Comparison of the Pharmacokinetics/Pharmacodynamics of a Fixed-Dose Combination of Rabeprazole/Magnesium Oxide 20/350 mg to the Enteric-Coated Rabeprazole 20 mg

Heejae Won[1,2], SeungHwan Lee[1]

[1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea
[2]Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Republic of Korea

BACKGROUND

- Proton pump inhibitors (PPIs), including rabeprazole is commonly used for acid-related disorders.
- However, the use of enteric-coated (EC) formulation of PPIs, due to their rapid degradation in acid environments, causes medical unmet needs such as delayed absorption and slow onset of action.
- The fixed-dose combination (FDC) of rabeprazole/magnesium oxide (MgO) 20/350 mg (DHNP-2001B) was newly developed to address these challenges observed with conventional EC formulation of rabeprazole 20 mg (Pariet® 20 mg).

OBJECTIVE

- This study aimed to evaluate pharmacokinetics (PKs) and pharmacodynamics (PDs) of FDC of rabeprazole/MgO 20/350 mg in comparison to the conventional EC formulation of rabeprazole 20 mg.

METHODS

Study Design

- A randomized, open-label, multiple-dose, 2-sequence, 2-period crossover study was conducted.
- Eligible subjects randomly received either the FDC or the conventional formulation for 7 days in the first period and the alternative in the second period with a 14-day washout.

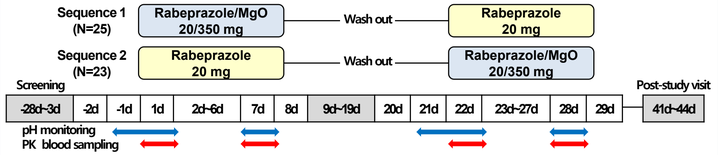

Figure 1. Study design.

Pharmacokinetic Assessment

- Blood samples were collected for PK analysis after the single- (Day 1) and multiple-dose (Day 7).
  - ➢ At pre-dose (0h), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 24 h post-dose
- Plasma concentrations of rabeprazole were determined by liquid chromatography with tandem mass spectrometry (LC-MS/MS).
- PK parameters were estimated using noncompartmental analysis using Phoenix WinNonlin® 8.3.

Pharmacodynamic Assessment

- Continuous 24-hour intragastric pH monitoring was conducted for PD analysis at before dose (Day -1) and after the single- (Day 1), multiple-dose (Day 7) using a Digitrapper™ pH-Z recorder.
- Calibration of the pH catheter with a standard solution of pH 4 and 7
- Subjects start their standardized meals 4.5 and 10.5 hours after dosing
- PD parameters included decrease from baseline in the integrated gastric acidity, percentage of time with gastric pH >4, mean and median gastric pH after the single- and multiple-dose.

RESULTS

- Thirty-seven healthy subjects completed the study and included in PK and PD analyses.
- The systemic exposures of rabeprazole were similar between the treatments after the single- and multiple-dose.
- The GMR (90% CI) of the FDC to the conventional formulation for the area under the curve within a dosing interval (τ) at steady state ($AUC_{τ,ss}$) was 0.9852 (0.8916 – 1.0887).
- The time to reach the maximum rabeprazole concentration of the FDC was 2.5-3 hours faster than the conventional rabeprazole.
- The extents of gastric acid suppression after the single- and multiple-dose were comparable between the treatments.
- The GMR (90% CI) of the FDC to the conventional formulation for percent decrease from baseline in the integrated gastric acidity over a 24-hour interval was 0.9650 (0.8932 – 1.0425) at steady state.

Table 1. Summary of pharmacokinetic parameters of rabeprazole after the single- and multiple-dose.

Dosing	Parameters	Rabeprazole/MgO 20/350 mg (N=37)	Rabeprazole 20 mg (N=37)	GMR* (90% CI)
Single-dose (Day 1)	T_{max} (h)	1.50 [1.00 - 2.50]	4.00 [2.00 - 8.00]	-
	C_{max} (μg/L)	688.44 ± 404.66	820.63 ± 361.93	-
	$AUC_τ$ (h·μg/L)	1320.50 ± 697.88	1534.15 ± 751.89	-
	$t_{1/2}$ (h)	2.85 ± 1.23	2.25 ± 1.17	-
	CL/F (L/h)	16.49 ± 8.88	12.77 ± 7.85	-
	V_z/F (L)	49.99 ± 47.37	23.59 ± 6.87	-
Multiple-dose (Day 7)	$T_{max,ss}$ (h)	0.50 [0.20 – 2.50]	3.50 [2.50 – 6.00]	-
	$C_{max,ss}$ (μg/L)	820.45 ± 408.57	776.71 ± 339.57	-
	$AUC_{τ,ss}$ (h·μg/L)	1517.24 ± 857.75	1525.17 ± 752.15	0.9852 (0.8916 - 1.0887)
	$t_{1/2,ss}$ (h)	3.01 ± 1.20	2.89 ± 2.27	-
	CL/F_{ss} (L/h)	18.49 ± 11.99	19.28 ± 22.05	-
	V_z/F_{ss} (L)	72.60 ± 50.18	120.27 ± 433.16	-

Notes: Data are presented as mean ± standard deviation, except for T_{max}, which is presented as median [min – max]
Abbreviations: C_{max}, maximum plasma concentration; $C_{max,ss}$, maximum plasma concentration at steady state; $AUC_τ$, area under the concentration-time curve over the dosing interval; $AUC_{τ,ss}$, area under the concentration-time curve over the dosing interval at steady state; T_{max}, time to reach C_{max}; $T_{max,ss}$, time to reach $C_{max,ss}$; CL/F, apparent clearance; CL_{ss}/F, apparent clearance at steady state; V_{ss}/F, apparent volume of distribution; V_{ss}/F, apparent volume of distribution at steady state;
*Geometric mean ratio (GMR) and 90% confidence interval (CI) of the FDC of rabeprazole/MgO 20/350 mg to the conventional EC formulation of rabeprazole 20 mg.

