

**Table 1. Mean±SD PK Parameters for Diazepam – All Subjects.**

PK Parameter	RBP group (N=19)	Placebo (N=19)	Ratios (%) and (90% CI) p-value <sup>a</sup>	
			Untransformed data	Log-transformed Data
AUC <sub>0-∞</sub> (ng*hr/ml)	12247±4489	16671±26579	72.5 (13.6;132) 0.429	98.6 (78.6;123.6) 0.913
Cmax (ng/ml)	511.3±281.8	490.5±406.9	105.5 (64.4;147) 0.818	109.9 (88.1;137.1) 0.469
Tmax (hr)	0.5±0.9	0.5±0.9	98.6 0.980	NA
Kel (1/hr)	0.02±0.01	0.02±0.01	100.2 0.981	NA
Half-life (hr)	50.9±26.1	165.6±517.7	29.8 0.311	NA
Cl <sub>total</sub> (ml/hr)	698±265	721±257	96.4 0.647	NA
Vss (ml)	17722±9864	18739±10774	94.9 0.593	NA
MRT (hr)	30.2±25.9	53.2±121.3	56.2 0.364	NA

<sup>a</sup>p-value for treatment effect from ANOVA analysis

#### Diazepam Protein Binding

The percent of free diazepam ranged from 1.13 to 1.76% during the placebo treatment period and from 1.15 to 1.80% during the RBP treatment period. Each subject had <2% free diazepam for both treatment periods. The differences in diazepam protein binding between the placebo and RBP treatment periods were not statistically significant (p=0.081), however, there was a significant period effect (p=0.001) present.

#### Nordiazepam Data

Subject 1316 had missing nordiazepam concentration data and was not included in the calculation of the mean PK parameters or in the analysis of the treatment differences. No statistically significant treatment effects were seen for any of the nordiazepam PK parameters when the RBP and placebo treatment periods were compared for all subjects or when the PMs were excluded. There were, however, significant period effects for kel and MRT for both untransformed and log-transformed data when all subjects were analyzed, and when the PMs were excluded from the analysis. The results of the PK calculations and the statistical analyses are provided in Table 2. The nordiazepam plasma concentration vs time profiles were very similar for the RBP and placebo groups.

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**Table 2. Mean±SD PK Parameters for Nordiazepam – All Subjects.**

PK Parameter	RBP group (N=18)	Placebo (N=18)	Ratios (%) and (90% CI) p-value <sup>a</sup>	
			Untransformed data	Log-transformed Data
AUC <sub>0-∞</sub> (ng*hr/ml)	8275±3827	7876±3223	106.7 (92;122) 0.437	104 (93.5;115.7) 0.526
C <sub>max</sub> (ng/ml)	32.3±6.3	30.9±6.3	104.5 (99.6;109) 0.127	104.5 (99.2;110.1) 0.157
T <sub>max</sub> (hr)	88.4±60.4	75.8±36.9	118.0 0.357	NA
K <sub>el</sub> (1/hr)	0.01±0.00	0.01±0.00	103.0 0.628	NA
Half-life (hr)	126.6±88.7	132.4±80.1	97.0 0.841	NA
Cl <sub>total</sub> (ml/hr)	1067±434	1068±332	99.1 0.878	NA
V <sub>ss</sub> (ml)	153953±37951	158397±42310	97.6 0.485	NA
MRT (hr)	170.2±97.8	167.7±88.2	103.3 0.625	NA

<sup>a</sup>p-value for treatment effect from ANOVA analysis

#### RBP Data

Mean AUC and C<sub>max</sub> values were higher and the T<sub>max</sub> was slightly shorter on Day 7 than on Day 1, but the concentration-time profile remained unchanged in both sets of data. PK parameters for RBP were consistent with those observed after multiple dosing of 20 mg in other studies.

