**CONCLUSIONS:**

This study demonstrated that a single 20 mg dose of RBP was well tolerated by subjects with renal failure. The incidence of adverse events was somewhat greater during hemodialysis than on the day following hemodialysis. Subjective comparisons to healthy subjects did not reveal any clinically significant differences in clinical laboratory parameters or the pharmacokinetic profile for RBP.

**REVIEWER'S COMMENTS:**

1. No formal statistical analysis was performed for the differences in PK parameters between healthy and renally impaired subjects.
2. None of the subjects in either the healthy or the renal cohorts were dosed on the same days. RBP administration spanned a time period from August of 1993 through June of 1994.
3. RBP concentrations may not have been adequately quantitated at lower concentrations due to poor

**TITLE:** A Pilot Study of the Safety, Tolerance, and Pharmacokinetics of E3810 in Healthy Male Volunteers and in Men With Chronic Hepatic Cirrhosis

**Protocol Number:** E3810-A001-004

**Study Dates:** August, 1993-December, 1994

**OBJECTIVES:**
To assess the safety, tolerance, and pharmacokinetics of RBP in healthy male volunteers and in men with chronic cirrhosis.

**METHODS:**
**Study Design:** single-center, open-label, parallel-cohort study

**Study Population:**
*Healthy cohort:* 13 normal healthy males aged 18 to 65 years with no indication of hepatic dysfunction in clinical and laboratory evaluations.

*Cirrhosis cohort:* 10 males with chronic cirrhosis. Subjects had a history and clinical evidence of stable, compensated cirrhosis of the liver. Previous confirmation of cirrhosis by percutaneous biopsy or liver/spleen scan had to be part of the subject's medical records prior to consideration for screening. Subjects could not have evidence of clinical ascites, hepatic coma, hepatorenal syndrome, extrahepatic bile duct obstruction, or acute or chronic hepatitis. Concurrent or planned administration of any medications was mutually agreed upon as acceptable for the nature of this study by the investigator and the sponsor. The onset of additional drug therapy during or within the month preceding the study was prohibited.

**Treatment and Drug Administration:**
*Healthy cohort:* 20 mg RBP as a single oral dose.
*Cirrhosis cohort:* 20 mg RBP as a single oral dose.
Study drug was administered after a fast of at least 8 hours with 250 ml water.

**Study Drug Supplies:**
20 mg enteric-coated RBP tablets; #B01517, #CT02420
***The lot numbers provided are for the placebo tablets, however, all 20 mg RBP tablets were produced using the to-be-marketed formulation.***

**Biological Sampling:**
Plasma samples were collected pre-dose and at 1, 2, 3, 4 , 5, 6, 8, 10, 12, 16, 20, and 24 hours after drug administration for measurement of plasma RBP concentrations.

**Pharmacokinetic Methods:**
The following PK parameters were estimated from the RBP plasma concentration-time profiles for each subject: $AUC_{0\text{-}24}$, Cmax, tmax, half-life, and $Cl_T$.

**Safety:**
Assessed via adverse events, clinical laboratory evaluations, vital signs, physical examinations, and ECGs.

**Statistical Methods:**
Pharmacokinetic parameters were summarized using descriptive statistics. PK parameters were compared between the two groups (normals, cirrhotics) using ANOVA and Wilcoxon's rank-sum test. Comparisons of PK data between the two cohorts were made descriptively with the assumption that the two cohorts were reasonably balanced with respect to collected demographic and background data.

**Analytical Methods:**
Quantification of plasma RBP samples was performed from February-July, 1994 and April-May, 1995, at [redacted] using an [redacted] Assay validation data are provided below.

| *Pre-study Validation:* | | |
|---|---|---|
| | [redacted] | Quality Control (samples were 16, 88, and 333 ng/ml) |
| **Linearity** | >0.999 at 55-444 ng/ml | - |
| **Sensitivity** | LOQ=5 ng/ml | - |
| **Interday Precision** | <7%CV | ≤10% CV |
| **Interday Accuracy** | 96-103% at 5.5-444 ng/ml | 98-102% |
| **Intraday Precision** | Not provided | <6% CV |
| **Intraday Accuracy** | Not provided | Not provided |
| **Specificity:** [redacted] | | |
| **Recovery:** 86% at 5.5 ng/ml to 99% at 55 ng/ml. | | |
| **Stability:** examined at 16, 88, and 333 ng/ml. 83-86% residual at room temp for 30 hours, 88-94% residual at room temp for 22 hours, 100-102% at 2-8°C for 71 hours, 85-97% residual at –20°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** | <6% CV | <6% CV |
| **Interday Accuracy** | 99-101% at 5.5-444 ng/ml | 98-108% |
| **Intraday Precision** | Not provided | Not provided |
| **Intraday Accuracy** | Not provided | Not provided |
| **Specificity:** RBP [redacted] in a number of the study sample | | |

**RESULTS:**
**Demographics:**
All subjects enrolled in this study were males; 16 were Hispanic and 7 were Caucasian. The mean ages, heights, and weights of the healthy cohort were 41 years, 174.9 cm, and 84 kg, respectively. For the cirrhotic patients, mean values were 52.2 years, 172.8 cm, and 79.9 kg for age, height, and weight, respectively.

