2. Instrument Performance Criteria -
   Interday ^{14}C-counting efficiency: 96.5±0.2
   Interday ^{14}C-background: 20.6±0.6
3. Precision and Accuracy - intraday accuracy and interday accuracy and precision parameters were <8% for all quality control samples (low, medium, and high) in all matrices. Intraday %CVs were not provided.
4. Reproducibility - the deviations in the duplicate analyses compared with the original results were 6.6% for plasma samples (n=13), 4.6% for whole blood samples (n=9), and 2.4% for urine samples (n=11).

II. Metabolic profiling of plasma, urine, and feces samples

A. *Method* - A workup was employed for all of the biological samples to prior to analysis. Components of these extracts were then separated by with a RBP and metabolites in plasma and fecal samples were quantitated using followed by of the relevant fractions. A mixture of the was analyzed in the same run as the study samples and the retention times compared using . The fraction collector was programmed based on actual retention times of RBP and its metabolites.

Urine samples were analyzed using Aliquots of urine samples from the first collection interval (0-4 hours) were also directly injected onto the without prior to ensure that there were no unidentified metabolites lost upon . All predose samples from each matrix were analyzed to establish background counts.

B. *Assay Validation* - the performance of the assay was measured as follows:
1. Efficiency of the flow detector was approximately 83.5%
2. Recovery of plasma, urine, and fecal samples after was 97%, 99%, and 80%, respectively.
3. of an injection of a test solution containing RBP and its metabolites revealed no of all compounds.
4. for each urine collection interval for all subjects revealed

RESULTS:

Study Population and Demographics:

All six male subjects who were enrolled completed the study. Their ages ranged from 56-64 years and their weights and heights were 77.7±9.3 kg and 177±6.2 cm, respectively (means±SD).

Administered Dose:

The actual individual doses administered were calculated from the radioactivity concentrations in the dosing vials of the oral solution. The mean±SD dose given was 48.02±0.54 µCi. Individual doses are presented below:

Subject	Administered Dose (μCi)
01	
02	
03	
04	
05	
06	
Mean±SD	48.02±0.54

Safety and Adverse Events:
Neither ECGs nor vital signs revealed any relevant changes over the course of the study. There were a number of out-of-range clinical laboratory results, however, these were not considered to be clinically relevant by the study investigator. There were no serious nor severe AEs observed. There were 23 AEs reported by 5/6 of the subjects, but these were considered to be mild in intensity. Ten AEs were considered to be possibly and 13 remotely related to the study medication. Overall, the study medication was well tolerated by all volunteers.

Pharmacokinetic Results:
Excretion balance
The recovery of ^{14}C-radioactivity, as well as the PK parameters derived from plasma ^{14}C-radioactivity profiles are summarized in Table 2.

Table 2. ^{14}C-radioactivity PK parameters.

Parameter	Means±SD	Range
Cmax (ng eq/ml)	1080±215	829-1387
Tmax (hr)	0.25[1]	0.25-0.50
Kel (hr^{-1})	0.058±0.012	0.036-0.066
$t_{½}$ (hr)	12.6±3.4	10.5-19.3
C_{24hr} (ng eq/ml)	13.0±2.91	9.63-17.3
C_{24hr}/Cmax (%)	1.20±0.06[1]	1.15-1.28
AUC_{0-24} (ng eq*hr/ml)	2712±705	1930-3711
$AUC_{0-\infty}$ (ng eq*hr/ml)	2950±739	2100-3983
A_{urine} (%)	90.0±1.7	87.8-92.6
A_{feces} (%)	9.8±1.8	8.0-12.7
A_{total} (%)	99.8±0.7	98.7-100.7

[1]Median values.

On average, more than 90% of the combined urinary and fecal radioactivity was excreted during the first 48 hours. Total ^{14}C-radioactivity recovery was virtually complete over the study period. Figure 1 (attached to the study report) depicts the mean cumulative excretion of ^{14}C-radioactivity at steady state.

Mean plasma and whole blood ^{14}C-radioactivity concentration profiles are presented in Figure 2 (attached). Visual inspection of the plasma concentration-time curve indicates rapid elimination of ^{14}C-radioactivity. Indeed, only 1.2% of the maximal concentration remained after 24 hours. During the first 4 hours after drug administration the ratio is approximately 0.6 and appeared to increase to around 0.75 at 16 hours. However, this data is misleading as n=3 at 16 hours (3/6 of the subjects had no detectable plasma radioactivity after 12 hours).

