RESULTS:

Demographics:

All subjects completed the study. Of the 19 subjects, 17 were Caucasian and 2 were Hispanic. Mean ages, heights, and weights were 26.7 years, 178.8 cm, and 73.6 kg, respectively, for the subjects in the RBP group, and 28 years, 179.8 cm, and 79.8 kg, respectively, for the placebo group.

Pharmacokinetics:

Tables 1 and 2 provide PK parameters obtained for ketoconazole. Figures 1-3 (attached to the study report) display the ketoconazole plasma concentration vs time profiles for all subjects, placebo-treated subjects, and RBP-treated subjects (respectively).

Table 1. Mean±SD PK Parameters for Ketoconazole

PK Parameter	RBP group Period 1 (N=10)	RBP group Period 2 (N=10)	Placebo group Period 1 (N=9)	Placebo group Period 2 (N=9)
AUC_{0-T} (μg*hr/ml)	57.4±21.8	39.3±22.7	50.9±20.2	54.3±19.9
$AUC_{0-\infty}$ (μg*hr/ml)	57.8±21.8	39.7±22.7	51.5±20.6	54.7±20.0
Cmax (μg/ml)	10.0±2.9	6.8±3.2	9.1±2.5	9.0±3.1
Tmax (hr)	2.3±1.1	2.7±0.7	2.1±0.3	2.30±0.9
kel (1/hr)	0.30±0.09	0.25±0.08	0.29±0.08	0.26±0.07
Half-life (hr)	2.4±0.6	3.1±1.3	2.6±0.8	2.8±0.5

As seen in Table 2 below, statistically significant treatment differences between the RBP and placebo groups were seen in the changes from Period 1 to Period 2 for AUC_{0-T}, $AUC_{0-\infty}$, and Cmax.

Table 2. Mean±SD Changes in PK Parameters for Ketoconazole (Period 2-Period 1)

PK Parameter	RBP group (N=10)	Placebo group (N=9)	p-value from analysis of RBP vs placebo
AUC_{0-T} (μg*hr/ml)	-18.1±23.0	3.4±12.8	0.024
$AUC_{0-\infty}$ (μg*hr/ml)	-18.1±23.0	3.2±13.1	0.026
Cmax (μg/ml)	-3.1±3.5	0±2.4	0.040
Tmax (hr)	0.4±1.4	0.2±1.0	0.748
kel (1/hr)	-0.05±0.08	-0.03±0.08	0.487
Half-life (hr)	0.6±1.4	0.2±0.6	0.386

The PK parameters for RBP are provided in Table 3; results are consistent with other studies that administer multiple doses of 20 mg RBP.

Table 3. PK Parameters for RBP.

Parameter	Mean ± SD
AUC_{0-T} (μg*hr/ml)	858±333
Cmax (μg/ml)	457±176
Tmax (hr)	3.5±1.7
kel (1/hr)	0.83±0.33
Half-life (hr)	1.0±0.7

Safety:

There were no serious adverse events nor clinically significant out-of-range vital signs, laboratory

values, or abnormal ECG results.

CONCLUSIONS:

Previous studies with RBP suggested that the PK parameters had large coefficients of variation, as is common with other delayed-release products. The parallel-group design of this study was intended to accommodate this variability.

Subjects who received placebo displayed similar ketoconazole PK profiles and parameters for both treatment periods. In contrast, subjects receiving RBP displayed decreased PK profiles and parameters when compared to Period 1. These significant changes that were observed for AUC_{0-T}, $AUC_{0-\infty}$, and Cmax indicate that some type of interaction occurred between RBP and ketoconazole, resulting in an approximately 30% decrease in the bioavailability of ketoconazole. This interaction is predictable on the basis of RBP's known potent antisecretory effects, and the requirement of gastric acid to maximize the BA of ketoconazole. Therefore, when concurrent ketoconazole and RBP therapy is indicated, consideration should be given to altering the ketoconazole dosing regimen and patients should be appropriately monitored for therapeutic response to ketoconazole.

