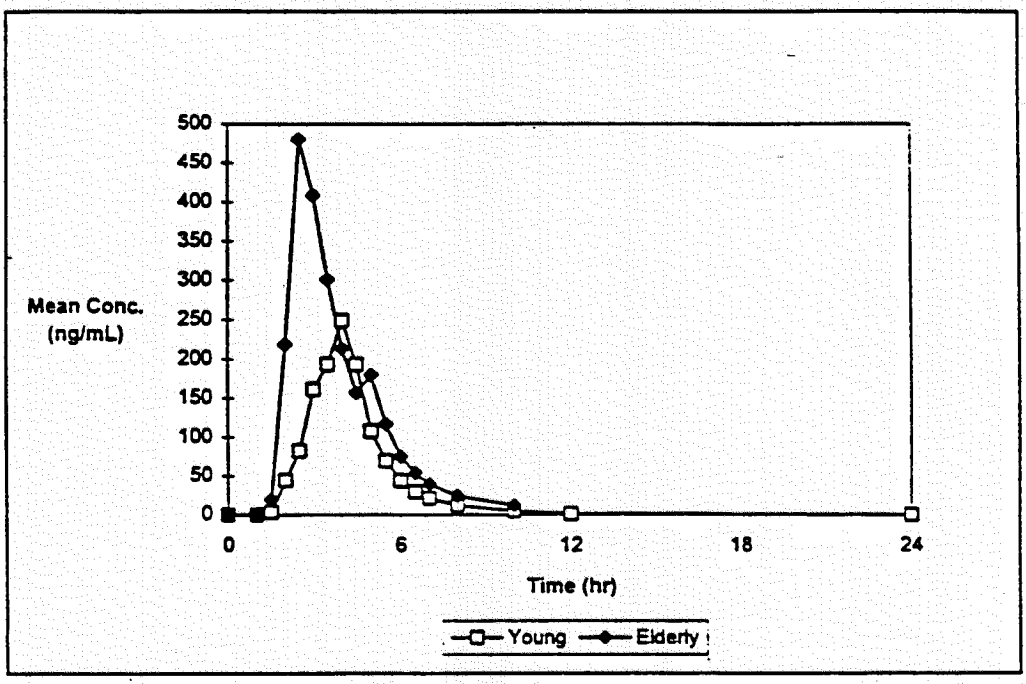
Figure 1. **Mean Rabeprazole Sodium Concentrations[a]**



[a] It was noted that in two of the elderly subjects T_{max} occurred 5 hours post-dose. This resulted in a small shoulder in the time concentration curve.

DRUG INTERACTION STUDIES

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

Protocol Number: E3810-A001-101

Study Dates: July-October, 1995

OBJECTIVE: To evaluate the effects of RBP on the absorption and disposition of warfarin.

METHODS:
Study Design: single-center, randomized, open-label, single-dose, parallel study in two groups

Study Population: 21 normal, healthy males between the ages of 18 and 45 years

Treatment and Drug Administration:
Period 1: a single, oral dose of 0.75 mg/kg warfarin on Day 1.
Period 2: a single, oral dose of 20 mg RBP or placebo daily for 14 days. A single 0.75 mg/kg dose of warfarin was administered on Day 8 two hours prior to the dose of RBP or placebo.

There was a washout period of 7 days between Periods 1 and 2. All doses were given after an overnight fast with 240 ml water, followed by an additional 3 hours of fasting.

Study Drug Supplies:
0.75 mg/kg warfarin (Lot#: JC122A [1 mg], EJC072A [5 mg], EHN310A [10 mg])
20 mg enteric-coated RBP tablets; #K48007ZZD
Placebo tablets; #K4Y002ZZB

Biological Sampling:
Blood samples were collected for determination of plasma concentrations of both warfarin enantiomers prior to (time 0) and at 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144, and 168 hours following administration on Day 1 and Day 8. Blood samples were collected for plasma RBP quantitation prior to and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours post-dose on Day 8.

Pharmacokinetic Methods:
The following PK parameters were estimated for both enantiomers of warfarin on Days 1 and 8, and for RBP on Day 8: AUC_{0-T}, $AUC_{0-\infty}$, Cmax, tmax, kel, and half-life.

