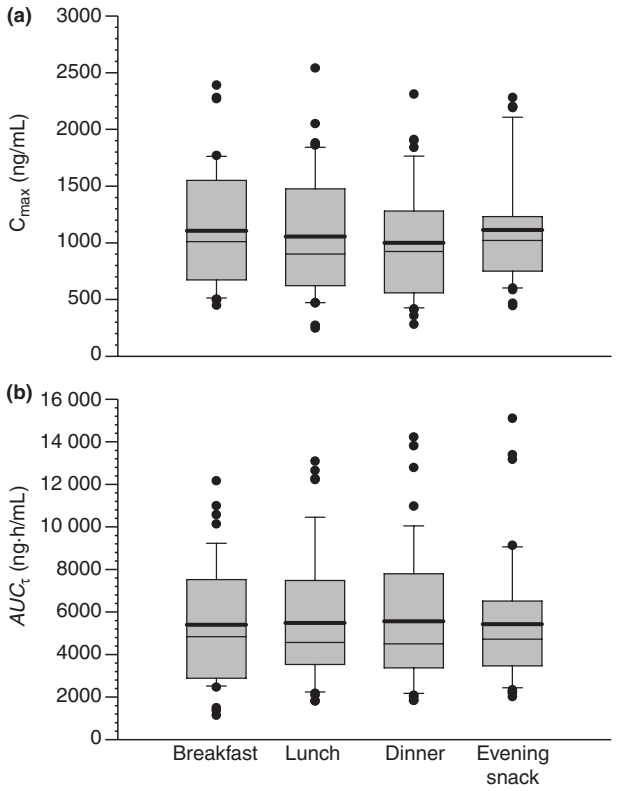


**Figure 2.** Comparison of dexlansoprazole $C_{max}$ (a) and $AUC_\tau$ (b) values on day 5 after daily administration of dexlansoprazole MR given 30 min before meals or an evening snack. The boundary of the box closest to 0 indicates the 25th percentile, the thinner line within the box marks the median, the thicker line within the box marks the mean, and the boundary of the box farthest from 0 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. $AUC_\tau$ = $AUC$ within a dosing interval; $C_{max}$ = maximum (peak) plasma drug concentration.

ratios of the central values were all well within the bioequivalence range of 0.80–1.25 for dexlansoprazole $C_{max}$ and $AUC$s, including the value of 1, indicating that bioavailability of dexlansoprazole was not affected when dexlansoprazole MR was administered before breakfast compared with that administered before lunch, dinner or an evening snack (Table 4).

## Pharmacodynamics

Mean intragastric pH profiles are shown in Figure 3. The 24-h mean intragastric pH profile was comparable for the breakfast, lunch and dinner regimens as shown

**Table 4.** Bioavailability of dexlansoprazole on day 5 after administration of dexlansoprazole MR 60 mg before lunch, dinner or evening snack relative to administration before breakfast

| Relative time of dosing | Pharmacokinetic parameter | Point estimate* | 90% CI* |
|---|---|---|---|
| Lunch vs. breakfast | $C_{max}$ | 0.94 | 0.848–1.036 |
| | $AUC_t$ | 1.00 | 0.940–1.063 |
| | $AUC_\tau$ | 1.02 | 0.966–1.071 |
| Dinner vs. breakfast | $C_{max}$ | 0.91 | 0.820–1.002 |
| | $AUC_t$ | 1.01 | 0.954–1.079 |
| | $AUC_\tau$ | 1.04 | 0.990–1.098 |
| Evening snack vs. breakfast | $C_{max}$ | 1.04 | 0.941–1.151 |
| | $AUC_t$ | 1.03 | 0.966–1.093 |
| | $AUC_\tau$ | 1.04 | 0.986–1.094 |

$C_{max}$: Maximum (peak) plasma drug concentration.
$AUC_t$: Area under the plasma drug concentration–time curve ($AUC$) from time zero to the time of the last quantifiable concentration.
$AUC_\tau$: Area under the plasma drug concentration–time curve within a dosing interval.
* The point estimates and the confidence intervals were obtained from the exponentiated results of analysis of the natural logarithm-transformed data.

in Figure 3b, whereas the snack regimen showed a slightly different profile. Intragastric pH increased quickly (≤1 h) to a level >4 for the breakfast regimen and remained there throughout most of the 24-h postdose interval, with the exception of the nighttime hours. However, the mean pH profiles for the lunch and dinner regimens were maintained above a value of 4 for the majority of the 24-h interval. There appeared to be a delayed effect when dexlansoprazole MR was taken before an evening snack; intragastric pH did not reach 4 until 6 h postdose. Nonetheless, this regimen produced a higher intragastric pH profile than the breakfast regimen from the middle of the night through lunchtime of the next day. The mean percentage of time intragastric pH > 4 during the 24-h postdose interval on day 5 was 71%, 74%, 70% and 64% for the breakfast, lunch, dinner and snack regimens respectively. The difference of 7 percentage points for the snack regimen relative to the breakfast regimen was statistically significant ($P$ = 0.016).