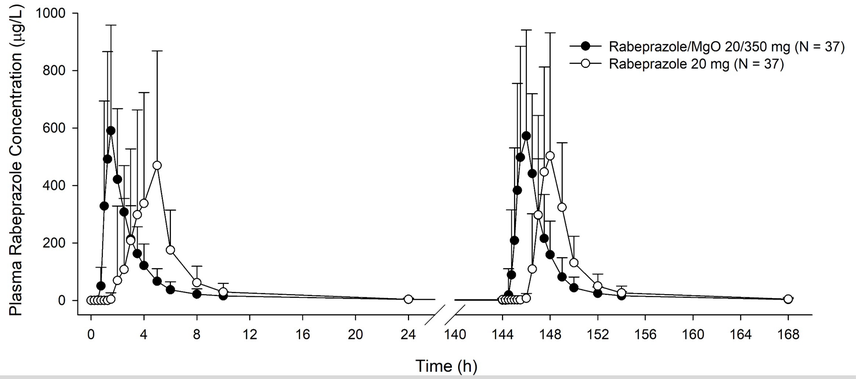

Figure 2. Mean plasma concentration-time profiles of rabeprazole after the single- and multiple-dose. Bars represent the standard deviations.

Table 2. Summary of pharmacodynamic parameters of rabeprazole after the single- and multiple-dose.

Dosing	Parameters	Rabeprazole/MgO 20/350 mg (N=37)	Rabeprazole 20 mg (N=37)	GMR* (90% CI)
Single-dose (Day 1)	% Δ Integrated gastric acidity	75.84 ± 13.82	74.24 ± 16.38	1.0474 (0.9582 – 1.1448)
	% Time with gastric pH > 4	43.47 ± 16.99	47.97 ± 15.95	-
	Mean gastric acid concentration	3.60 ± 2.16	3.91 ± 1.98	-
	Median gastric acid concentration	1.98 ± 2.70	1.43 ± 1.69	-
Multiple-dose (Day 7)	% Δ Integrated gastric acidity	80.61 ± 15.55	81.36 ± 14.78	0.9650 (0.8932 – 1.0425)
	% Time with gastric pH > 4	59.93 ± 15.64	59.33 ± 17.56	-
	Mean gastric acid concentration	2.79 ± 2.12	2.86 ± 2.18	-
	Median gastric acid concentration	0.29 ± 1.03	0.31 ± 0.66	-

Notes: Data are presented as mean ± standard deviation
Abbreviations: Δ, percentage decrease from baseline;
*Geometric mean ratio (GMR) and 90% confidence interval (CI) of the FDC of rabeprazole/MgO 20/350 mg to the conventional EC formulation of rabeprazole 20 mg.

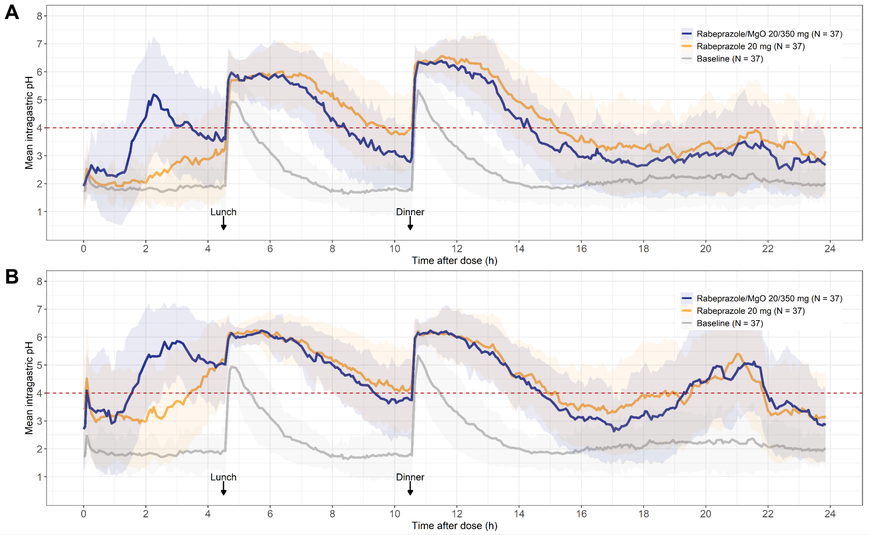

Figure 3. Mean intragastric pH-time profiles of rabeprazole after the (A) single- and (B) multiple-dose.

CONCLUSIONS

- The FDC of rabeprazole/MgO 20/350 mg (DHNP-2001B) showed rapid absorption compared to the conventional formulation of rabeprazole 20 mg (Pariet® 20 mg), without altering the overall systemic exposure and the intragastric acid suppression effect.

CONFLICTS OF INTEREST

- This study was sponsored by DaehanNupharm Co., Ltd., Republic of Korea.
- Authors do not have any conflicts of interest for this study.