Pharmacodynamic Methods:
Prothrombin times (PT) were used to estimate the following PD parameters: AUC_{0-72}, Pmax (maximum prothrombin time), and Tmax (observed time of maximum PT).

Safety:
Assessed via adverse events, clinical laboratory evaluations, vital signs, and physical examination. In addition, prothrombin time was monitored for 72 hours after warfarin dosing on both Days 1 and 8.

Statistical Methods:
Summary statistics were calculated for the PK and PD parameters. Differences between treatments in the mean change-from-baseline values for the PK and PD parameters were compared for statistical significance with ANOVA by a model of the form: RESPONSE = TREATMENT + ERROR,

using the GLM procedure of SAS Release 6.08. Treatment effects were considered statistically significant if the probability associated with the calculated F-statistic was less than 0.05.

Analytical Methods:

RBP concentrations were quantitated October, 1995 at detection. Plasma warfarin levels were determined in December, 1995-February, 1996 at

RBP Pre-study Validation:		
		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 11-444 ng/ml 88% at 5.5 ng/ml	92-104%
Intraday Precision	Not provided	Not provided
Intraday Accuracy	Not provided	Not provided
Specificity: RBP with no interference		
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 hours, 95-103% residual at room temp for 24 hours, 100-102% at 2-8°C for 71 hours, 85-97% residual at –70°C for 61 weeks, 95-99% after 3 freeze/thaw cycles.		
RBP In-study Validation:		
		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	<6% CV	<8% CV
Interday Accuracy	95-108% at 5.5-444 ng/ml	92-97%
Intraday Precision	Not provided	Not provided
Intraday Accuracy	Not provided	Not provided
Specificity: RBP with no interference in study sample		

R- and S-Warfarin Pre-study Validation:		
		Quality Control (samples were 25, 50, 200, 800 ng/ml)
Linearity	0.995 at 25-1000 ng/ml	-
Sensitivity	LOQ=25 ng/ml	-
Interday Precision	<12% CV	<12% CV
Interday Accuracy	98-103% at 25-1000 ng/ml	95-107%
Intraday Precision	Not provided	<7% CV
Intraday Accuracy	Not provided	97-103%
Recovery: 90-102% at three QC levels		
Stability: examined at three QC levels. 90-95% residual at room temp for 4 hours, 99-107% at room temp for 24 hours, 90-95% after 3 freeze/thaw cycles, 90-102% at –20°C for 31 months.		

R- and S-Warfarin In-study Validation:		
		Quality Control (samples were 25, 50, 200, and 800 ng/ml)
Linearity	>0.998 at 25-1000 ng/ml	-
Sensitivity	LOQ=25 ng/ml	-
Interday Precision	<5%	<12% CV
Interday Accuracy	98-102% at 25-1000 ng/ml	103-106%
Intraday Precision	Not provided	Not provided
Intraday Accuracy	Not provided	Not provided

RESULTS:

Demographics:

The mean age of the subjects participating in this study was 28.3 years for the RBP group and 26.6 years for the placebo group. Mean height and weight were 183.4 cm and 179 cm, and 83.4 kg and 76.6 kg for the RBP and placebo groups, respectively. Of the 21 subjects, 17 were Caucasian, 2 were Hispanic, 1 was of African descent, and 1 was Asian.

Pharmacokinetics:

One subject was dropped from the study due to a prolonged PT, therefore, was excluded from the PK data analysis. Comparison of the changes in PK parameters for both warfarin enantiomers between Period 1 and Period 2 did not reveal any statistically significant differences ($p>0.1$ for all parameters) between the RBP-treated subjects and the placebo-treated subjects. Tables 1-4 below provide the summarized PK parameters and analysis results for both R-warfarin and S-warfarin.

Table 1. Mean±SD PK Parameters for R-Warfarin.