**Table 3. Mean±SD PK Parameters for RBP.**

Parameter	Day 1	Day 7
AUC <sub>0-t</sub> (ng*hr/ml)	498±315	590±399
AUC <sub>0-∞</sub> (ng*hr/ml)	521±324	609±409
C <sub>max</sub> (ng/ml)	228±104	317±144
T <sub>max</sub> (hr)	3.9±1.2	3.5±0.9
kel (1/hr)	0.80±0.34	0.83±0.28
Half-life (hr)	1.2±1.0	1.0±0.6

#### **Safety:**

Each subject who completed the study received a total of 35 doses of RBP (20 mg oral), 35 doses of placebo (20 mg oral), and a total of two doses of diazepam 0.1 mg/kg IV over a 5-minute infusion during two treatment periods. There were no deaths or serious adverse events in this study. The adverse events that were reported were mild to moderate in nature. There were no clinically significant abnormal clinical laboratory values, out-of-range vital signs, or abnormal ECGs reported.

#### **CONCLUSIONS:**

Although a total of 55 adverse events were reported during the study, approximately 40% of these adverse events were associated with the parenteral administration of diazepam. RBP was well tolerated at the 20 mg dose level when administered once a day, with a single dose of diazepam 0.1 mg/kg, administered on the eighth day of RBP dosing.

Overall, RBP did not have a statistically significant effect on any of the diazepam pharmacokinetic parameters when comparisons were made including all subjects or when analyses were conducted excluding the poor metabolizers, indicating that no significant drug interactions were detected. In addition, the protein binding of diazepam was unaffected by the concomitant administration of RBP. Furthermore, there were no statistically significant differences in PK parameters for nordiazepam between the RBP and placebo treatment.

**REVIEWER'S COMMENTS:**

1. Diazepam plasma concentrations were within therapeutic levels.
2. The importance of the significant period effects observed for MRT and kel for nordiazepam are unknown.

APPEARS THIS WAY  
ON ORIGINAL

**TITLE:** A study of the effect of E3810 and omeprazole on the pharmacokinetics of intravenous diazepam in Japanese healthy male volunteers

**Protocol Number:** E3810-J081-020

**Publication (reference):** *Gut* Vol. 39(suppl):A47, 1996

*Clin Pharmacol Ther* Vol. 58:143-154, 1995

*Clin Pharmacol Ther* Vol. 58:155-164, 1995

*Clin Pharmacol Ther* Vol. 55:165, 1994

*Clin Pharmacol Ther* Vol. 55:141, 1994

*Japn J Clin Pharmacol Ther (Rinsho Yakuri)* Vol. 25(1):83-84, 1994

*Japn J Clin Pharmacol Ther (Rinsho Yakuri)* Vol. 26(1):247-248, 1995

**Study Dates:** September, 1992 through February, 1993

**OBJECTIVES:**

1. to evaluate the effects of RBP on the pharmacokinetics of diazepam and demethyl-diazepam compared with those of omeprazole in healthy male volunteers,
2. to evaluate the influence of repeated administration on the pharmacokinetics of RBP compared with that of omeprazole,
3. to evaluate whether S-mephenytoin 4'-hydroxylase is responsible for the metabolism of RBP

**METHODS:**

**Study Design:** randomized, open-label, placebo-controlled, crossover study.

**Study Population:** 15 normal, healthy Japanese males, aged 20 years or greater

**Treatment and Drug Administration:**

The study consisted of 3 phases:

Phase I occurred before commencement of the study, when subjects were classified according to their capacity to hydroxylate S-mephenytoin at pre-study screening test. The total number of subjects was 15, consisting of 6 poor metabolizers (PM) of S-mephenytoin and 9 extensive metabolizers (EM), on the basis of the results of their screening test. The subjects were divided into three groups: A, B and C, each containing 2 PMs and 3 EMs.

- Phase 2 was the treatment phase. The study was performed as a crossover study with three arms, separated by washout periods of 21 days or more. In each period, the subjects received 20 mg of RBP, 20 mg of omeprazole, or placebo, orally, for 23 days (Days 1 to 23). On Day 8, 0.1 mg/kg of diazepam was intravenously administered over 5 minutes, starting one hour after the eighth drug administration. Subjects were hospitalized from the evening of Day 7 until the completion of blood sampling scheduled 24 hours after the start of diazepam administration on Day 9. Drug assignment was as follows:
  - Group A- (Step I) RBP 20 mg, (Step II) omeprazole, (Step III) placebo;
  - Group B- (Step I) placebo, (Step II) RBP 20 mg, (Step III) omeprazole 20 mg;
  - Group C- (Step I) omeprazole 20 mg, (Step II) placebo, (Step III) RBP 20 mg.