Metabolic Profile data

Plasma:

Parent RBP was the major radioactive component in the early plasma samples. Over half (58.7±9.1%, mean±SD) of the total radioactivity in the 0.25 hour samples were associated with parent drug, and it remained the major component for up to 1.5 to 2 hours after dosing. However, the levels then tended to decline fairly rapidly, and were generally below the analytical assay LOQ by 3 or 4 hours.

None of the samples exhibited quantifiable levels of the DM metabolite. Only trace activities were associated with either the DMTE or the S derivatives of RBP, and then only after the first hour following drug administration.

The TE and TEC were the main radioactive components present in the later plasma samples. In general, TE levels were greatest at 1.5 hours and then declined in parallel to those of TEC, to yield non-quantifiable levels after 8 hours. Very little plasma radioactivity was associated with the MA conjugate and was present in only half of the subjects.

Urine:

For all six subjects, the main drug component in urine as observed with radioflow detection was TEC; this represented approximately 36.9±4.0% (mean±SD) of the radioactivity in the 0-4 hour urine collection interval. The next most prominent [redacted] on [redacted] analysis corresponded to MA, and accounted for 19.0±3.7% of the radioactivity. Two other prominent peaks were also eluted on [redacted] however, did not correspond to any of the reference standards and were referred to as Unk. 1 and Unk. 2. They accounted for 10.5%±1.8% and 8.3%±1.4%, respectively, of the total radioactivity in the 0-4 hour samples. Two other minor [redacted] which represented DM and TE, were detected but accounted for <3% of the total radioactivity in all of the samples. The various components and their contribution to the percent of total radioactivity recovered in each of the different urine collection intervals is presented in the table below.

Table 3. Percent (mean±SD) of the ^{14}C-radioactivity of RBP and metabolites recovered.

	0-4 hrs	4-8 hrs	8-12 hrs	12-24 hrs
RBP	-	-	-	-
TE	<3	-	-	-
DM	<3	-	-	-
DMTE	-	-	-	-
TEC	36.9±4.0	38.6±4.7	30.0±6.2	19.6±6.9
S	-	-	-	-
MA	19.0±3.7	34.5±3.5	41.2±4.1	53.4±6.8
Unk. 1	10.5±1.8	-	-	-
Unk. 2	8.3±1.4	6.9±0.9	7.1±1.5	-

In addition to describing the contribution of each metabolite to the recovery of radioactivity from each urine collection interval, results were expressed as the quantities of RBP metabolites excreted into the urine as a percentage of the dose administered. A proportion of the 0-4, 4-8, 8-12, and 12-24 hour urine collections for each volunteer were pooled by weight. After determining the total radioactivity by [redacted] three aliquots of each subject's pooled sample were injected directly onto [redacted] and the elution of radioactivity associated with the different metabolite [redacted]. As the amounts of radioactivity in certain samples were close to the [redacted] the results of the

triplicate analyses were summarized as medians rather than means. (The mean±SD recovery of the radioactivity represented by all of the peaks from the [redacted] corresponded to 78.4%±3.5% of the dose. This value is very close to the 79.8%±2.5% found by direct liquid scintillation counting in the excretion balance portion of the study, thus the recoveries can be considered complete and reliable.)

The pooled samples for all six subjects contained two major components that corresponded to MA and TEC, which accounted for median values of 24.7% (range, 22.0-26.8%) and 28.6% (range, 23.7-33.2%) of the dose, respectively. Quantities of the two minor metabolites, Unk. 1 and Unk. 2, contributed 4.0% (range, <LOQ-6.4%) and 5.2% (range, <LOQ-6.5%) to the dose recovered. The sum of these 4 metabolites represented a median of approximately 64% recovery. The difference (~15%) between these summed values and the total radioactivity recovered from the HPLC was most likely due to small amounts of polar compounds which eluted prior to the 4 main components. These have been shown in dogs to be conjugates of the known metabolites.

Feces:

Although all of the volunteers excreted only a small proportion (9.8%±1.8%) of the total administered radioactivity in their feces, most of this was recovered in the 24-48 and 48-72 hour collections. TEC represented approximately 25-30% and MA from 2-3% of the total fecal radioactivity recovered. Small quantities (<1%) of DM and TE were recovered as well. It should be noted that only about 35% of the radioactivity recovered from the feces was accounted for by identified metabolites.

CONCLUSION:

Elimination of ^{14}C-radiolabelled RBP from plasma and whole blood after a 20 mg dose at steady state in healthy male subjects was rapid and virtually complete by 24 hours. The results indicate that the systemic exposure to most of the metabolites was minimal. Parent RBP was the primary drug-related component detected in plasma during early timepoints after dosing. RBP was replaced at later times by TE and TEC, which declined in parallel, suggesting that the PKs of the TEC were formation-rate limited. This, coupled with the clearance of TEC in urine and feces, tends to minimize the systemic exposure to all of the known metabolites of RBP in humans. Additional metabolites of RBP may be present in the human systemic circulation, however, as RBP and its known metabolites did not account for all of the radioactivity recovered from plasma. One possible explanation is that the two uncharacterized metabolites detected in urine (Unk. 1 and Unk. 2) were also present, but not identified, in plasma.