Figure 1. - Mean Ketoconazole Serum Concentrations - All Subjects

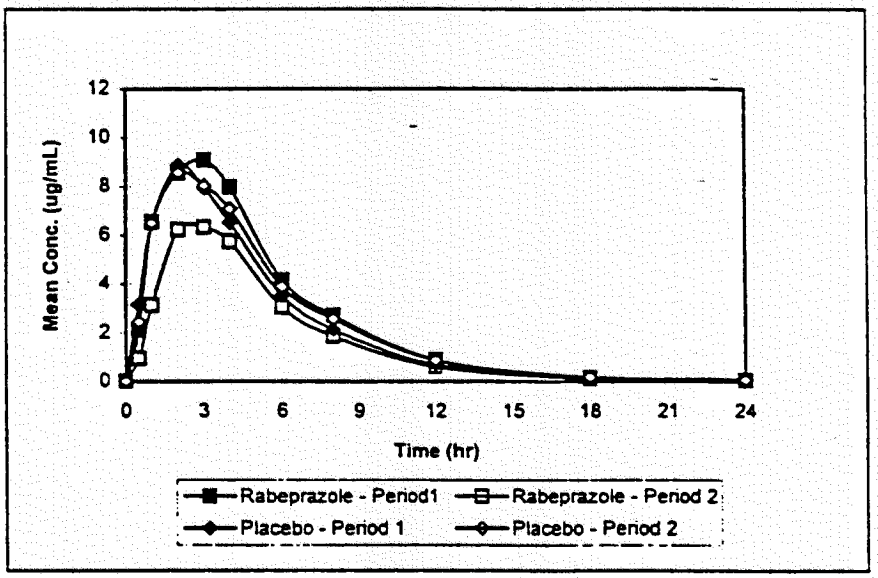


Figure 2. - Mean Ketoconazole Serum Concentrations - Placebo Subjects

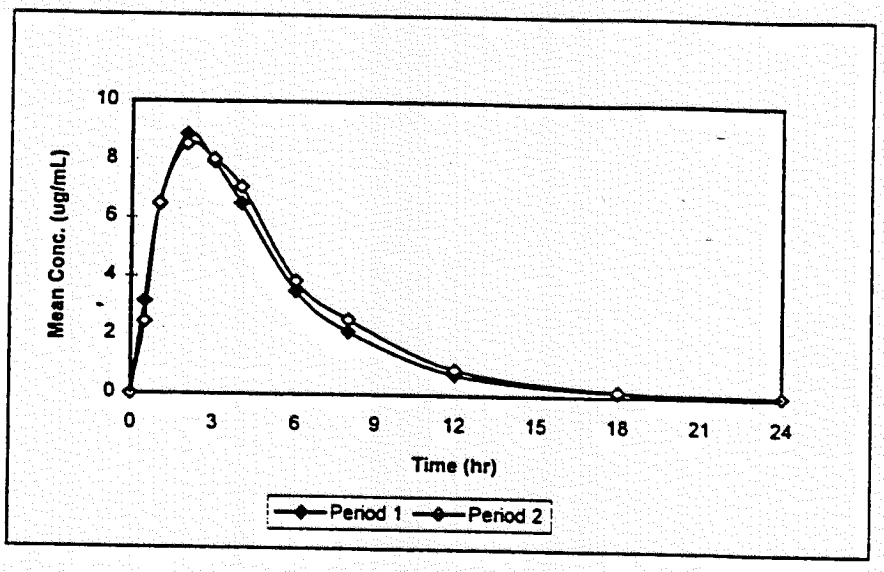
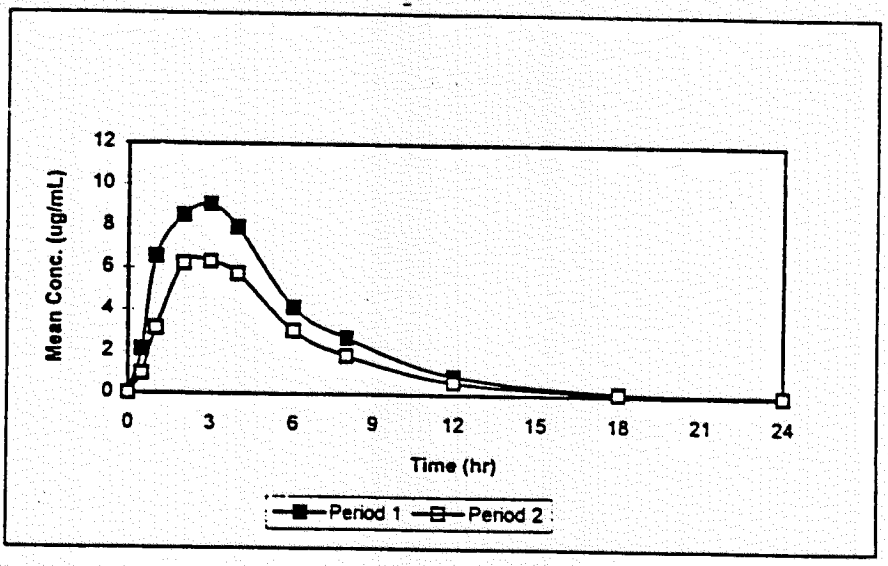


Figure 3. - Mean Ketoconazole Serum Concentrations - Rabeprazole Subjects



TITLE: A Study to Evaluate the Effects of Rabeprazole Sodium on the Pharmacokinetics of Phenytoin

Protocol Number: E3810-A001-104

Study Dates: August-Oct 1995

OBJECTIVES: To evaluate the effects of RBP on the disposition of phenytoin at pseudo-steady state.