PK Parameter	RBP group Period 1 (N=10)	RBP group Period 2 (N=10)	Placebo group Period 1 (N=10)	Placebo group Period 2 (N=10)
AUC_{0-T} (ng*hr/ml)	194312±17858	322531±400064	212702±31506	207601±35161
$AUC_{0-\infty}$ (ng*hr/ml)	217059±25549	359038±436260	242942±46601	235743±48779
Cmax (ng/ml)	3782±159	5935±6492	4084±509	4154±623
Tmax (hr)	1.3±0.5	1.1±0.3	1.4±1.0	1.5±1.0
Kel (1/hr)	0.01±0.00	0.02±0.01	0.01±0.00	0.01±0.00
Half-life (hr)	50.0±7.9	48.4±12.3	53.0±9.5	51.0±8.7

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

PK Parameter	RBP group (N=10)	Placebo group (N=10)	p-value from analysis of RBP vs placebo
AUC_{0-T} (ng*hr/ml)	128219±407891	-5100±7116	0.315
$AUC_{0-\infty}$ (ng*hr/ml)	141979±444043	-7199±11136	0.302
Cmax (ng/ml)	2153±6466	70±736	0.325
Tmax (hr)	-0.2±0.4	0.1±1.3	0.493
Kel (1/hr)	0±0	0±0	0.613
Half-life (hr)	-1.5±10.2	-1.9±5.1	0.913

Table 3. Mean±SD PK Parameters for S-Warfarin.

PK Parameter	RBP group Period 1 (N=10)	RBP group Period 2 (N=10)	Placebo group Period 1 (N=10)	Placebo group Period 2 (N=10)
AUC_{0-T} (ng*hr/ml)	125195±24430	124021±24978	127099±23869	123759±27951
$AUC_{0-\infty}$ (ng*hr/ml)	130719±28559	130710±32267	131727±28019	128328±31542
Cmax (ng/ml)	3865±204	3954±281	4158±537	4223±622
Tmax (hr)	1.3±0.5	1.1±0.3	1.4±1.0	1.2±0.4
Kel (1/hr)	0.02±0.01	0.02±0.01	0.02±0.00	0.02±0.00
Half-life (hr)	32.3±8.0	32.8±8.8	31.3±7.2	30.6±6.3

Table 4. Mean±SD Changes in PK Parameters for S-Warfarin (Period 2-Period 1)

PK Parameter	RBP group (N=10)	Placebo group (N=10)	p-value from analysis of RBP vs placebo
AUC_{0-T} (ng*hr/ml)	-1174±10215	-3340±6025	0.571
$AUC_{0-\infty}$ (ng*hr/ml)	-10±12444	-3399±6254	0.452
Cmax (ng/ml)	89±310	65±753	0.927
Tmax (hr)	-0.2±0.4	-0.2±0.8	>0.999
Kel (1/hr)	0±0	0±0	0.405
Half-life (hr)	0.5±3.6	-0.7±1.9	0.344

The mean PK parameters for RBP are presented in Table 5. Data are consistent with other studies which administered multiple doses of 20 mg RBP.

Table 5. Mean±SD PK Parameters for RBP.

Parameter	Mean ± SD (N=10)
AUC_{0-T} (ng*hr/ml)	718±430
$AUC_{0-\infty}$ (ng*hr/ml)	843±365
Cmax (ng/ml)	368±209
Tmax (hr)	4.4±3.6
kel (1/hr)	0.88±0.30
Half-life (hr)	0.9±0.3

Pharmacodynamics:

The PD responses, based on prothrombin time, were similar for both treatment periods for both RBP- treated subjects and placebo-treated subjects; there were no statistically significant differences. PD parameters and statistical analysis results are summarized in Tables 6 and 7.

Table 6. Mean±SD PD Parameters – Prothrombin Time.

PK Parameter	RBP group Period 1 (N=10)	RBP group Period 2 (N=10)	Placebo group Period 1 (N=11)	Placebo group Period 2 (N=10)
AUC_{0-72} (sec*hr)	499±99	429±96	538±129	413±85
Pmax (sec)	12±2	11±2	13±3	10±2
Tmax (hr)	48±0	50±5	49±4	49±4

Table 7. Mean±SD Changes in PD Parameters – Prothrombin. (Period 2-Period 1).