Recovery of ^{14}C-radioactivity from urine and feces was nearly complete. Greater than 90% of the total quantity of radioactivity was excreted into the urine within the first 48 hours, predominantly as two metabolites, namely the TEC and MA derivatives of the parent compound. Their recoveries accounted for approximately 30% and 25%, respectively, of the administered dose, and together they represented about 70% of the total radioactivity excreted into the urine within 24 hours. The relatively low fecal excretion suggests that elimination of RBP or its metabolites by the biliary route was minor. RBP was well tolerated and appeared to be safe in the 6 subjects studied.

REVIEWER'S COMMENTS:

1. Overall, a well-designed and executed study. Excretion balance and the metabolic profile of RBP was determined at steady-state.
2. No validation criteria were provided for the [redacted] assay with [redacted] used to determine the metabolic profile for urine samples. Therefore, only qualitative data can

reliably be drawn.

3. The population included in this study was older (ages: 56-64 years). Study A001-112, included in this NDA, revealed significant differences in PK parameters for RBP for subjects over the age of 65 years when compared to younger subjects (mean age: 23.3 years).

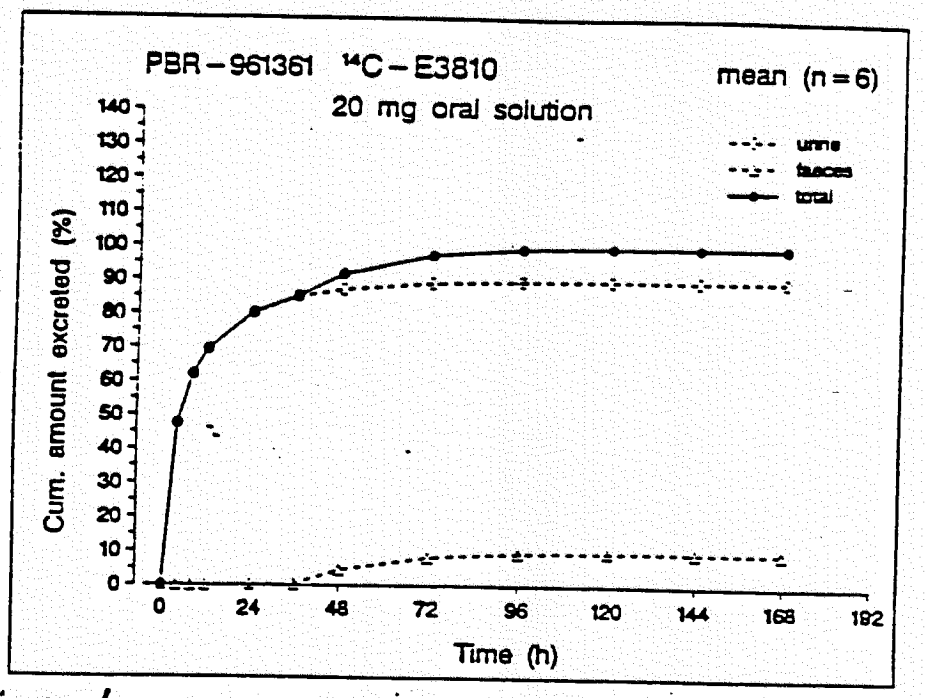

Figure 1.
Mean cumulative excretion of ^{14}C-radioactivity (% of dose) after a single administration of 20 mg ^{14}C-E3810 at steady state