METHODS:
Study Design: single-center, double-blind, randomized, parallel-group, drug interaction study

Study Population: 24 healthy, adult males, 18-45 years of age. Subjects were excluded if they had a resting heart rate <48 beats/minute or advanced heart block, a history of unexplained syncope, or a history of seizures.

Treatment and Administration:
Period 1: each subject received a single 200 mg dose of phenytoin (administered as 2 x 100 mg capsules) on Days 1-3. On Day 4, 250 mg of phenytoin was administered intravenously.

Period 2: subjects were randomized to receive either 20 mg RBP or placebo daily for 13 days beginning on Day 1. On Days 8-10, subjects were given a single 200 mg dose of phenytoin administered as before, in addition to continued dosing with either RBP or placebo. On Day 11, 250 mg phenytoin was administered intravenously at least 2 hours before the dose of RBP or placebo.

There was a 3-day washout period between Periods 1 and 2. No information was provided with respect to drug administration as related to meals. A Schedule of Events is attached to the study report.

Study Drug Supplies:
100 mg phenytoin (Dilantin® Kapseals®) capsules; #06535F
250 mg iv phenytoin sodium; #04135P
20 mg RBP tablets; #K48007ZZD ***This is the to-be-marketed formulation.***
Placebo tablets; #K4Y002ZZB

Pharmacokinetic Sampling:
Blood samples for analysis of plasma concentrations of phenytoin were obtained prior to iv dosing on Day 4, Period 1 and Day 11, Period 2, and at 10, 20, 30, and 45 minutes, and 1, 2, 3, 4, 6, 12, 18, 24, 36, 48, and 72 hours post-dose. During Day 11, Period 2, blood samples were collected for the analysis of plasma RBP levels prior to dosing and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours post-dose.

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

Pharmacokinetic Methods:
The following PK parameters were calculated using SAS for both phenytoin and RBP: AUC_{0-T}, $AUC_{0-\infty}$, Cmax, tmax, kel, and half-life.

Statistical Methods:
Summary statistics were calculated for each PK parameter. Differences between treatments in the mean change-from-baseline values were compared by ANOVA employing a model of the form: RESPONSE = TREATMENT + ERROR using the GLM procedure of SAS.

Analytical Methods:
Blood samples were analyzed for RBP concentrations in October, 1995, at [redacted] by [redacted] Blood samples were analyzed for phenytoin concentrations at [redacted] Assay validation data are reported below.

RBP Pre-study Validation:		
	[redacted]	Quality Control (samples were 16, 88, and 333 ng/ml)
Linearity	>0.999 at 5.5-444 ng/ml	-
Sensitivity	LOQ=5.5 ng/ml	-
Interday Precision	<7% CV	<10% CV
Interday Accuracy	97-106% at 5.5-444 ng/ml	92-104%
Intraday Precision	Not provided	Not provided
Intraday Accuracy	Not provided	Not provided
Specificity: RBP [redacted]		
Recovery: 86% at 5.5 ng/ml to 101% at 444 ng/ml with <14% CV.		
Stability: examined at 16, 88, and 333 ng/ml. 100-108% residual at room temp. for 30 min, 96-103% residual at room temp. for 24 hours, 100-102% at 2-8°C for 71 hours, 87-97% residual at -70°C for 61 weeks, 95-99% after 3 freeze/thaw cycles.		
In-study Validation:		
	[redacted]	Quality Control (samples were 16, 88, and 333 ng/ml)
Linearity	>0.999 at 5.5-444 ng/ml	-
Sensitivity	LOQ=5.5 ng/ml	-
Interday Precision	<9%	<9% CV
Interday Accuracy	95-106% at 5.5-444 ng/ml	91-98%
Intraday Precision	Not provided	Not provided
Intraday Accuracy	Not provided	Not provided
Specificity: RBP [redacted]		
Phenytoin Pre-study Validation:		
	[redacted]	Quality Control (samples were 0.1, 0.25, 7.5, and 20 ug/ml)
Linearity	>0.999 at 0.1-25 ug/ml	-
Sensitivity	LOQ=0.1 ug/ml	-
Interday Precision	<5% CV	<12% CV
Interday Accuracy	94-102% at 0.1-25 ug/ml	96-103%
Intraday Precision	Not provided	<6% CV
Intraday Accuracy	Not provided	93-102%
Specificity: Phenytoin [redacted]		
Recovery: 59-78% at 3QC concentrations.		
Stability: examined at 3 QC levels. 97-103% residual at room temp for 4 hours, 85-109% residual at room temp for 24 hours, 99-103% after 3 freeze/thaw cycles, stable at -70°C for 9 months.		