PK Parameter	RBP group (N=9)	Placebo group (N=11)	p-value from analysis of RBP vs placebo
$AUC_{0\text{-}72}$ (sec*hr)	-71±37	-95±52	0.242
Pmax (sec)	-2±1	-2±1	0.062
Tmax (hr)	2.4±5.1	0±5.7	0.331

Safety:
There were no deaths or serious adverse events. One subject was discontinued from the study before the second dose of warfarin due to a prolonged prothrombin time. There were 28 adverse events: four which were moderate in severity and 24 which were mild. There was no marked difference in the number of adverse event reports for subjects receiving RBP and for those receiving placebo. There were no clinically significant out-of-range vital signs or laboratory values.

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.

There were no statistically significant differences in any of the PK or PD parameters for warfarin when baseline values were compared to those obtained during either RBP or placebo administration. These findings suggest that there was no interaction between RBP and a single oral dose of warfarin when co-administered. RBP, given as multiple 20 mg doses, was well-tolerated when co-administered with a single dose of 0.75 mg/kg warfarin.

REVIEWER'S COMMENTS:
1. There were numerous late warfarin sampling deviations of >1 hour at the later scheduled sampling times, which would underestimate AUC.
2. Three of the subjects began the study approximately 3 weeks after the others.

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

Protocol Number: E3810-A001-102

Study Dates: July-September, 1995

OBJECTIVE: To evaluate the effects of RBP on the absorption and disposition of digoxin.

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

Study Population:
16 normal, healthy, males between the ages of 18-45 years. Subjects were excluded from the study if they had any relevant deviation from normal in physical examination, ECG, or clinical laboratory tests; had any history of cardiac arrhythmias or resting heart rate was <48 beats/minute; or had a P-R interval greater then 0.22 seconds, second or third degree heart block.

Treatment and Drug Administration:
Period 1: Subjects received an initial 0.375 mg dose of digoxin on Day 1 of the study. On Days 2-24, subjects received a daily 0.25 mg dose of oral digoxin.
Period 2: On Day 11 subjects were randomized to receive either 20 mg RBP or placebo, which was administered daily (in addition to the digoxin dose already being administered) through Day 24. On Day 24 the digoxin dose was administered at least 2 hours before administration of the RBP or placebo dose.

All doses were administered orally in the morning with 240 ml of water. No information was provided with respect to meal administration.

Study Drug Supplies:
0.25 mg digoxin (Lanoxin®) tablets; #4Y2349
20 mg enteric-coated RBP tablets; #K48007ZZD. ***This is the to-be-marketed formulation.***
Placebo tablets; #K4Y002ZZB

Biological Sampling:
On Day 10, blood and urine samples were collected for determination of digoxin concentrations before the digoxin dose, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, and 24 hours post-dose. Also on Day 10, 24-hour urine was collected for determination of digoxin and creatinine concentrations.

On Day 24, after 14 days of dosing with both digoxin and either RBP or placebo, blood and urine samples were collected for determination of digoxin PK profile predose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72, 96, 120, and 144 hours post-dose. Blood collection for determination of plasma RBP concentrations were collected before the RBP or placebo dose, and at 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours post-dose. Also on Day 24, urine was collected for 24 hours for determination of urine digoxin concentration.

Pharmacokinetic Methods:
The following PK parameters were calculated for digoxin using SAS: $AUC_{0\text{-}24}$, Cmax, Tmax, Cmin, kel, half-life, and Cl_{renal}. In addition, $AUC_{0\text{-}t}$, Cmax, Tmax, kel, and half-life were determined for RBP.

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

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 GLM procedure of SAS. The attainment of steady-state was assessed using a two-way ANOVA with day and treatment as factors to compare Cmin values on Days 10 and 12 and on Days 24 and 25.

Analytical Methods:
Plasma RBP concentrations were determined Sept-Oct, 1995, at [redacted] by [redacted] Serum digoxin samples were quantified in December, 1995, at [redacted] Assay validation data for RBP and digoxin in plasma and serum, respectively, are provided below.