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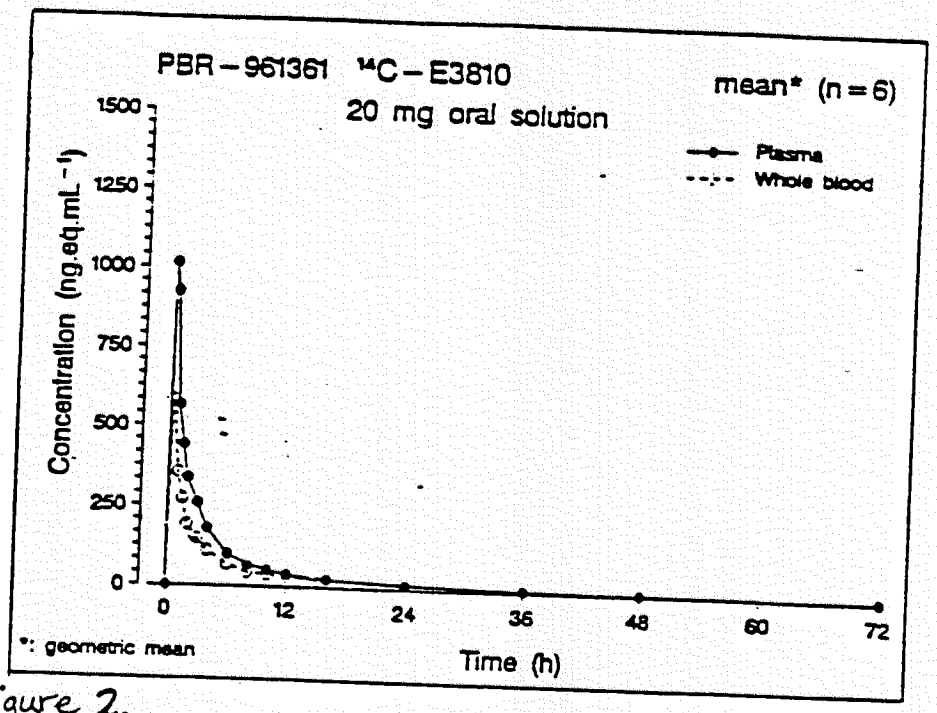


Figure 2.
Mean ^{14}C-radioactivity concentrations in plasma and whole blood versus time after administration of 20 mg ^{14}C-E3810 at steady state

MCR

TITLE: Interaction of Human Liver Cytochrome P450 with [redacted]307640 *In Vitro*

Protocol Number: A46:ADME

Laboratory/Author: [redacted]

The interactions *in vitro* of [redacted]307640 (RBP, rabeprazole) with the cytochromes P450 (CYP450) were studied using human liver microsomes, specific inhibitors of the CYP450s, and cDNA-expressed enzymes. The kinetics of formation of the two major oxidative metabolites, desmethyl-(DM) RBP and RBP-sulfone (S), were determined using two human liver microsomal samplesat RBP substrate concentrations of 2.5-500 μM (<1-7 μM observed in plasma after oral doses of 10-80 mg). The kinetic data indicated that high and low affinity sites were present for the production of both metabolites of RBP. The $km_{apparent}$ and $Vmax_{apparent}$ for DM-RBP formation by microsomes from human liver E (HL-E) for the high affinity site were 18.8±4.4 μM and 402±52 pmol product/min/mg protein. The high affinity site $km_{apparent}$ and $Vmax_{apparent}$ for RBP-S formation by microsomes from HL-E was 4.4±2.1 μM and 81.8±18 pmol product/min/mg protein. The rates of DM-RBP and RBP-S formation by the high affinity site were determined using 14 human liver microsomal samples characterized for CYP450 marker catalytic activities and immunoquantified levels of the CYP450. Rates of formation of DM-RBP significantly correlated with the immunoquantified levels of CYP 2C19 and the ability of the microsomes to 4'-hydroxylate S-mephenytoin. RBP-S formation significantly correlated with the immunoquantified levels of CYP 3A and the ability of the microsomes to 1'-hydroxylate midazolam. Inhibition studies and use of expressed CYP450 systems confirmed the correlation data demonstrating that CYP 2C19 catalyzed the formation of DM-RBP and CYP 3A catalyzed RBP-S formation. Further, RBP competitively inhibited S-mephenytoin 4'-hydroxylation and midazolam 1'-hydroxylation as did the structurally related compound, omeprazole. For the inhibition of S-mephenytoin 4'-hydroxylation and midazolam 1'-hydroxylation, RBP had higher $ki_{apparent}$ values than that of omeprazole (9.2±1.0 μM vs 4.1±0.4 μM for S-mephenytoin 4'-hydroxylation, and 59.4±6.0 μM vs 43.6±5.7 μM for midazolam 1'-hydroxylation for RBP and omeprazole, respectively). These studies demonstrate that the high affinity enzymes which catalyze the formation of the DM and S metabolites of RBP are, respectively, CYP 2C19 and CYP 3A. In addition, the inhibition data suggest that RBP has less potential to inhibit the metabolism of CYP 2C19 substrates compared to omeprazole, and that RBP and omeprazole have a similarly low potential to inhibit the metabolism of CYP 3A substrates.