During Phase 3, the follow-up phase, subjects visited the study site for final medical evaluation. Subjects were to have no intake of any other drugs during the two weeks before commencement of the study, nor any intake of other investigational drugs, except mephenytoin, during the 6 months before commencement of the study.

**Study Drug Supplies:**

20 mg enteric-coated RBP tablets; #K21002ZZA. . *This is the to-be-marketed formulation.*

Placebo: enteric-coated tablet identical in shape and appearance to 20 mg tablet of RBP; #K051600

Omeprazole (Omepral<sup>®</sup>)- 20 mg tablet. Lot number 0170

**Pharmacokinetic Analysis:**

Pharmacokinetic parameters were calculated using model-independent analysis for the following parameters: C<sub>max</sub>, t<sub>max</sub>, AUC<sub>0-24</sub>, k<sub>el</sub>, half-life, CL, MRT, and V<sub>dss</sub>. C<sub>max</sub>, t<sub>max</sub> and AUC<sub>0-24</sub> were used as PK parameters for the evaluation of bioequivalency. The following measures were also used to evaluate the PK profile during treatment phase: concentration of diazepam and its metabolite (demethyldiazepam) in plasma; concentrations of RBP and its metabolites (thioether-RBP, UM-1 and UM-2) in plasma; concentrations of omeprazole and its metabolites (hydroxy-omeprazole and omeprazole sulfone) in plasma; concentrations of RBP metabolites (UM-1 and UM-2) in urine; and concentrations of omeprazole metabolite (hydroxy-omeprazole) in urine.

**Safety:**

Assessed via physical examination, adverse events, vital signs, electrocardiogram, and clinical laboratory studies.

**Statistical Methods:**

The initial statistical analysis to evaluate the differences in the mean kinetic parameters (C<sub>max</sub>, AUC, half-life, CL, MRT, and V<sub>dss</sub>) among the three treatments within the same phenotype was conducted by the three-way ANOVA. When this statistical analysis showed a significant difference, the differences in the mean kinetic parameters between two treatments within the same phenotype group were tested by Tukey's test.

The PK parameters obtained for PMs and EMs were compared by a two sample *t*-test. The comparison of t<sub>max</sub> was conducted by the Wilcoxon signed rank test.

The statistical differences in the mean kinetic parameters between the results after the first and seventh doses was based on the paired *t*-test. The comparison of t<sub>max</sub> after the first and the seventh doses was conducted by the Wilcoxon rank sum test. A p-value less than 0.05 was considered statistically significant.

**RESULTS:****Pharmacokinetics:**

Metabolism of RBP is under coregulatory control of CYP2C19 as is that of omeprazole, however, the magnitude of CYP2C19-mediated metabolism of RBP appears to be smaller than that of omeprazole. The metabolic capacity of omeprazole tended to decrease with the repeated doses in EMs, whereas no such change was observed for RBP. This finding suggests that the metabolism of omeprazole, mediated by way of CYP2C19, occurs in a saturable fashion during repetitive dosings. Omeprazole decreased the metabolism of diazepam in EMs but not in PMs of S-mephenytoin, whereas RBP showed no appreciable interaction with diazepam. The difference in interaction with diazepam between the two proton pump inhibitors appears to be derived from the different potential to inhibit the activity of CYP2C19 in a competitive fashion.

Omeprazole increased the AUC<sub>0-16day</sub> of demethyldiazepam in EMs, whereas RBP increased it in PMs, but not in EMs. The former interaction may be due to competitive inhibition of CYP2C19, whereas the latter may be due to competitive inhibition of CYP3A.

**Safety:**

No serious adverse events were noted in this study. Fifty-one subjects reported central nervous system symptoms such as sleepiness after the infusion of diazepam on Day 8 regardless of treatment or phenotype. According to the investigator, in most cases the event was caused by the administration of diazepam.

All adverse events were mild to moderate in nature. There were no clinically significant abnormal findings in vital signs, ECGs, or clinical laboratory studies.