Urine digoxin levels were determined September, 1995, at [redacted] The assay calibration range was validated over the concentrations of 0.1 to 5.0 ng/ml, with an LOQ of 0.1 ng/ml.

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	<6% CV	<9% CV
Interday Accuracy	95-110% at 5.5-444 ng/ml	94-102%
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.		
RBP 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	<7% CV	<9% CV
Interday Accuracy	94-111% at 5.5-444 ng/ml	96-101%
Intraday Precision	Not provided	Not provided
Intraday Accuracy	Not provided	Not provided
Specificity: RBP [redacted] with no interference in study sample [redacted]		

Digoxin Pre-study Validation:		
	[redacted]	Quality Control (samples were 0.15, 0.45, 2, 4 ng/ml)
Linearity	>0.999 at 0.15-8 ng/ml	-
Sensitivity	LOQ=0.15 ng/ml	-
Interday Precision	<15% CV	<9% CV
Interday Accuracy	93-107% at 0.15-8 ng/ml	97-109%
Intraday Precision	Not provided	<7% CV
Intraday Accuracy	Not provided	98-106%
Stability: examined at 0.45, 2, and 4 ng/ml. 99-112% residual at room temp for 4 hours, 98-111% after 3 freeze/thaw cycles.		
Digoxin In-study Validation:		
	[redacted]	Quality Control (samples were 0.45, 2, and 4 ng/ml)
Linearity	>0.999 at 0.15-8 ng/ml	-
Sensitivity	LOQ=0.15 ng/ml	-
Interday Precision	<7% CV	<10% CV
Interday Accuracy	98-102% at 0.15-8 ng/ml	98-104%
Intraday Precision	Not provided	Not provided
Intraday Accuracy	Not provided	Not provided

RESULTS:

Demographics:

Of the 16 subjects who completed the study, 13 were Caucasian, 2 were of African descent, and 1 was Hispanic. The mean ages, heights, and weights of the subjects were 25.8 years, 70.5 inches, and 169.8 pounds. Subjects in the RBP and placebo groups had similar baseline characteristics.

Pharmacokinetics:

Tables 1-4 provide the PK parameters obtained for both digoxin and RBP. Therapeutic digoxin concentrations (>0.8 ng/ml) were achieved for all subjects with the dosing regimen used. Figures 1-3 (attached to the study report) display the digoxin plasma concentrations for all subjects, RBP-dosed subjects, and placebo-dosed subjects, respectively.

Table 1. Mean±SD PK Parameters for Digoxin.

PK Parameter	RBP group Period 1 (N=9)	RBP group Period 2 (N=9)	Placebo group Period 1 (N=7)	Placebo group Period 2 (N=7)
AUC_{0-24} (ng*hr/ml)	15.6±4.8	18.6±4.5	15.8±4.6	14.6±4.3
Cl_{renal} (L/hr)	11.2±2.9	9.1±2.3	10.9±2.0	10.7±2.6
Cmax (ng/ml)	1.5±0.3	1.9±0.5	1.6±0.5	1.5±0.4
Tmax (hr)	1.1±0.7	0.9±0.2	1.4±0.9	1.2±0.6
Kel (1/hr)	0.02±0.01	0.02±0.01	0.02±0.01	0.02±0.01
Half-life (hr)	35.7±19.4	35.5±12.9	30.7±8.2	39.0±16.9

As seen in Table 2 below, statistically significant treatment differences ($p<0.05$) between the RBP and placebo groups were observed in the changes from Period 1 to Period 2 for AUC_{0-24} and Cmax. There were no significant differences between the treatment groups with respect to Tmax, kel, half-life, or Cl_{renal} ($p>0.1$). Co-administration of RBP increased the overall bioavailability of digoxin by approximately 20%.