Phenytoin In-study Validation:		
		Quality Control **(samples were 0.25, 7.5, and 20 ug/ml)**
Linearity	>0.998 at 0.1-25 ug/ml	-
Sensitivity	LOQ=0.1 ug/ml	-
Interday Precision	<6% CV	<6% CV
Interday Accuracy	99-101% at 0.1-25 ug/ml	94-104%
Intraday Precision	Not provided	Not provided
Intraday Accuracy	Not provided	Not provided
Specificity: Phenytoin		

RESULTS:

Demographics:

Of the 24 subjects who began the study, 14 were Caucasian, 7 were Hispanic, and 3 were of African descent. Baseline characteristics were similar between the two treatment groups.

Pharmacokinetics:

Tables 1-3 provide PK parameters obtained for phenytoin and RBP.

Table 1. Mean±SD PK Parameters for Phenytoin

PK Parameter	RBP group Period 1 (N=11)	RBP group Period 2 (N=11)	Placebo group Period 1 (N=10)	Placebo group Period 2 (N=10)
AUC_{0-T} (μg*hr/ml)	257±153	250±147	206±90	187±89
Cmax (μg/ml)	10.3±2.0	10.3±1.9	10.2±1.1	9.5±1.5
Tmax (hr)	0.3±0.2	0.4±0.6	0.2±0.1	0.2±0
Kel (1/hr)	0.04±0.02	0.04±0.02	0.05±0.01	0.05±0.01
Half-life (hr)	22.7±15.7	22.3±15.2	16.9±6.7	16.8±6.7

As seen in Table 2 below, there were no statistically significant treatment differences observed between the RBP and placebo groups in the changes from Period 1 to Period 2 for any of the PK parameters.

Table 2. Mean±SD Changes in PK Parameters for Phenytoin (Period 2-Period 1)

PK Parameter	RBP group (N=10)	Placebo group (N=9)	p-value from analysis of RBP vs placebo
AUC_{0-T} (μg*hr/ml)	-7.1±20.1	-18.6±15.0	0.164
Cmax (μg/ml)	0.0±0.9	-0.7±0.8	0.077
Tmax (hr)	0.1±0.6	-0.0±0.1	0.717
Kel (1/hr)	-0.00±0.00	0.00±0.00	0.643
Half-life (hr)	-0.4±1.5	-0.1±0.9	0.512

PK parameters for RBP were consistent with those observed after multiple dosing of 20 mg in other studies.

Table 3. PK Parameters for RBP.

Parameter	Mean ± SD
AUC_{0-T} (ng*hr/ml)	601±219
$AUC_{0-\infty}$ (ng*hr/ml)	613±221
Cmax (ng/ml)	317±103
Tmax (hr)	4.0±1.7
Kel (1/hr)	0.92±0.26
Half-life (hr)	0.8±0.2

Safety:

Two subjects were discontinued from the study by the Investigator because of adverse events of hypotension. Both of these events were moderate and reported during Period 1 when only phenytoin was administered. Another subject voluntarily withdrew from the study on Day 9, Period 2. A total of 67 mild and moderate adverse events were reported in this study; the majority of these were reported during Period 1 during administration of phenytoin alone. There were no clinically significant laboratory values nor abnormal ECG results.

CONCLUSIONS:

Previous studies with RBP suggested that the PK parameters had large coefficients of variation, as is common with other delayed-release products. The parallel-group design of this study was intended to accommodate this variability.

No statistically significant treatment differences were seen in the changes from Period 1 to Period 2 for AUC_{0-T} or Cmax, indicating that no interaction occurred between RBP and phenytoin over the 72-hour sampling interval (see Comments below). The absence of marked differences in the number of adverse events reported by subjects receiving RBP vs those receiving placebo indicates that RBP was well-tolerated when given with phenytoin in this study.