**CONCLUSIONS:**

RBP was generally well tolerated by healthy subjects with concomitant dosing of diazepam. There was no evidence of a drug interaction between RBP and diazepam in either the EMs or PMs, however, RBP did appear to increase the  $AUC_{0-16\text{days}}$  of demethyldiazepam in the PMs, but not the EMs.

**REVIEWER'S COMMENTS:**

This study was not reviewed in depth as a very similar study was previously reviewed and reported (see Study #A001-113).

APPEARS THIS WAY  
ON ORIGINAL

**TITLE:** A study on the effect of a single dose of antacid on the pharmacokinetics of E3810 in healthy male volunteers

**Protocol Number:** E3810-J081-028

**Study Dates:** April-May, 1995

**OBJECTIVE:** to study the effect of a single dose of antacid on the PKs of RBP in healthy, male volunteers.

**METHODS:**

**Study Design:** randomized, open-label, three-way cross-over study

**Study Population:** 12 healthy, Japanese, male subjects between the ages of 21 and 33 years

**Treatment and Drug Administration:**

Twelve subjects were randomly divided into 6 groups of 2 subjects each, and the RBP treatments were allocated according to the following list (3 steps are listed for each group):

- Group A - (1) without Maalox<sup>®</sup>, (2) concomitant Maalox<sup>®</sup>, (3) Maalox<sup>®</sup> one hour before RBP;
- Group B - (1) without Maalox<sup>®</sup>, (2) Maalox<sup>®</sup> one hour before RBP, (3) concomitant Maalox<sup>®</sup>
- Group C - (1) concomitant Maalox<sup>®</sup>, (2) without Maalox<sup>®</sup>, (3) Maalox<sup>®</sup> one hour before RBP
- Group D - (1) concomitant Maalox<sup>®</sup>, (2) Maalox<sup>®</sup> one hour before RBP, (3) without Maalox<sup>®</sup>
- Group E - (1) Maalox<sup>®</sup> one hour before RBP, (2) without Maalox<sup>®</sup>, (3) concomitant Maalox<sup>®</sup>
- Group F - (1) Maalox<sup>®</sup> one hour before RBP, (2) concomitant Maalox<sup>®</sup>, (3) without Maalox<sup>®</sup>

To the "without Maalox<sup>®</sup>" groups, one 20 mg tablet of RBP was administered orally with 120 mL of water under fasting conditions. To the "concomitant Maalox<sup>®</sup>" groups, 30 mL of Maalox<sup>®</sup> suspension was administered orally under fasting conditions, immediately after which one 20 mg tablet of RBP was given with 90 mL of water. To the "Maalox<sup>®</sup> one hour before RBP" groups, 30 mL of Maalox<sup>®</sup> suspension was administered orally under fasting conditions, one hour after which one 20 mg tablet of RBP was given with 90 mL of water. On the day of drug administration, lunch, supper, and a snack were served at 13:00, 18:00, and 21:00, respectively. The wash-out period between treatments was one week.

**Study Drug Supplies:**

20 mg enteric film-coated RBP tablet; #K39001ZZD. *This is the to-be-marketed formulation.* Maalox<sup>®</sup> suspension, 56 gm of aluminum hydroxide gel and 4 gm of magnesium hydroxide in 100 mL suspension; #YAY009Y.

**Biological Sampling:**

Blood was sampled for the determination of RBP plasma levels prior to dosing and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, and 12 hours after RBP dosing for the "without Maalox" group. Sampling was performed prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, and 12 hours post-dose for the "concomitant Maalox" and "Maalox one hour before RBP" groups.

**Pharmacokinetic Analysis:**

C<sub>max</sub>, T<sub>max</sub>, AUC<sub>0-12</sub>, and half-life were calculated using model-independent analysis.

**Safety:** Assessed by physical examination, adverse events, vital signs, ECG, and clinical laboratory studies.

**Statistical Methods:**

The initial statistical analysis to evaluate differences in mean PK parameters among the three treatments was conducted using a three-way ANOVA. When a significant difference was detected, the differences in mean PK parameters between two treatments were tested by Tukey's test. The Friedman test was also performed on Tmax.