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

PK Parameter	RBP group (N=9)	Placebo group (N=7)	p-value from analysis of RBP vs placebo
AUC_{0-24} (ng*hr/ml)	3.0±3.5	-1.3±2.1	0.012
Cl_{renal} (L/hr)	-2.2±2.6	-0.2±1.8	0.106
Cmax (ng/ml)	0.4±0.4	-0.1±0.3	0.012
Tmax (hr)	-0.2±0.7	-0.2±1.2	0.987
Kel (1/hr)	0±0.02	0±0.01	0.839
Half-life (hr)	-0.6±29.9	8.9±13.8	0.528

Cmin was measured predose on Days 10 and 24 and 24 hours post-dose on Days 11 and 24. The values for Days 10 and 12 were compared in Period 1 and for Days 24 and 25 during Period 2. The results of the ANOVA for Cmin show that steady-state was achieved in both Period 1 and 2. Mean Cmin values between Period 1 and Period 2 increased 22% for the RBP group and decreased 9% for the placebo group. These changes did not reach statistical significance. Table 3 provides the mean digoxin Cmin values.

Table 3. Mean±SD digoxin Cmin values on Days 10, 12, 24, and 25.

	RBP group	Placebo group
Period 1: (prior to RBP dosing)		
Day 10	0.475±0.134	0.497±0.122
Day 11	0.492±0.108	0.505±0.126
Period 2: (after RBP dosing)		
Day 24	0.595±0.150	0.485±0.094
Day 25	0.583±0.150	0.426±0.160

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

Table 4. Mean±SD PK Parameters for RBP.

Parameter	Mean ± SD
AUC_{0-t} (ng*hr/ml)	830±278
Cmax (ng/ml)	507±200
Tmax (hr)	2.6±0.5
kel (1/hr)	0.79±0.16
Half-life (hr)	0.9±0.2

Safety:
All adverse events were mild to moderate in nature. There were no clinically significant out-of-range vital signs or laboratory values or abnormal ECG results.

CONCLUSIONS

Statistically significant treatment differences were observed in the RBP-treated group for the changes from Period 1 to Period 2 for digoxin AUC_{0-24} (19% increase) and Cmax (29% increase), indicating that an interaction occurred between RBP and digoxin. The trough digoxin concentrations increased by a modest and statistically insignificant 22% in this group. These results are consistent with an increase in the absorption of digoxin when co-administered with RBP.

This increase in serum digoxin concentrations would not be clinically significant in most patients, however, in patients with severely compromised congestive heart failure or impaired renal function, the effect could be significant. It is therefore recommended that such patients requiring concurrent therapy with RBP and digoxin, have serum digoxin concentrations monitored following initiation of RBP therapy and, if necessary, titration of the digoxin dose.

REVIEWER'S COMMENTS:

1. The elimination rate and half-life for digoxin could not be adequately assessed during Period 1, as blood samples were collected for only 24 hours after digoxin dosing. Since the half-life of digoxin is close to 40 hours, it is likely that the terminal phase of the digoxin concentration vs time profile was not manifest over the 24-hour sampling period for most of the subjects. Indeed, the majority of the subjects had vastly different half-life values in Period 1 when compared to Period 2, when blood was sampled over a 144-hour time span. Therefore, it is not possible to assess whether the increases noted for AUC and Cmax could be attributed, in part, to the inhibition of digoxin metabolism by RBP. Metabolism of RBP occurs partially by CYP450 3A4 and it has recently been observed that this enzyme contributes to the metabolism of digoxin in rats (*Pharmacology*. 56:308-313, 1998.)
2. The potential for an interaction between RBP and digoxin was assessed at steady state.