**Protocol Violations:**
- One subject enrolled in the healthy cohort had evidence of cirrhosis.
- One subject was a smoker but agreed to discontinue smoking prior to, during, and 24 hours after the study.
- The majority of the subjects (14/23) exceeded the upper limit of ideal weight for their heights.

**Pharmacokinetics:**
For cirrhotic subjects compared to healthy subjects, $AUC_{0-24}$ was more than doubled, $C_{max}$ was approximately 50% greater, the elimination half-life was 2- to 3-fold higher, and the $Cl_T$ was decreased to less than half. These results are consistent with slower elimination of the drug in subjects with impaired liver function, who may have impaired drug metabolism capabilities. Mean and median PK parameters are provided below.

| Parameter | Healthy Subjects (N=13) Means±SD [median] | Cirrhotics (N=10) Means±SD [median] |
|---|---|---|
| $AUC_{0-24}$ (ng*hr/ml) | 809±544 [668] | 1776±496 [1758] |
| Cmax (ng/ml) | 401±246 [398] | 635±199 [694] |
| Tmax (hr) | 3.7±1.0 [3] | 4.6±2.8 [4] |
| Half-life (hr) | 1.7±1.7 [1.3] | 3.7±2.2 [2.9] |
| $Cl_T$ (ml/min) | 550±260 [499] | 201±57 [190] |

**Safety:**
Upon evaluation of the results of the screening laboratory results, three subjects from the healthy cohort were discontinued, one due to positive results for THC and an abnormal ECG, one due to elevated SGOT and SGPT associated with an abnormal liver/spleen scan, and the third due to an abnormal ECG and abnormal clinical chemistry results. All three subjects had received the 20-mg dose of RBP before discontinuation, and they are included in the safety evaluation.

There were no deaths or serious adverse events in the study. Mild adverse events were reported for 1/10 cirrhotic subjects and 3/13 healthy subjects. Two healthy subjects had headaches that were considered related to RBP, and one healthy subject had dizziness, numbness around the mouth, and blurred vision that were considered possibly or definitely related to drug.

Most abnormal clinical laboratory values were clinically insignificant and none were considered likely to be related to RBP. There were no clinically significant changes in the vital signs or ECG recordings.

**CONCLUSIONS:**
RBP was well tolerated by healthy volunteers and in men with stable, chronic cirrhosis of the liver at the 20 mg single dose used in this study.

Differences in the pharmacokinetics of RBP were observed between healthy subjects and cirrhotics. Cirrhotics had greater mean $AUC_{0-24}$, Cmax, and elimination half-life, and lower mean $Cl_T$ as compared to healthy volunteers. Any adjustment in dosing requirements are difficult to assess after just a single-dose administration.

**REVIEWER'S COMMENTS:**
1. Single-dose administration may not allow for adequate assessment of drug accumulation in subjects with impaired drug elimination capacities.
2. No formal statistical results were reported for PK parameters.

3. Many of the cirrhotic patients had concomitant diseases and or medical conditions.
4. There were numerous protocol violations in this study.
5. Subjects in this study were not dosed on the same dates.
6. Subjects were given only a single dose of RBP, therefore, it is difficult to adequately assess safety issues.

**RECOMMENDATION:**
The sponsor needs to reanalyze the data to determine if there were statistically significant differences for the PK parameters between the healthy and cirrhotic cohorts. The Medical Officer will be requested to evaluate whether adjustments in RBP administration will be necessary for this population.