**Analytical Methods:**

Blood was analyzed for RBP concentrations May-June, 1995, by using

The following assay validation parameters were provided in the study report:

Linearity: >0.999 from 10-2000 ng/ml

Sensitivity: LOQ= 10 ng/ml

Precision: Interday - <4% CV at 25ng/ml and 1605 ng/ml

Intraday - <7% CV at 25ng/ml and 1605 ng/ml

Accuracy: Interday - 105 % at 25 ng/ml, 102% at 1605 ng/ml

Intraday - 97-112% at 25 ng/ml, 99-104% at 1605 ng/ml

Specificity:

**RESULTS:**

**Demographics:**

All 12 subjects completed the study. The mean age, height, and weight for the subjects was 25.5 years, 173.1 cm, and 64.3 kg, respectively. Subjects between groups had similar baseline characteristics.

**Pharmacokinetics:**

There were no statistically significant differences observed for any of the PK parameters for any of the three treatment groups. The PK results are provided in Table 1. RBP plasma concentrations for all three treatment groups are attached to the study report.

**Table 1. Mean±SD RBP PK parameters for each treatment group.**

Parameter	Without Maalox (N=12)	Concomitant Maalox (N=12)	Maalox 1 hr before RBP (N=12)
AUC <sub>0-12</sub> (ng*hr/ml)	1020.8±713.0	942.9±604.7	960.1±624.4
Cmax (ng/ml)	516.8±269.5	630.5±321.7	601.3±315.5
Tmax (hr)	3.6±1.1	3.4±1.1	4.0±1.3
Half-life (hr)	1.2±0.7	1.1±0.6	1.1±0.6

**Safety:**

Adverse events were all mild-to-moderate in nature and resolved without treatment. No significant abnormal findings in vital signs, 12-lead ECGs, or clinical laboratory tests were observed during the study.

**CONCLUSIONS:**

In clinical practice, it can be assumed that antacids may be taken concomitantly with RBP for symptom relief. Maalox<sup>®</sup> was selected because it is one of the most widely used antacid

products. There were no statistically significant differences observed in  $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-12}$ , or half-life when RBP was administered alone, concomitantly with Maalox<sup>®</sup>, or one hour after Maalox<sup>®</sup> administration. Therefore, it can be concluded from this study that no interaction occurred between RBP and this antacid. In addition, RBP was well tolerated at the 20 mg dose level.

**REVIEWER'S COMMENTS:**

1. It is not clear whether the data submitted for analytical methods was a methods validation report or the results of the analysis of actual study samples. The assay validation data was deficient in several areas, such as: no precision and accuracy provided for standard curve samples, no recovery data, no stability data, etc.
2. RBP plasma levels were only measured up to 12 hours after drug administration. However, only 2 subjects from each treatment group had RBP concentrations that were >LOQ at 12 hours, and these were very near the LOQ.

APPEARS THIS WAY  
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## PHARMACODYNAMIC STUDIES

**TITLE:** A comparison of two doses of the proton pump inhibitor E3810 (rabeprazole sodium) versus famotidine and pirenzepine using 24 hour monitoring of gastric pH in healthy volunteers.

**Protocol Number:** E3810-J081-007

**Study Dates:** July-December 1989

**OBJECTIVES:**

To compare the effects of RBP with famotidine and pirenzepine on gastric pH.

**METHODS:**

**Study Design:** randomized, open-label, 4-way cross-over

**Study Population:** 8 healthy, adult, Japanese volunteers between the ages of 18 and 39 years

**Treatment and Administration:**

Subjects were randomized into 4 groups as follows:

Group 1 - 10 mg RBP after breakfast

Group 2 - 20 mg RBP after breakfast

Group 3 - 40 mg famotidine: 20 mg after breakfast and 20 mg after dinner

Group 4 - 75 mg pirenzepine: 25 mg after each meal

All drugs were administered 30 minutes after meals and for 4 consecutive days. There was a washout period of at least 5 days between treatment periods. All subjects received all 4 treatments. On the last day of drug administration (Day 4), gastric pH was monitored from 07:00 for 24 hours for each subject during each treatment. Meals were provided at 08:00, 12:00, and 19:00.