Figure 1. - Mean Digoxin Concentrations - All Subjects

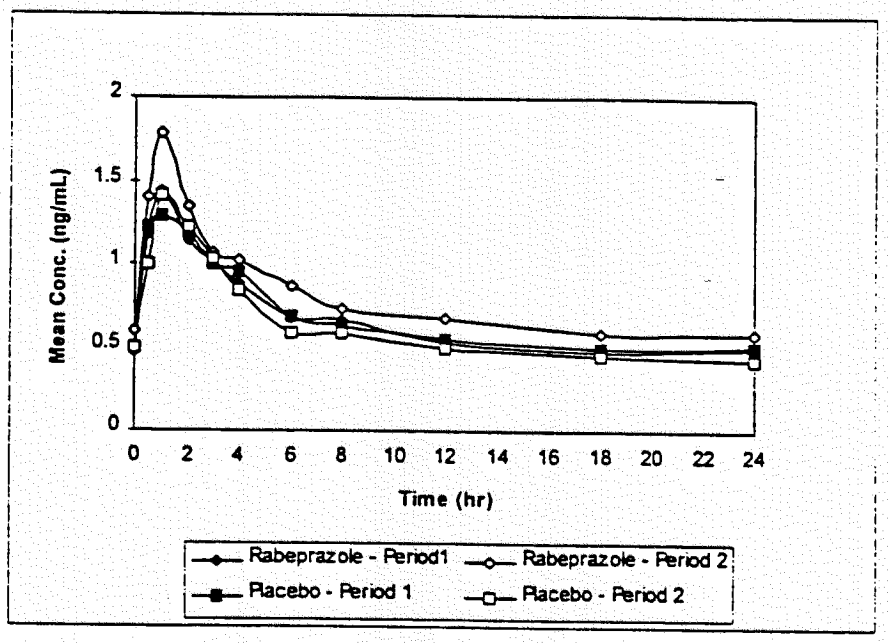


Figure 2. - Mean Digoxin Concentrations - Rabeprazole Subjects

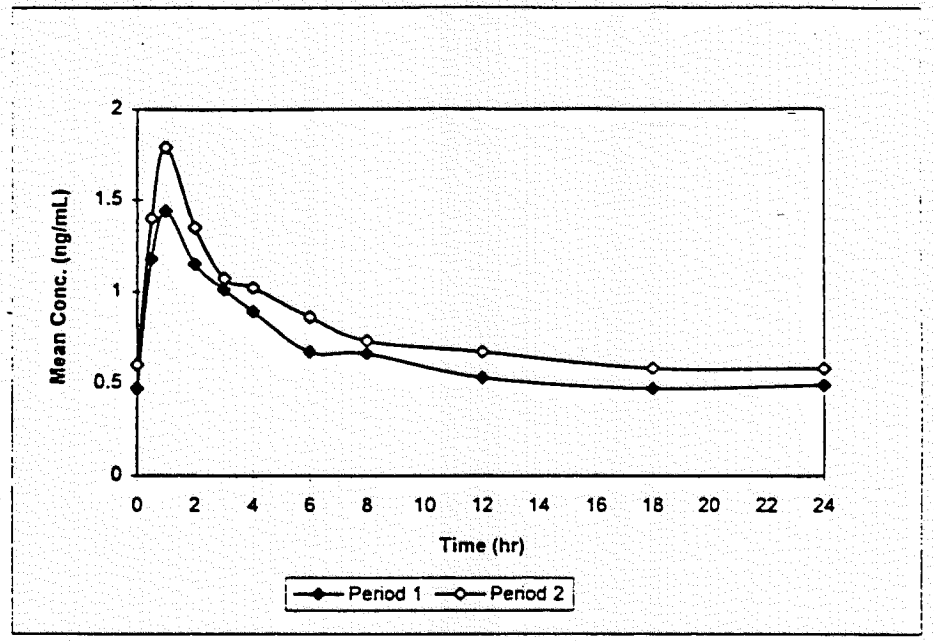
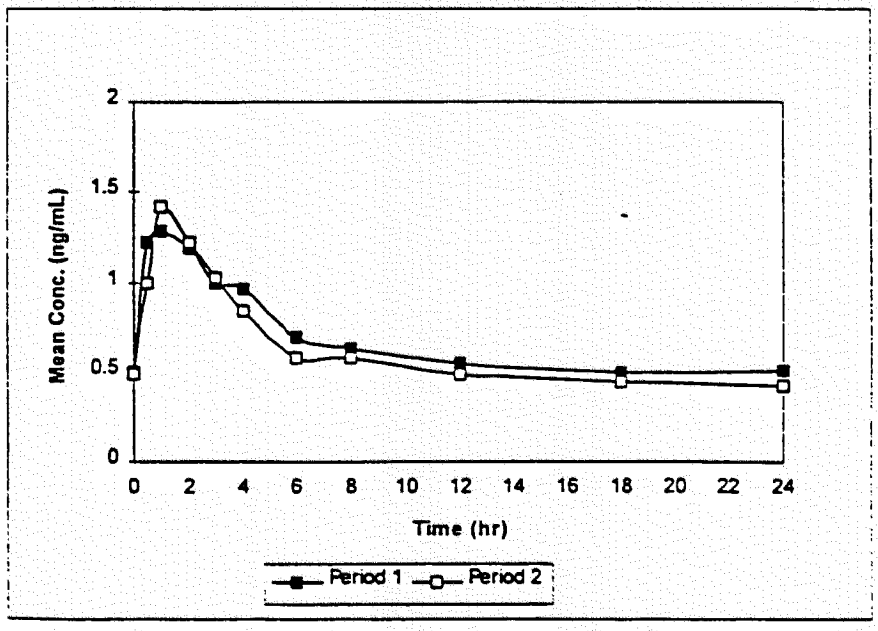