TITLE: An Ascending, Single-Dose Safety and Tolerance Study of an Oral Formulation of E3810 in Healthy Male Volunteers

Protocol Number: E3810-A001-001

Study Dates: October, 1991-March, 1992

OBJECTIVES:
1. to assess the safety and tolerance of increasing strengths of RBP in healthy male volunteers following single oral doses
2. to examine the plasma concentrations of RBP resulting from single oral doses
3. to obtain preliminary information regarding the influence of RBP on plasma gastrin and intragastric pH

METHODS:
Study Design: .double-blind, placebo-controlled, sequential-group, single-dose study

Study Population: 40 healthy male volunteers, between the ages of 19 and 38 years, and within 15% of normal body weight range

Treatment and Administration:
Subjects were divided into four groups:
Group I - 10 mg RBP (N=8) or placebo (N=2)
Group II - 20 mg RBP (N=8) or placebo (N=2)
Group III - 30 mg RBP (N=8) or placebo (N=2)
Group IV - 40 mg RBP (N=8) or placebo (N=2)

An initial Sham-dose Phase was conducted to confirm tolerance to the intragastric pH probe, and to measure baseline intragastric pH and renal function. Approximately one week later subjects were readmitted to the clinic for the Treatment Phase. RBP or placebo was administered with 250 ml water following a fast of at least 8 hours. Food and liquid intake were closely supervised during the study.

Study Drug Supplies:
10 mg enteric-coated RBP tablets; #K16001BZZ. ***This was not the to-be-marketed formulation or strength.*** Placebo tablets were film-coated and of identical appearance to the RBP tablets; #K9X0700.

Biological Sampling:
Plasma RBP - blood samples were collected just before administration of RBP and at 1, 1.5, 3, 4, 5, 6, 7, 11, 16, 20, and at 24 hours post-dose.
Plasma gastrin - blood samples were collected at -1, 5, 11, 16, 20, 24, 32, 40, and 48 hours during the Treatment Phase.
Intragastric pH - random intragastric pH recordings were collected for at least 48 hours after drug administration using an intragastric pH electrode inserted into the antral portion of the stomach..

Pharmacokinetic Analysis:
The following PK parameters were determined: Cmax, tmax, kel, half-life, $AUC_{0\text{-}24}$, Cl/F. Oral clearance was plotted and regressed as a function of RBP dose to assess PK linearity.

Statistical Analysis:
PK parameters were compared among dose groups using ANOVA and Wilcoxon's test. Results were compared between active dose and corresponding placebo within each dose cohort. In addition, each active dose was compared with placebo pooled from all cohorts.

Due to large initial peaks inherent in the random digitrapper readings, the statistical analysis of intragastric pH readings was based on the cumulative area of the reading over elapsed time from initial readings. A mixed model was used to analyze the intragastric pH readings. The primary analysis focused on the time period from the initial random reading to the first reading with an elapsed time of 10 hours or more. Values with elapsed time beyond 10 hours were excluded from the analysis because the drug seemed to have no noticeable influence on the random readings. Since, by design, the area of the first observation always equaled zero, it was not used in the analysis.

Safety and Tolerability:
Assessed via AEs, vital signs, EEGs, and clinical laboratory tests.

Analytical Methods:
RBP was analyzed by [redacted] / April-June, 1992, at [redacted] / Both pre-study validation and validation during the analysis of the study samples was performed and the results are provided below.

Pre-study Validation

[redacted] / *samples:*
Linearity - ≥0.999 for range of 5.5 to 444 ng/ml
Interday Precision - <8% CV
Interday Accuracy - >96%

Quality control samples:

	Interday Precision -	Interday Accuracy -
16 ng/ml	10.8% CV	101.6%
88 ng/ml	5.9% CV	97.6%
333 ng/ml	6.5% CV	100.9%
	Intraday Precision -	Intraday Accuracy -
16 ng/ml	<13% CV	90-109%
88 ng/ml	<4% CV	91-103%
333 ng/ml	<2% CV	92-107%

Specificity:
[redacted] / All RBP [redacted]

In-Study Validation

[redacted] / *samples:*
≥0.999 for range of 5.5 to 444 ng/ml
Interday Precision - <7% CV
Interday Accuracy – 98-102%

Quality control samples:
Interday Precision - <8% CV
Interday Accuracy – 94-106%
Intraday Precision - <5% CV

Intraday Accuracy – 94-106%

Specificity:
RBP retention time = 6.3 to 11 minutes
IS retention time = 7.3 to 13 minutes
revealed no QC and for RBP and A number of from study samples were included and found to be acceptable. Six of the eight subjects who received placebo had a peak on their hat coincided with the retention time for RBP. However, the was not well-formed and did not have the appearance of the RBP from dosed individuals. Furthermore, upon addition of RBP to the plasma samples, a distinct separation was evident between the interfering and the true RBP

Recovery:
RBP = 86.2%
IS = 94.7%

Stability:
QC samples were stored at -20°C for 11 weeks when they were reanalyzed and quantitated via The % of initial analysis mean was 92.4% for the 16 ng/ml, 86.9% for the 88 ng/ml, and 80.2% for the 333 ng/ml samples. However, some of the study samples were stored for >12 weeks; the recovery of samples after storage for >11 weeks is unknown. In addition, no freeze/thaw, short term/room temperature, nor autosampler stability data were provided.