**TITLE:** A Study of the Safety, Tolerance, Pharmacokinetics, and Pharmacodynamics of Rabeprazole Sodium in Healthy Volunteers and in Subjects with Impaired Hepatic Function

**Protocol Number:** E3810-A001-108

**Study Dates:** June, 1996-July, 1997

**OBJECTIVE:** to assess the safety, tolerance, pharmacokinetics, and pharmacodynamics of RBP in healthy volunteers and in subjects with impaired hepatic function

**METHODS:**
**Study Design:** two-center, open-label, multiple-dose

**Study Population:**
*Healthy cohort:* 12 healthy volunteers between 18 and 65 years of age who had no indication of hepatic dysfunction in clinical and laboratory evaluations
*Impaired cohort:* 13 subjects with impaired hepatic function between 18 and 65 years of age. These subjects had evidence of impaired hepatic function (Grade A or B as defined by the Child-Pugh Classification; attached to study report) and, with the exception of impaired hepatic function, were in good health, as determined by medical history and physical examination.

Subjects in the healthy cohort were matched to subjects in the impaired cohort for gender, age (within ±7 years of age), and weight (within ± 5 kg).

**Treatment and Drug Administration:**
Day 1: gastric pH was monitored for 24 hours. RBP was not administered on Day 1.
Day 2: subjects received a single 20 mg dose of RBP administered orally after an overnight fast.
Days 3-7: subjects received a single, daily, oral, 20 mg dose of RBP.
Day 8: subjects received their last 20 mg dose of RBP after an overnight fast. Gastric pH was monitored through 24 hours after dosing.

All RBP doses were given with 240 ml water. Meal times were standardized as follows: breakfast at 8:30 AM, lunch at 12:00 Noon, supper at 6:00 PM, and a snack at 9:00 PM.

**Study Drug Supplies:**
20 mg enteric-coated RBP tablets; #K5Y006ZZA. ***This is the to-be-marketed formulation.***

**Biological Sampling:**
Pharmacokinetics:
Blood samples for the determination of RBP plasma concentrations were collected prior to dosing on Days 2-7, prior to dosing on Day 8 and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 hours post-dose on Day 8.
Pharmacodynamics:
A pH probe was placed intranasally into the stomach on the morning of Day 1 and gastric pH was monitored for 24 hours. The probe was withdrawn on the morning of Day 2. At 7AM on Day 8, the pH probe was again placed into the stomach 1 hour before the RBP dose (8AM). Gastric pH was monitored for 24 hours and the pH probe was removed at 7:00 AM on Day 9. Gastric pH measurements were recorded every 5 seconds during the 24-hour monitoring periods, downloaded into a microcomputer, and analyzed for pH over time.

**Pharmacokinetics Methods:** The following non-compartmental parameters were determined from the RBP plasma concentration data collected on Day 8: Cmax, Cmin, Tmax, Kel, half-life, $AUC_{0-\infty}$, $AUC_{0-t}$, $CL_{oral}$ (normalized for body weight in kg), and Vd. Cmin was also reported on Days 2-7.

**Pharmacodynamics:** The following comparisons were summarized from the 24-hour gastric pH monitoring on Days 1 and 8: median and mean pH over 24 hours, % of time that pH >4 during the 24-hour period, median and mean nocturnal pH, and % of time nocturnal pH >4. The 24-hour pH monitoring period consisted of 23 hours that occurred after RBP dosing and 1 hour that was prior to dosing. The nocturnal time interval was from 11:00 PM to 7:00 AM.

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

**Statistical Methods:**
Pharmacokinetics: ANOVA was used to determine differences in the PK parameters between the cohorts. The Shapiro-Wilks Test statistic was used as a quantitative measure of normality; when the assumption of normality was not met, the Wilcoxon Rank Sum Test was used. Trough plasma concentrations of RBP were summarized by descriptive statistics.
Pharmacodynamics: PD data were summarized with descriptive statistics. The Wilcoxon Rank Sum Test was conducted on the median gastric pH data between the cohorts, as well as the percent time variables.

**Analytical Methods:** RBP plasma concentrations were quantitated July-August, 1997, at [redacted] Assay validation data are provided below.

| ***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** | Not provided | <5% CV |
| **Interday Accuracy** | Not provided | 100-104% |
| **Intraday Precision** | Not provided | <6% CV |
| **Intraday Accuracy** | 96-110% | 88-101% |
| **Specificity:** RBP [redacted] | | |
| **Recovery:** 86% at 5.5 ng/ml to 101% at 444 ng/ml. | | |
| **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, 99-106% after 6 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** | <7% CV | <12% CV |
| **Interday Accuracy** | 96-103% at 5.5-444 ng/ml | 94-102% |
| **Intraday Precision** | Not provided | Not provided |
| **Intraday Accuracy** | Not provided | Not provided |
| **Specificity:** [redacted] study samples acceptable. | | |

## RESULTS:

### Demographic:

There was one dropout in this study due to a serious adverse event (see **Safety** below). The following table presents the summary of baseline demographic characteristics of the subjects who completed the study.