The mean intragastric pH during the 24-h period after administration of dexlansoprazole MR before lunch was higher than when the drug was administered before breakfast (4.83 vs. 4.63, respectively;

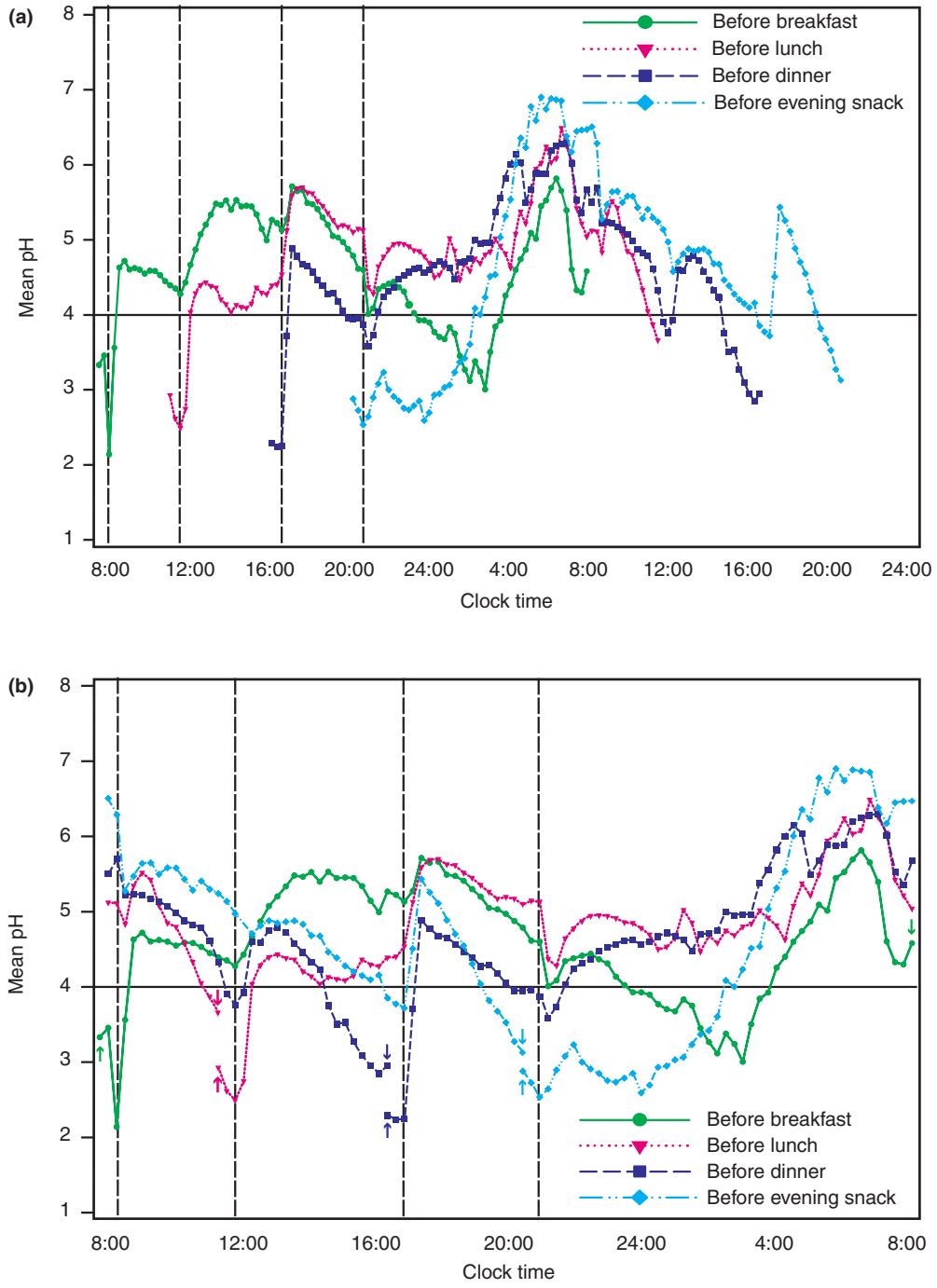


**Figure 3.** Mean intragastric pH measurements. Note: the *x*-axes in (a) and (b) have been displayed in two different ways to compensate for the fact that data could not be collected for >24 h. The pH profiles are based on 15-min gastric pH medians. (a) The *x*-axis shows hour 8:00 in the morning on day 5 through hour 24:00 on day 6 to depict the sequential time course of intragastric pH recorded in the study. The vertical lines indicate the time meal consumption began on day 5. The 24-h pH profile measurement for each regimen and dosing of the study drug start 30 min before meal consumption and end 24 h later. (b) On the 24-h scale, the *x*-axis shows hour 8:00 on the morning of day 5 to hour 8:00 on day 6. Upward and downward pointing arrows indicate the beginning and end of the monitoring periods for each regimen, respectively. For the lunch, dinner and snack regimens, data after 8:00 h on day 6 are transposed to the beginning of the chart so that the mean 24-h pH profiles of all four regimens can be compared in a single 24-h view that reflects the diurnal effect of treatment on pH.