REVIEWER'S COMMENTS:

1. $AUC_{0-\infty}$ values for phenytoin were not reported, although it is included in the study protocol. Many subjects had significant plasma concentrations of phenytoin at 72 hours post-dose, therefore, half-life calculations may not be accurate, as the terminal elimination phase could not be adequately assessed.
2. It is difficult to assess any impact of RBP on phenytoin absorption, as PK parameters were determined after iv administration of phenytoin.
3. Phenytoin plasma concentrations did not reach therapeutic levels (10-20 μg/ml) in many subjects, therefore, the relevance of the data obtained is questionable.
4. Subjects 421, 422, 423, and 424 were not included in the initial study with the other subjects; their dosing dates were >1 month after the other 20 subjects.
5. Numerous subjects received their phenytoin dose after the scheduled dosing time.
6. There were numerous phenytoin blood sampling deviations; these were later than the scheduled times, which would tend to underestimate AUC values.
7. Overall, the data generated by this study provide less than ideal information in order to allow for adequate assessment of any drug interaction between phenytoin and RBP.

TITLE: A Study to Evaluate the Effects of Rabeprazole Sodium on the Pharmacokinetics of Anhydrous Theophylline

Protocol Number: E3810-A001-105

Study Dates: July-August 1995

OBJECTIVES: To evaluate the effects of RBP on the pharmacokinetics of theophylline

METHODS:
Study Design: single-center, double-blinded, randomized, parallel group, drug interaction study

Study Population: 25 healthy males, 18-45 years of age

Treatment and Administration:
Period 1: each subject received a single 250 mg dose of theophylline on Day 1
Period 2: subjects were randomized to receive either 20 mg RBP or placebo daily for 8 days beginning on Day 1. On Day 8, subjects were given another single 250 mg dose of theophylline 2 hours prior to the Day 8 RBP or placebo dose.

There was a 3-day washout period between Periods 1 and 2. No information was provided with respect to drug administration and food intake.

Study Drug Suppies:
250 mg theophylline (Theolair®) tablets; #950099
20 mg RBP tablets; #K48007ZZD ***This is the to-be-marketed formulation.***
Placebo tablets; #K4Y002ZZB

Pharmacokinetic Sampling:
Blood samples for analysis of serum theophylline concentrations were obtained prior to dosing on Day 1, Period 1 and Day 8, Period 2, and at 15, 30, 45, and 60 minutes, and at 1.5, 2, 4, 6, 8, 12, 18, 24, and 30 hours post-dose. During Day 8, Period 2, blood samples were collected for the analysis of plasma RBP levels prior to dosing and at 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours post-dose.

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

Pharmacokinetic Methods:
The following PK parameters were calculated using SAS for both theophylline and RBP: AUC_{0-T}, $AUC_{0-\infty}$, Cmax, tmax, kel, and half-life.

Statistical Methods:
Summary statistics were calculated for each PK parameter. Differences between treatments in the mean change-from-baseline values were compared by ANOVA employing a model of the form: RESPONSE = TREATMENT + ERROR using the GLM procedure of SAS.

Analytical Methods:
Blood samples were analyzed for RBP concentrations September-October, 1995, at [redacted] Blood samples were analyzed September-October,

1995, for theophylline concentrations at [redacted] Assay validation data are reported below.

RBP Pre-study Validation:		
	[redacted]	Quality Control (samples were 16, 88, and 333 ng/ml)
Linearity	>0.999 at 5.5-444 ng/ml	-
Sensitivity	LOQ=5.5 ng/ml	-
Interday Precision	<10% CV	<4% CV
Interday Accuracy	90-109% at 5.5-444 ng/ml	100-106%
Intraday Precision	Not provided	<6% CV
Intraday Accuracy	Not provided	88-101%
Specificity: RBP		
Recovery: 86% at 5.5 ng/ml to 101% at 444 ng/ml with <14% CV.		
Stability: examined at 16, 88, and 333 ng/ml. 100-108% residual at room temp. for 30 min, 96-103% residual at room temp. for 24 hours, 100-102% at 2-8°C for 71 hours, 87-97% residual at -70°C for 61 weeks, 95-99% after 3 freeze/thaw cycles.		
RBP In-study Validation:		
	[redacted]	Quality Control (samples were 16, 88, and 333 ng/ml)
Linearity	>0.997 at 5.5-444 ng/ml	-
Sensitivity	LOQ=5.5 ng/ml	-
Interday Precision	<9% CV	<6% CV
Interday Accuracy	92-111% at 5.5-444 ng/ml	93-96%
Intraday Precision	Not provided	Not provided
Intraday Accuracy	Not provided	Not provided
Specificity: RBP		
Theophylline Pre-study Validation:		
	[redacted]	Quality Control (samples were 0.05, 0.075, 2.0 and 40 ug/ml)
Linearity	>0.999 at 0.05-50 ug/ml	-
Sensitivity	LOQ=0.05 ug/ml	-
Interday Precision	<6% CV	<10% CV
Interday Accuracy	Not provided	99-104%
Intraday Precision	Not provided	<10% CV
Intraday Accuracy	Not provided	91-107%
Specificity: Theophylline		
Recovery: No data provided.		
Stability: examined at 3QC levels: 100-106% residual at -20°C for 3.5 years. No other stability data was provided.		
Theophylline In-study Validation:		
	[redacted]	Quality Control (samples were 0.1, 2, and 20 ug/ml)
Linearity	>0.997 at 0.05-25 ug/ml	-
Sensitivity	LOQ=0.05 ug/ml	-
Interday Precision	<7% CV	<5% CV
Interday Accuracy	99-102% at 0.05-25 ug/ml	105-107%
Intraday Precision	Not provided	Not provided
Intraday Accuracy	Not provided	Not provided
Specificity: Theophylline		