RESULTS:

Study Population and Demographics:
All 40 subjects who were enrolled completed the study. They were all male with ages ranging from 19-38 years. Demographic characteristics were similar between the active and placebo groups for each dose cohort, although no formal statistical tests were performed.

Table 1. Demographic Characteristics of Subjects.

Dose Group	Treatment	Race			Mean±SD Age (years)	Mean±SD Height (cm)	Mean±SD Weight (kg)
		White	Black	Other			
10 mg	RBP	7	1	0	22.6 (6.4)	182.5 (3.9)	76.2 (8.1)
	Placebo	2	0	0	20.5 (0.7)	185.4 (3.5)	78.4 (6.8)
20 mg	RBP	6	0	2	22.0 (2.4)	178.9 (5.9)	77.0 (7.8)
	Placebo	0	0	2	21.0 (0)	172.7 (7.2)	72.9 (8.1)
30 mg	RBP	8	0	0	21.9 (2.2)	178.7 (5.7)	73.9 (4.6)
	Placebo	2	0	0	20.0 (0)	184.1 (5.4)	83.7 (9.0)
40 mg	RBP	7	1	0	25.4 (4.7)	180.0 (5.7)	80.7 (8.1)
	Placebo	1	1	0	22.5 (2.1)	175.9 (2.8)	75.9 (14.1)
Pooled Placebo Group		5	1	2	21.0 (1.3)	179.5 (6.9)	77.7 (8.6)

Safety and Adverse Events:
There were no serious AEs observed and no subjects withdrew from the study due to an AE. There were 6 AEs, consisting primarily of headache, reported by 5/40 of the subjects. These were considered to be transient and mild in intensity. Changes from baseline in ECGs and vital signs were considered to be clinically insignificant and were comparable between the active and placebo groups. There were a number of out-of-range clinical laboratory results, however, these were not considered to be clinically relevant by the study investigator. Of note is that there were 9 treatment emergent abnormally high values for total urine creatinine in the 32 subjects who received RBP. Overall, the study medication was well tolerated by all volunteers.

Plasma Gastrin Levels:
Plasma gastrin values were significantly higher in the RBP-treated groups for most time points when compared to the corresponding placebo group, however, no formal statistical comparisons were made. A summary of the mean values for each treatment regimen at each time point is attached.

Pharmacokinetic Results: PK parameters, including dose-normalized AUC_{0-24} and Cmax values, are provided in Tables 2 and 3 below. Figure 1 displays the RBP plasma concentration vs time data for all 4 dosing regimens. When oral clearance was plotted and regressed as a function of RBP dose, the slope was not statistically significantly different from zero, indicating dose-independence for this parameter.

Table 2. PK Parameters for RBP.