**Study Drug Supplies:**

RBP - 10 mg enteric-coated tablets; #K931400. *This was not the to-be-marketed formulation.*

Famotidine - 20 mg tablets

Pirenzepine - 25 mg tablets

**Biological Sampling:**

Pharmacokinetics -

Blood was sampled prior to, and at 3 and 6 hours after RBP administration on the day of gastric pH monitoring for the determination of plasma RBP concentrations.

Pharmacodynamics -

Gastric pH was measured using a micro pH electrode inserted intranasally into the middle region of the stomach. pH values were recorded at 10 second intervals using a portable pH recorder.

**Pharmacodynamic Analysis:**

The holding times (proportion of the total measurement time during which the pH was maintained above the specified value, expressed as % of time) were calculated using the raw data for pH values from 1-6 over the 24-hour pH monitoring period. The actions of the three study drugs (4 treatment groups) were compared, particularly with respect to their holding times at pH 4. The pH holding times for four 6-hour intervals, 07:00-13:00, 13:00-19:00, 19:00-01:00, and 01:00-07:00 were also analyzed in order to clarify any differences. The Wilcoxon test, Tukey's test and Dunnett's t-test were used to conduct multiple comparisons of basal conditions and study drugs. The level of significance was 0.05 for all tests.

**Safety:** Assessed by clinical laboratory tests and adverse events.

**RESULTS:**

**Study Population and Demographics:**

Eight healthy, Japanese volunteers between the ages of 19 and 22 years. No other information was provided.

**Safety:** No adverse drug events or other abnormal findings were observed.

**Pharmacokinetics:** No PK results were reported (no reason provided).

**Pharmacodynamics:**

A multiple comparison of the basal versus post-treatment pH holding times revealed that the 24-hour value for 20 mg RBP (76.4%) was significantly higher ( $p \leq 0.05$ , Wilcoxon test) than those of the basal (41.3%), famotidine (36.4%), and pirenzepine (19.7%) values.

The highest pH holding times during the 24-hour and four 6-hour intervals were observed for 20 mg RBP, with significant differences from basal levels noted for the pH 3-6 range over 24 hours ( $p \leq 0.05$ ) and the pH 2-6 range for the 13:00-19:00 and 19:00-01:00 intervals. The pH holding times for 10 mg RBP were higher than the basal levels for the 24-hour and four 6-hour intervals, but lower than those of 20 mg RBP. Significant differences in holding time between 10 mg RBP and basal levels were only observed at pH 2 and 3 (13:00-19:00,  $p \leq 0.05$ ) and at pH 6 (19:00-01:00,  $p \leq 0.05$ ).

A multiple comparison among the treatments was conducted using Tukey's test and Dunnet's t-test. The pH 4 holding time was used as an indicator (the sponsor claims that a gastric pH of 4 has been shown to almost completely suppress gastric acid secretion). It was found that significant differences existed between 20 mg RBP and basal levels for the entire 24-hour period. However, no significant differences were observed between 10 mg RBP and basal levels. In addition, there were no significant differences found between either the 10 mg or 20 mg RBP doses and basal conditions for any of the four 6-hour intervals. The following table provides a summary of the mean pH holding times at pH 4.

**Table 1. Mean pH 4 holding times (%).**

	<b>24 hour</b>	<b>07:00-13:00</b>	<b>13:00-19:00</b>	<b>19:00-01:00</b>	<b>01:00-07:00</b>
<b>Basal</b>	41.3	38.0	36.8	46.0	44.4
<b>10 mg RBP</b>	64.7	44.3	78.8	74.5	61.1
<b>20 mg RBP</b>	76.4 <sup>a</sup>	58.5	85.9	85.6	75.7
<b>Famotidine</b>	36.4	29.7	25.2	27.4	63.2
<b>Pirenzepine</b>	19.7	17.4	23.8	22.6	15.1

<sup>a</sup> $p \leq 0.05$  vs 24-hour basal, based on Tukey's test and Dunnet's t-test

**CONCLUSIONS:**

In this study, although both 10 mg and 20 mg RBP resulted in increased holding times at various gastric pH values over a 24-hour period, statistically significant differences between basal values and drug treatment were observed for the 20 mg RBP dose only.