**Table 5.** Mean intragastric pH during the total 24-h postdose time interval on day 5

| Analysis (day 5) | Result for each dosing regimen | | | | *P*-value for pairwise comparisons* | | |
|---|---|---|---|---|---|---|---|
| | (Reference) breakfast ($n$ = 46) | Lunch ($n$ = 45) | Dinner ($n$ = 45) | Snack ($n$ = 44) | Lunch vs. breakfast | Dinner vs. breakfast | Snack vs. breakfast |
| Mean (s.d.) | 4.63 (0.660) | 4.83 (0.821) | 4.67 (0.675) | 4.60 (0.786) | 0.039* | 0.534 | 0.948 |
| Least squares mean | 4.64 | 4.85 | 4.70 | 4.64 | | | |

* $P \leq 0.05$; from an ANOVA with effects for regimen, sequence, period and subject nested within sequence.

Table 5). This small difference (0.20) in mean 24-h intragastric pH was statistically significant ($P < 0.05$). Mean 24-h intragastric pH values for the dinner and snack regimens were not significantly different from the breakfast regimen.

## Safety

Thirty-nine subjects (81%) experienced at least one treatment-emergent adverse event; the rates were comparable across dosing regimens. Headache was the most common treatment-emergent adverse event (19% of subjects). A majority of treatment-emergent adverse events were not considered related to study drug. All adverse events were assessed by the investigator to be mild or moderate in severity.

The one subject who withdrew because of an adverse event experienced gastrointestinal and abdominal pains, nausea and vomiting symptoms, and gastrointestinal haemorrhages, which the investigator considered as related to study drug. During follow-up of a second subject who withdrew because of pregnancy, she experienced a spontaneous abortion. It was recorded as a serious adverse event, which the investigator determined as possibly related to study drug or to a history of spontaneous abortions.

No deaths or other serious adverse events occurred during the study. No clinically important changes were observed in laboratory test results, vital signs, electrocardiograms or physical examinations.

## DISCUSSION

The relative effect of administering PPIs at different times of day has been infrequently studied except for trials that directly compared the benefits of morning vs. evening dosing.[18–23] Study designs were varied, but results generally showed either no difference in pharmacodynamics between morning and evening dosing[22, 23] or better gastric acid control with morning dosing.[18–21] To our knowledge, there has been only one study of an investigational PPI (tenatoprazole) that evaluated dosing at three different times of day, 7:00 AM and 7:00 PM under fasting conditions and 9:30 PM, 2 h after a meal.[24] In this study, *AUC* and $C_{max}$ values were significantly higher after morning dosing, but pH control was superior after the fasting evening dose.

The present study is the first report of the pharmacokinetics and pharmacodynamics of a PPI administered at four different times of day: before a standard breakfast, lunch, dinner or evening snack that approximates meals typical for each respective time of day. The absorption of dexlansoprazole was delayed when dexlansoprazole MR was administered before lunch, dinner or an evening snack compared with administration before breakfast. However, this delay was not considered clinically meaningful because there were no apparent differences in the systemic exposure of dexlansoprazole when administered with the alternative regimens; all regimens were pharmacokinetically bioequivalent. In particular, the mean values of plasma half-life were similar with each regimen (1.27–1.44 h).

The mean intragastric pH profiles for the breakfast, lunch and dinner regimens were similar. There were no statistically significant differences in mean 24-h pH between dosing before dinner or an evening snack vs. breakfast. These differences were also no more than 0.1, which is considered not clinically meaningful. The statistically significant but small increase in the mean 24-h intragastric pH of 0.2 for the lunch regimen comparing with that of the breakfast regimen was not considered clinically meaningful.