RESULTS:

Demographics:

All subjects completed the study. Of the 25 subjects, 21 were Caucasian and 4 were Hispanic. Mean ages, heights, and weights were 27.7 years, 69.9 inches, and 152.5 pounds, respectively. Subjects in the two treatment groups had similar baseline characteristics.

Pharmacokinetics:

The following tables provides PK parameters obtained for theophylline and RBP. All subjects achieved plasma concentrations of theophylline that were within the recommended therapeutic range (5-15 μg/ml).

Table 1. Mean±SD PK Parameters for Theophylline

PK Parameter	RBP group Period 1 (N=12)	RBP group Period 2 (N=12)	Placebo group Period 1 (N=13)	Placebo group Period 2 (N=13)
AUC_{0-T} (μg*hr/ml)	82.0±19.2	81.2±15.7	82.3±12.8	84.7±10.4
$AUC_{0-\infty}$ (μg*hr/ml)	89.0±25.7	87.9±20.4	88.0±15.6	91.1±13.3
Cmax (μg/ml)	7.8±1.6	7.9±1.4	7.9±1.0	8.1±1.0
Tmax (hr)	1.4±0.9	1.1±0.5	1.5±0.9	1.1±0.5
kel (1/hr)	0.10±0.02	0.10±0.02	0.10±0.02	0.10±0.02
Half-life (hr)	7.3±1.9	7.5±1.7	7.0±1.6	7.4±1.5

As seen in Table 2 below, there were no statistically significant treatment differences between the RBP and placebo groups in the changes from Period 1 to Period 2 for any of the PK parameters.

Table 2. Mean±SD Changes in PK Parameters for Theophylline (Period 2-Period 1)

PK Parameter	RBP group (N=10)	Placebo group (N=9)	p-value from analysis of RBP vs placebo
AUC_{0-T} (μg*hr/ml)	-0.9±5.4	2.4±4.7	0.119
$AUC_{0-\infty}$ (μg*hr/ml)	-1.1±7.6	3.1±5.7	0.128
Cmax (μg/ml)	0.1±1.6	0.2±0.9	0.915
Tmax (hr)	-0.3±1.2	-0.4±1.0	0.403
kel (1/hr)	-0.0±0.01	0.01±0.01	0.444
Half-life (hr)	0.2±0.5	0.4±0.5	0.838

The PK parameters obtained for RBP are consistent with those found after multiple 20 mg doses in other studies.

Table 3. PK Parameters for RBP.

Parameter	Mean ± SD
AUC_{0-T} (ng*hr/ml)	612±436
$AUC_{0-\infty}$ (ng*hr/ml)	670±427
Cmax (ng/ml)	412±295
Tmax (hr)	3.8±2.7
kel (1/hr)	1.01±0.25
Half-life (hr)	0.7±0.2

Safety:

There were no serious adverse events nor clinically significant out-of-range vital signs, laboratory values, or abnormal ECG results.

CONCLUSIONS:

Previous studies with RBP suggested that the PK parameters had large coefficients of variation, as is common with other delayed-release products. The parallel-group design of this study was intended to accommodate this variability.

No statistically significant treatment differences were observed in the changes from Period 1 to Period 2 for any of the theophylline PK parameters, indicating that no interaction occurred between RBP and a single dose of theophylline. In addition, RBP was well-tolerated at multiple doses of 20 mg.

TITLE: A Study of the effect of rabeprazole on the pharmacokinetics of diazepam in healthy male volunteers

Protocol Number: E3810-A001-113

Study Dates: June-September, 1996

OBJECTIVE: The objective of this study was to evaluate the effect of RBP on the pharmacokinetics of diazepam in healthy male volunteers.