**REVIEWER'S COMMENTS:**

1. No individual raw data, including pH monitor recordings, were provided.
2. Incomplete information provided for subject demographics, safety parameters, and pharmacokinetics.
3. Neither the to-be-marketed formulation or strength of RBP was used in this study.

APPEARS THIS WAY  
ON ORIGINAL

**TITLE:** A study of the effects of the proton pump inhibitor E3810 (rabeprazole sodium) on gastric pH - comparison of morning vs. evening dosing regimen using continuous monitoring of gastric pH.

**Protocol Number:** E3810-J081-008

**Study Dates:** July 1989 - March 1990

**OBJECTIVES:**

To compare the effects of once daily administration of the new proton pump inhibitor, RBP, in the morning or evening, on intragastric pH using 24-hr continuous monitoring of gastric pH in patients with gastric ulcer (GU) or duodenal ulcer (DU).

**METHODS:**

**Study Design:** open-label, multi-center, comparative study

**Study Population:**

15 male or female, Japanese adults aged 18 to 74 years and diagnosed with GU or DU regardless of ulcer history, site, or size. Endoscopy was performed before the study to assess the stage of ulcer disease.

**Treatment and Administration:**

Patients were randomly assigned to receive 20 mg RBP (2x10 mg tablets) either after breakfast (08:30) or after dinner (18:00) for 4 consecutive days. Meals were provided at 08:00, 12:00, and 17:30 hours. Intragastric pH was measured twice in each patient, before starting drug administration and on Day 4 after either the morning or evening RBP administration. Intragastric pH monitoring was performed for 24 hours after drug administration on Day 4.

**Study Drug Supplies:**

10 mg enteric-coated RBP tablets; #K931400. *This was not the to-be-marketed formulation.*

**Pharmacodynamic Sampling/Analysis:**

A pH sensor was inserted intranasally into the greater curvature of the stomach body. The sensor was connected to the recorder of a portable pH meter carried by the patient.

Gastric pH values were analyzed by calculating the pH 3 holding time, the sum of the length of time when gastric pH was above the cutoff value of pH 3.0. The pH 3 holding times were determined for two 12-hour periods; day time (08:00 to 20:00) and night time (20:00 to 08:00 the next morning).

Blood samples were collected before breakfast prior to initiating the study and after completion of the study for the determination of plasma pepsinogen and gastrin concentrations, which were quantified by RIA.

**Pharmacokinetic Sampling/Analysis:**

Blood samples were to be collected for the determination of plasma RBP levels before dosing and at 3 and 6 hours after dosing in both the post-breakfast and post-dinner groups.

**Safety:**

Assessed by adverse events and clinical laboratory values.

**Statistical Analysis:**

Mean pH values were calculated every 30 minutes from the raw pH data, and the median values in each group were determined and compared. Analyses were conducted using a t-test with a significance level of 5%.

**RESULTS:****Demographics:**

Analysis of gastric pH data was performed in 7 post-breakfast cases (2 GU and 5 DU) and 7 post-dinner cases (4 GU and 3 DU). No other demographic information was provided.

**Pharmacokinetics:**

The plasma levels of RBP were not measured as stated in the protocol (no reason given).

**Pharmacodynamics:**

Significant ( $p \leq 0.001$ ) extension of the pH 3 holding time was achieved with both modes of RBP administration compared to basal values. The 24-hour pH 3 holding times in the post-breakfast group were  $356 \pm 262$  minutes predose and  $1418 \pm 37$  minutes on Day 4 of dosing. The corresponding times in the post-dinner group were  $468 \pm 343$  minutes and  $1304 \pm 129$  minutes. Likewise, the mean pH 3 holding times for the morning and night-time intervals were significantly greater at Day 4 compared to predose values in both the post-breakfast and post-dinner groups (see Table 1).