Figure 3. - Mean Digoxin Concentrations - Placebo Subjects



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

Protocol Number: E3810-A001-103

Study Dates: July-August 1995

OBJECTIVES: To evaluate the effects of rabeprazole sodium on the pharmacokinetics of ketoconazole

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

Study Population: 19 normal, healthy, males, 18-45 years of age

Treatment and Administration:
Period 1: each subject received a single 400 mg dose of ketoconazole (administered as 2 x 200 mg tablets) 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 400 mg dose of ketoconazole administered as before.

There was a 7-day washout period between Periods 1 and 2. All doses were given with 240 ml water after an overnight fast and were followed by an additional 3 hours of fasting.

Study Drug Suppies:
200 mg ketoconazole (Nizoral®) tablets; #95G325E
20 mg RBP tablets; #K48007ZZD. ***This is the to-be-marketed formulation.***
Placebo tablets; #K4Y002ZZB

Pharmacokinetic Sampling:
Blood samples for analysis of serum ketoconazole concentrations were obtained prior to dosing on Day 1, Period 1 and Day 8, Period 2, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, and 24 hours. 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 ketoconazole 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 October, 1995, at [redacted] detection. Blood samples were analyzed for ketoconazole 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 [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.		

RBP In-study Validation:		
	[redacted]	Quality Control (samples were 16, 88, and 333 ng/ml)
Linearity	>0.998 at 5.5-444 ng/ml	-
Sensitivity	LOQ=5.5 ng/ml	-
Interday Precision	<10% CV	<9% CV
Interday Accuracy	94-108% at 5.5-444 ng/ml	91-96%
Intraday Precision	Not provided	Not provided
Intraday Accuracy	Not provided	Not provided
Specificity: RBP [redacted]		

Ketoconazole Pre-study Validation:		
	[redacted]	Quality Control (samples were 0.05, 0.1, 0.75, and 7.5 µg/ml)
Linearity	>0.999 at 0.05-10 µg/ml	-
Sensitivity	LOQ=0.05 µg/ml	-
Interday Precision	<9% CV	<14% CV
Interday Accuracy	98-103% at 0.05-10 µg/ml	100-103%
Intraday Precision	Not provided	<4% CV
Intraday Accuracy	Not provided	94-103%
Specificity: Ketoconazole [redacted]		
Recovery: 71% at 0.1 µg/ml to 93% at 7.5 µg/ml with <4% CV.		
Stability: examined at 0.1, 0.75, and 7.5 µg/ml. 98-10% residual at room temp for 4 hours, 100-111% residual at room temp for 48 hours, 94-103% after 3 freeze/thaw cycles.		

Ketoconazole In-study Validation:		
		Quality Control (samples were 0.1, 0.75 , and 7.5 µg/ml)
Linearity	>0.999 at 0.05-10 µg/ml	-
Sensitivity	LOQ=0.05 µg/ml	-
Interday Precision	<5% CV	<5% CV
Interday Accuracy	96-108% at 0.05-10 µg/ml	96-102%
Intraday Precision	Not provided	Not provided
Intraday Accuracy	Not provided	Not provided
Specificity: Ketoconazole		