METHODS:
Study Design: randomized, single-center, placebo-controlled, blinded, two-way crossover

Study Population: 20 normal, healthy males between the ages of 18-45 years

Treatment and Drug Administration:
Prestudy - Prior to the start of the treatment periods, each subject received a single 100 mg dose of mephenytoin for assessment of mephenytoin hydroxylation status.
Period 1 - Subjects received either a single oral 20 mg dose of RBP or placebo daily for 35 days. On Day 8, one hour after administration of RBP or placebo, a 0.1 mg/kg dose of diazepam was administered as a 5-minute intravenous infusion using a syringe pump.
Period 2 – Subjects received the alternate treatment (RBP or placebo).

Periods 1 and 2 were separated by a 21-day washout interval. All drugs were given after a 10-hour fast with 240 ml water, followed by 4 additional hours of fasting. Subjects were fed according to a standardized procedure.

Study Drug Supplies:
20 mg enteric-coated RBP tablets; #K5Y006ZZA. ***This is the to-be-marketed formulation.***
Enteric-coated placebo tablets, identical in size and shape to the RBP tablets; #K5X009ZZZ.
Diazepam (Valium®, Roche Products, Lot No. 0118).
100 mg mephenytoin tablet (Mesantoin®, Sandoz Pharmaceuticals Corp., Lot No. 375X9056).

Biological Sampling:
Plasma Samples for Determination of Diazepam and Nordiazepam
Blood samples were collected prior to diazepam administration on Day 8 and at the following times after the start of the diazepam administration: 15, 30, and 45 minutes, 1, 2, 4, 8, and 12 hours, and 1, 2, 4, 8, 12, 16, 20, 24, and 28 days.

Plasma Samples for Rabeprazole
Blood samples were collected prior to administration of RBP or placebo on Days 1 and 7, and at the following times post-dose: 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours. Blood samples taken 24 hours post-dose on Days 1 and 7 were collected prior to administration of the next dose of RBP or placebo on Days 2 and 8, respectively.

Serum Samples for Determination of Diazepam Protein Binding
Blood samples were collected 2 hours after the start of diazepam administration on Day 8.

Urine Samples for Mephenytoin Hydroxylation Status
Urine volume was measured and 10-mL aliquots for the determination of 4'-hydroxymephenytoin concentrations were stored frozen at -70°C until analyzed.

Safety: Assessed via clinical laboratory tests, vital signs, ECG recordings, and the occurrence of adverse events.

Pharmacokinetic Methods:

Diazepam and Nordiazepam Analysis

The following non-compartmental PK parameters were determined from concentration-time data for plasma diazepam and nordiazepam for those subjects who completed both treatment periods of the study: Cmax, Tmax, kel, half-life, $AUC_{0-\infty}$, AUC_{0-t}, CL_{total}, Vdss (apparent volume of distribution at steady-state), and MRT (mean residence time). The parameters were calculated using SAS Release 6.09

Rabeprazole Analysis

Cmax, Tmax, and AUC_{0-t} were determined from the RBP plasma concentration-time data and calculated using SAS Release 6.09.

Statistical Methods:

Diazepam and Nordiazepam Analysis

Summary statistics (mean, SD, min, max) were provided for the diazepam and nordiazepam PK parameters. Mean PK parameters were tested for statistically significant differences due to sequence, subject (within sequence), period, and treatment by ANOVA using the GLM procedure of SAS Release 6.09 for untransformed data and log-transformed data (where appropriate). The sequence effect was tested using the MSE for subjects within sequence as the error term at 0.10 significance level. All other main effects were tested against the residual error (error mean square) from the ANOVA at 0.05 significance level.

Ratios of (RBP+diazepam)/diazepam were determined for all diazepam and nordiazepam PK parameters. Confidence intervals (90%) around the ratios were calculated for $AUC_{0-\infty}$ and Cmax, using the mean squared error and least square means from the ANOVA. Log transformations were performed on the $AUC_{0-\infty}$ and Cmax values, and ANOVA was performed on these log-transformed values as described previously. Least squares means were calculated for each parameter.

Diazepam Protein Binding Analysis

The diazepam protein binding data were analyzed by an ANOVA model with terms for treatment, sequence, subject (within sequence), and period. All effects except for sequence were tested using 0.05 significance level, and sequence effect was tested using 0.10 significance level.

Rabeprazole Analysis

Summary statistics (mean, SD, min, max) were provided for the RBP pharmacokinetic parameters. No formal statistical analysis was planned for the RBP data.

Mephenytoin Analysis

The phenotype of each subject was discerned on the basis of an index calculated using the following formula:

$$\text{Index} = \log_{10}\left\{\left[\frac{\text{Amount of 4'-OH MEP excreted in urine}}{\text{Dose of MEP}}\right] \times \left[\frac{\text{MW of MEP}}{\text{MW of 4'-OH MEP}}\right] \times 100\right\}$$

where, MW=molecular weight and MEP=mephenytoin.