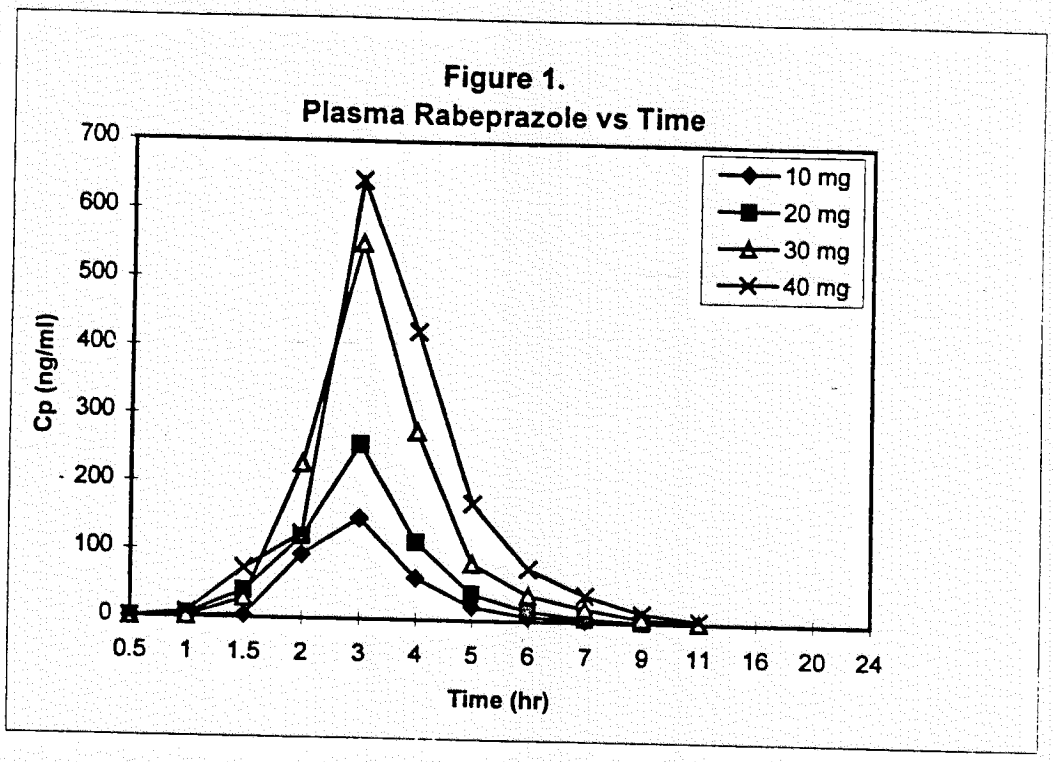
PK Parameter	Dose Group (Means±SD)			
	10 mg (N=8)	20 mg (N=8)	30 mg (N=8)	40 mg (N=8)
Cmax (ng/ml)	184±135	294±101	615±228	800±536
tmax (hr)	2.9±0.6	2.9±0.4	2.9±0.4	2.8±0.9
$t_{½}$ (hr)	0.73±0.16	0.70*±0.16	0.86±0.29	1.01±0.36
Cl/F (ml/min/kg)	9.5±4.6	9.6±5.9	7.6±4.9	7.9±5.3
AUC_{0-24} (ng*hr/ml)	315±211	545±215	1182±536	1554±1023

*Excluding subject 17 with $t_{½}$ =4.75 hrs

Although an increasing trend in AUC and Cmax was observed with higher doses, there were no statistically significant differences between treatment groups when adjusted for dose ($p>0.05$). Similar trends were observed when the data were weight-normalized. This data indicates that the PKs of RBP were linear between doses of 10 to 40 mg.

Table 3. Dose-normalized PK Parameters for RBP (normalized to 10 mg dose).

PK Parameter	Dose Group (Means±SD)			
	10 mg (N=8)	20 mg (N=8)	30 mg (N=8)	40 mg (N=8)
Cmax (ng/ml)	184±135	147±51	205±76	200±134
AUC_{0-24} (ng*hr/ml)	315±211	273±108	394±179	389±256



Effects on Plasma Intragastric pH: Table 4 provides the mean data for the random pH readings obtained for subjects in each treatment regimen. Intragastric pH was consistently higher for the RBP-treated subjects compared with either placebo or sham-dose phase readings, however, no statistical analysis of the treatment differences was provided.

Table 4. Descriptive Statistics for Random Readings (pH).

Group	Number Observations	Mean	SD
Sham Dose Period	40 subjects 5 reading each	1.393	0.822
Placebo	8 subjects 10 reading each	1.365	1.073
10 mg	8 subjects 10 readings each	1.962	1.339
20 mg	8 subjects 10 readings each	2.045	1.475
30 mg	8 subjects 10 readings each	2.282	1.624
40 mg	8 subjects 10 readings each	2.642	1.611

PK/PD Relationship: Unfortunately, the number of plasma gastrin determinations and intragastric pH readings were inadequate to allow for an examination of any meaningful PK/PD relationships; i.e., most of the PD data were collected when RBP plasma concentrations were below the assay LOQ.

CONCLUSION:

RBP was safe and well-tolerated by normal subjects at the doses used in this study. There were no clinically significant differences in safety parameters between the active and placebo groups. The pharmacokinetics of RBP appeared to be linear at single doses ranging from 10 to 40 mg based on AUC_{0-24}, Cmax, and Cl/F. The PD effects of RBP were difficult to assess in this study, as only a single dose was administered. While gastric pH appeared to increase with increasing doses of RBP, none of the mean values were >pH 3 for any of the treatments.

REVIEWER'S COMMENTS:

1. Due to the parallel-group design of this study, there was large intra- and inter-group variability for the PK data.
2. The significance of the intragastric pH data was difficult to assess after only a single dose of RBP.

TITLE: A single ascending dose study to evaluate the safety, tolerance, and pharmacokinetic profiles of E3810 in healthy male volunteers.