**Table 1. Mean  $\pm$  SD pH 3 holding times (minutes).**

		Post-breakfast group	Post-dinner group
Predose	08:00 to 20:00	84.0 $\pm$ 61.4	215.1 $\pm$ 169.6
	20:00 to 08:00	271.9 $\pm$ 226.0	252.6 $\pm$ 212.1
Day 4	08:00 to 20:00	712.0 $\pm$ 14.8 <sup>a</sup>	650.0 $\pm$ 73.3 <sup>b</sup>
	20:00 to 08:00	706.0 $\pm$ 37.0 <sup>a</sup>	653.7 $\pm$ 76.7 <sup>b</sup>

<sup>a</sup> $p < 0.001$  vs corresponding times predose

<sup>b</sup> $p < 0.001$  vs corresponding times predose

Gastric pH levels in the post-breakfast group remained at a pH value of approximately 2 throughout the 24-hour pre-dosing period. By Day 4 the gastric pH level was above 5 for most of the 24-hour period. Similar results were observed for the post-dinner group.

Mean serum gastrin levels increased for both GU and DU patients, although the increases were not statistically significant. Serum pepsinogen levels were higher than the normal range for patients with both types of ulcers, pre- and post-dosing with RBP. In addition, a significant elevation ( $p \leq 0.001$ ) of serum pepsinogen level was observed in the DU patients after RBP administration.

**Safety:** No safety results were reported.

**CONCLUSIONS:**

The gastric pH 3 holding time was significantly prolonged over a 24-hour period following 4 days of dosing in both the post-breakfast and post-dinner RBP dosing groups. Similar results were obtained when the 24-hour period was divided into two 12-hour periods. In addition, both groups exhibited a marked increase in median gastric pH values over the 24-hour period. As expected, RBP caused increases in both serum gastrin and pepsinogen levels.

**REVIEWER'S COMMENTS:**

1. There was no raw nor individual data (including pH recordings) provided with this study report.
2. Incomplete information was provided for subject demographics.
3. No safety data were provided as stated in the protocol.
4. No PK data were provided as stated in the protocol.
5. Neither the to-be-marketed formulation nor strength of RBP was used in this study.

APPEARS THIS WAY  
ON ORIGINAL

**TITLE:** A study of the effects of the proton pump inhibitor E3810 (rabeprazole sodium) on gastric juice secretion - basal and gastrin-stimulated gastric acid and pepsin secretion in healthy volunteers

**Protocol Number:** E3810-J081-018

**Study Dates:** October-November 1992

**OBJECTIVES:** to examine the effects of the new proton pump inhibitor, RBP, on basal and gastrin-stimulated gastric acid and pepsin secretion in healthy volunteers.

**METHODS:**

**Study Design:** open-label, single-center, pharmacodynamic study

**Study Population:**

5 healthy Japanese adults aged 18-29 years with basal gastric acid secretion of 2.0 mEq/hr or greater

**Treatment and Administration:**

Subjects were given 20 mg RBP once a day after breakfast for 7 consecutive days.

Gastric juice was sampled on 4 different occasions during the study:

1. Day 0 – prior to RBP administration
2. Day 1 – starting 6 hours after the initial RBP dose, for a total of 2.5 hours
3. Day 7 – starting 6 hours after the final RBP dose, for a total of 2.5 hours
4. Day 8 – starting 24 hours after the final RBP dose, for a total of 2.5 hours

Subjects were fed breakfast (08:00), lunch (12:00), and dinner (18:00) during the study, however, only received breakfast and dinner on gastric juice sampling days. In addition, no breakfast was provided on Day 8.

**Drug Supplies:**

20 mg enteric-coated RBP tablets; #K21002ZZA. *This is the to-be-marketed formulation.*

**Pharmacodynamic Sampling:**

Gastric juice was sampled according to the procedure established by the Gastric Juice measurement Subcommittee of the Japanese Society of Gastroenterology. Briefly, a gastric tube was inserted through the nose into the stomach and gastric juice samples were obtained at 10 minute intervals by aspiration with the subject in the left lateral recumbent position. The first 3 samples (30 minutes) were basal secretion, followed by amogastrin-stimulated secretion, 4µg/kg intramuscular [redacted] during the next 120 minutes. Gastric juice secretion, acid secretion, gastric pH, and pepsin secretion were measured and the percent reductions in all parameters (except gastric pH) were calculated.

**Pharmacokinetic Sampling:**

The protocol stated that blood was to be collected on Days 1 and 7 at 5, 6, 7, 8, and 9 hours after RBP administration for the determination of RBP concentrations in plasma.

**Safety:** Assessed via adverse events and clinical laboratory tests.