An antimode was applied to determine the poor metabolizer phenotype, which had an index smaller than 0.3 (2% excreted as 4'-hydroxymephenytoin). If the index was less than 0.3, then the subject was classified as a poor metabolizer (PM). If the index was greater than 0.3, then the subject was classified as an extensive metabolizer (EM).

Analytical Methods:
The measurement of protein binding of diazepam in the presence and absence of RBP was provided by Samples were analyzed by labeling with ^{3}H-diazepam, Assay validation data provided were acceptable.

Urine 4'-hydroxymephenytoin concentrations were analyzed using a validated at The LOQ of the assay was 0.1 μg, and the interassay and intraassay %CVs were <10% and <6%, respectively.

Diazepam, nordiazepam, and RBP plasma concentrations were quantitated at

RBP Pre-study Validation:		
		Quality Control (samples were 10, 40, and 400 ng/ml)
Linearity	>0.998 at 5.0-500 ng/ml	-
Sensitivity	LOQ=5.0 ng/ml	-
Interday Precision	<6% CV	<8% CV
Interday Accuracy	98-104% at 5.0-500 ng/ml	94-101%
Intraday Precision	Not provided	<9% CV
Intraday Accuracy	Not provided	98-102%
Specificity: RBP		
Recovery: RBP: 47% at 10 ng/ml to 54% at 400 ng/ml. IS: 70%		
Stability: examined at 10, 40, and 400 ng/ml. 103-107% residual at room temp for 4 hr, 88-98% residual at room temp for hours, acceptable at -20°C for 3.5 months, 95-97% after 3 freeze/thaw cycles.		
RBP In-study Validation:		
		Quality Control (samples were 10, 40, and 400 ng/ml)
Linearity	>0.995 at 5-500 ng/ml	-
Sensitivity	LOQ=5.0 ng/ml	-
Interday Precision	<7% CV	<9% CV
Interday Accuracy	96-103% at 5.0-500 ng/ml	90-98%
Intraday Precision	Not provided	Not provided
Intraday Accuracy	Not provided	Not provided
Specificity: RBP		

Diazepam Pre-study Validation:*		
		Quality Control (samples were 5, 10, 75, 750 ng/ml)
Linearity	>0.999 at 5-1000 ng/ml	-
Sensitivity	LOQ=5 ng/ml	-
Interday Precision	<8% CV	<6% CV
Interday Accuracy	99-102% at 5-1000 ng/ml	98-102%
Intraday Precision	Not provided	<5% CV
Intraday Accuracy	Not provided	97-103%
Recovery: 79-83% at QC concentrations, 92% for IS		
Stability: examined at 10, 75, and 750 ng/ml. 101-104% residual at room temp for 4 hours, 99-106% at room temp for 48 hours, 97-108% residual after 53 months at -20°C, 100-102% after 3 freeze/thaw cycles.		
Specificity: Diazepam		
Diazepam In-study Validation:		
		Quality Control (samples were 10, 75, and 750 ng/ml)
Linearity	>0.999 at 5-1000 ng/ml	-
Sensitivity	LOQ=5 ng/ml	-
Interday Precision	<5%	<5% CV
Interday Accuracy	99-101% at 5-1000 ng/ml	96-105%
Intraday Precision	Not provided	Not provided
Intraday Accuracy	Not provided	Not provided
Specificity:		

*Nordiazepam assay validation data was consistent with diazepam data.

RESULTS:

Demographics:

One subject discontinued the study prematurely, after receiving one dose of placebo, due to elevated liver function tests. Of the 20 subjects enrolled into the study, 16 were Caucasian, 2 were of African descent, and 2 were Hispanic. The mean ages, heights, and weights of the subjects were 29 years, 177.8 cm, and 74.8 kg, respectively. Two of the subjects were classified as poor metabolizers of mephenytoin and the remaining 17 subjects were extensive metabolizers.

Pharmacokinetics:

Nineteen of the 20 subjects enrolled completed the study and therefore provided data for PK analyses. Pharmacokinetic analyses were conducted using all available data for subjects who completed the study (referred to as "All Subjects"), and all subjects who completed the study excluding the two subjects classified as poor metabolizers (referred to as "Excluding PMs").

Diazepam Data

There were no statistically significant treatment differences observed for any of the diazepam PK parameters for either the analysis including all subjects nor the analysis excluding the PMs. Likewise, there were no statistically significant sequence or period effects observed for either analysis for any of the diazepam PK parameters. The diazepam concentration vs time profiles were virtually identical for the RBP and placebo treatment groups. Results of the PK calculations and statistical analyses are provided in Table 1 below.