Protocol Number: #E3810-J081-001

Study Dates: July-September, 1988

OBJECTIVE: To evaluate the safety and pharmacokinetics of RBP after single oral doses

METHODS:
Study Design: randomized, double-blind, placebo-controlled, ascending single oral dose

Study Population: 18 healthy male Japanese volunteers

Treatment and Drug Administration:
The study was carried out in consecutive escalating dose steps. Subjects were randomly divided into two groups of 9 subjects each. Subjects in Group A received 1, 10, and 40 mg of RBP while subjects in Group B were given 3, 20, and 80 mg RBP. In each group, 6 subjects were given RBP while 3 received placebo. Drug was administered after 12 hours of fasting with 120 ml water, followed by an additional 5 hours of fasting. The treatment schedule is outlined below.

Group	Subject	Step					
		I	II	III	IV	V	VI
A	1	Placebo	2 week	10 mg	2 week	40 mg	
	2	1 mg	washout	10 mg	washout	Placebo	
	3	Placebo		10 mg		40 mg	
	4	1 mg		Placebo		40 mg	
	5	1 mg		Placebo		40 mg	
	6	1 mg		10 mg		Placebo	
	7	1 mg		Placebo		40 mg	
	8	Placebo		10 mg		40 mg	
	9	1 mg		10 mg		Placebo	
B	10		Placebo	2 week	20 mg	2 week	80 mg
	11		3 mg	washout	20 mg	washout	Placebo
	12		3 mg		Placebo		80 mg
	13		3 mg		20 mg		Placebo
	14		3 mg		20 mg		Placebo
	15		3 mg		Placebo		80 mg
	16		Placebo		20 mg		80 mg
	17		Placebo		20 mg		80 mg
	18		3 mg		Placebo		80 mg

Study Drug Supplies:
1 mg enteric-coated RBP tablets; #K862002.
10 mg enteric-coated RBP tablets; #K862003. ***These were not the to-be-marketed formulations nor strength of RBP.***
Placebo enteric film-coated tablets; #K860401.

Biological Sampling:

RBP and metabolites -

1 and 3 mg dose: blood was collected prior to and at 2, 3, 4, and 5 hours after dosing
10 mg dose: prior to and 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, and 8 hours after dosing
20 mg dose: prior to and 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, and 9 hours after dosing
40 and 80 mg: prior to and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, and 9 hours after dosing
Urine was collected for 12 hours prior to and for 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36, 36-48, 48-60, and 60-72 hours after dosing.
Feces were collected for 0-24, 24-48, and 48-72 hours after the 20 and 40 mg doses of RBP.

Serum gastrin - blood was collected before and at 2, 4, 5, 6, 8, and 24 hours after dosing

Pharmacokinetic Analysis:

Non-compartmental PK parameters were calculated using standard methods. Values were reported for AUC_{0-t}, $AUC_{0-\infty}$, Cmax, tmax, half-life, and CL/F for RBP and its metabolites. Urinary excretion of the metabolites was expressed as % of RBP dose. CL/F was plotted and regressed as a function of RBP dose to assess PK linearity.

Safety:

Assessed by physical exams and monitoring of vital signs, ECGs, subjective symptoms, and clinical laboratory tests.

Statistical Methods: The results of serum gastrin levels were analyzed by a paired t-test.

Analytical Methods:

Serum gastrin - RIA method using a commercially available kit. The LOQ was 25 pg/ml.

RBP and metabolites in plasma and urine - [redacted] Performed by Eisai Co., Ltd., Tokyo. Pre-study validation: May-Sept, 1988. Analysis of study samples: Plasma: 7/88-9/88, Urine: 9/88-11/88.

RBP Pre-study Validation - Plasma						
[redacted]				Quality Control (determined retrospectively from in-study data)		
	RBP	Sulfone	Thioether	RBP (200 ng/ml)	Sulfone (200 ng/ml)	Thioether (200 ng/ml)
Linearity	>0.999	>0.997	>0.999	-	-	-
LOQ	5 ng/ml	20 ng/ml	20 ng/ml	-	-	-
Interday Precision	<15% CV	<5%CV	22% CV at LOQ	<3% CV	<3% CV	2% CV
Interday Accuracy	95-130% LOQ 95-126% all others	102-109% LOQ 96-102% all others	85-113% LOQ 94-104% all others	97-108%	98-111%	98-107%
Intraday Precision	<7% CV	<8% CV	<10% CV	<3% CV	<4% CV	<3% CV
Intraday Accuracy	42-122% LOQ 78-113% all others	ND at LOQ 93-112% all others	ND at LOQ 96-109% all others	ND	ND	ND
Specificity: No blank						
Recovery: RBP - ranged from 112% at 5 ng/ml to 86% at 400 ng/ml. Sulfone - ≥79% at all concentrations. Thioether - ≥91% at 50-400 ng/ml; no data at assay LOQ, but only 44% recovery at 10 ng/ml.						