After breakfast, lunch and dinner, intragastric pH quickly rose to a level >4 that was maintained throughout most of the 24-h postdose interval. A statistically significant 7 percentage point difference in the percentage of time pH was >4 for the snack regimen (64%) relative to the breakfast regimen (71%) may be attributed to a delay in absorption of dexlansoprazole after administration before an evening snack because the subjects had not fasted as they had before breakfast. In addition, smaller quantity of food may stimulate fewer pumps or may not stimulate gastric emptying to the extent that a larger meal may, thereby diminishing the effect of the PPI. Lastly, absorption may be delayed by decreased gastrointestinal motility during nighttime hours resulting from normal circadian rhythms.[25] However, the delayed effect following an evening snack did not alter overall 24-h pH control and therefore may not be clinically meaningful. Nevertheless, if a patient who receives dexlansoprazole MR before an evening snack continues to experience symptoms, it may be prudent for that patient to consider administration of dexlansoprazole MR before a standard meal.

The pharmacokinetics and pharmacodynamics of dexlansoprazole MR administered under fasting and various fed conditions (30 min before breakfast, or 5 or 30 min after breakfast) have been evaluated in an earlier phase 1, four-way crossover study in healthy subjects.[26] There was a modest, but significant decrease in the percentage of time that intragastric pH was >4 when dexlansoprazole MR was administered 30 min after breakfast compared with administration 30 min before breakfast. Based on these data, it was concluded that dexlansoprazole MR can be administered without regard to meals or the timing of meals, although some patients may benefit from administering the dose before a meal if postmeal symptoms are not resolved.[27] This is in contrast with recommendations for the conventional-release PPIs, esomeprazole, lansoprazole and omeprazole, that they be taken before meals to avoid a negative pharmacokinetic food effect.[2–4, 28–30]

The results from the earlier food effect trial with dexlansoprazole MR described above along with those from the current trial demonstrate that this PPI offers a greater dosing flexibility for patients with acid-related disorders, which may improve compliance, an important and common issue for patients receiving PPI therapy for acid-related disorders.[31] It may also allow flexibility in scheduling dosing so that patients may target the time of day when their symptoms are most troublesome.

The results of these two food-effect trials may also convey interesting new insight into the biology of proton pumps and its relevance to acid suppression therapy. These data conflict with the theory that a morning PPI dose produces the greatest acid suppression because this is when the largest number of pumps is available for inhibition.[7, 10] This concept was first published in 1995 when the only available PPIs had a conventional-release formulation, giving a single, early duodenal release of drug. With a conventional formulation, there is little drug available after the initial few hours following dosing to block new pumps synthesized during the remaining 20 h of the day. Add to this the negative effect of food on the pharmacokinetics of these conventional-released PPIs and the theory of dosing before breakfast was conceived. However, with dexlansoprazole MR, the formulation is different and an alternative dosing regimen may be feasible because of the above theory being less relevant.

In this study, dexlansoprazole MR was generally well tolerated by healthy subjects. One subject reported a serious adverse event and one subject prematurely discontinued because of an adverse event. No clinically significant changes were seen in laboratory variables, vital signs and ECG evaluations during the study.

The use of intragastric pH as a surrogate for clinical benefit may be considered a limitation of this study. Although no firm target has been established, studies have suggested that there exists a clinically relevant relationship between the duration of sustained 24-h intragastric pH > 4 and healing of erosive oesophagitis.[32–34] In addition, we did not assess changes in acid volume produced after treatment with dexlansoprazole MR at different times of day, an observation that may have offered a correlate of clinical interest. As the previous food effect study with dexlansoprazole MR[26] concluded that the drug could be administered without regard to meals or the timing of meals, a possible limitation of the current study may be that each dose was administered 30 min before a meal. Whereas variations in dose timing may be a relatively common occurrence in real world clinical practice (e.g. at bedtime or mid-afternoon), the intent of this study was to assess pharmacokinetics and pharmacodynamics after administration of drug at specific times of day. To achieve this, standardized timing and meals were necessary to minimize confounding variables that probably would have required a larger cohort to resolve. The lack of a

comparator or baseline (predose) pH determinations may also be viewed as limitations. As the objective was to evaluate the effects of administration of dexlansoprazole MR with various meals on pharmacokinetic and pharmacodynamic measures, it was more important that each subject served as his/her own control. Although there was no intent to correlate an individual subject's pharmacokinetic and pharmacodynamic parameters, if pharmacokinetic differences were observed, it would have been important to understand whether the pharmacodynamic profile was affected, and assessment of baseline pH would have been of value. However, as no pharmacokinetic effect was noted in this population of healthy subjects, the lack of baseline pharmacodynamic measures does not limit the interpretation of the data.

In conclusion, the data from this study indicate that the pharmacokinetics of dexlansoprazole were not affected when dexlansoprazole MR was given at different times of the day in conjunction with meals that would be typically consumed throughout the day. Dexlansoprazole MR provides comparable pH control across a 24-h period regardless of the time of day in conjunction with meals. Administration of dexlansoprazole MR before an evening snack may not provide optimal acid control for some patients and it may be more appropriate for these patients to dose before a larger meal. Dexlansoprazole MR was generally well tolerated by the healthy subjects in this study.

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