**Table 1. Summary of Baseline Demographics**

| | Healthy (N=12) | Hepatically Impaired (N=12) | Total (N=24) |
|---|---|---|---|
| Gender | | | |
| Male | 6 | 6 | 12 |
| Female | 6 | 6 | 12 |
| Race | | | |
| Caucasian | 9 | 10 | 19 |
| African descent | 3 | 3 | 6 |
| Mean Age (years) | 45 | 46 | 45 |
| Mean weight (kg) | 74.6 | 72.7 | 73.6 |
| Mean height (cm) | 171.3 | 163.9 | 167.5 |

The subjects with hepatic impairment were predominantly classified as Child-Pugh category A, indicating mild liver disease.

### Pharmacokinetics:

The results of the PK calculations and the statistical analyses are summarized in Table 2. The kel could not be determined for 5 of the healthy subjects due to insufficient plasma concentration data, therefore, values for $AUC_{0-\infty}$, kel, half-life, CL, and Vd could not be calculated for these individuals. Figure 1 (attached to the study report) displays the mean RBP plasma concentration vs time profiles for the healthy and hepatically impaired cohorts.

**Table 2. Summary of Mean±SD PK Parameters.**

| Parameter | Healthy[a,c] | Hepatic[a] (N=12) | p-value[b] | |
|---|---|---|---|---|
| | | | Log-transformed | Untransformed |
| $AUC_{0-24}$ (ng*hr/ml) | 796.1±565.3 | 1175.6±713.9 | 0.225 | 0.175 |
| Cmax (ng/ml) | 382.7±274.5 | 447.0±323.6 | 0.753 | 0.614 |
| Tmax (hr) | 4.9±3.6 | 2.3±0.8 | 0.049 | 0.049 |
| $AUC_{0-\infty}$ (ng*hr/ml) | 1093±541.8 | 1331.6±704.3 | 0.628 | 0.452 |
| Kel (1/hr) | 0.39±0.18 | 0.26±0.31 | 0.069 | 0.342 |
| Half-life (hr) | 2.1±0.8 | 12.3±18.3 | 0.069 | 0.164 |
| $CL_{oral}$ (L/hr/kg) | 0.33±0.23 | 0.36±0.42 | 0.353 | 0.353 |
| Vd (L/kg) | 0.94±0.66 | 4.84±6.97 | 0.121 | 0.162 |

[a] Arithmetic mean from the untransformed data.
[b] ANOVA for all parameters except Tmax and $CL_{oral}$ (Wilcoxon Rank Sum Test).
[c] N=12 for $AUC_{0-24}$, Cmax, and Tmax and N=7 for $AUC_{0-\infty}$, kel, half-life, CL, and Vd.

Compared to healthy subjects, the hepatically impaired subjects had larger AUC and Cmax values, increased volume of distribution, and a terminal half-life that was longer by approximately 10 hours. There were no differences in $Cl_{oral}$, however. Although differences in the PK parameters between the cohorts were noted, results of the ANOVA, both original scale as well as the log-transformed data, indicated that no statistically significant differences existed between healthy volunteers and hepatically impaired subjects ($p>0.05$ for all parameters). Even

though the difference between the cohorts for the mean values of half-life was large, the lack of a statistically significant difference was due to the high variability in this parameter for the hepatically impaired cohort. For example, two subjects in this group had half-lives of 22 hours and 65 hours, respectively. Tmax and $CL_{oral}$ were analyzed using the Wilcoxon Rank Sum Test. Tmax was significantly different between the cohorts (p=0.049), but oral clearance was not (p=0.353).

**Pharmacodynamics:**

Data from all 24 subjects were included in the analysis. There was a statistically significant difference in median pH over 24 hours, with the healthy subjects having greater values than the hepatically impaired subjects on Day 8, but not on Day 1. For the nocturnal median pH assessment, Day 1 did not result in any statistically significant difference between the treatment cohorts, however, a statistically significant difference was detected at Day 8. The percent of time the gastric pH was >4 over 24 hours was not found to be statistically significant on either day, although there was a trend for the differences to be statistically different. Similar results were determined for the percent time nocturnal gastric pH was >4. Table 3 provides a summary of the mean results for the PD data.

**Table 3. Summary of PD Parameters (gastric pH).**

| Parameter | Mean±SD[a] | | Comparison of Cohorts |
|---|---|---|---|
| | Healthy (N=12) | Hepatic (N=12) | p-value[b] |
| Median pH over 24 hr | | | |
| Day 1 | 3.3±1.8 | 2.5±1.2 | 0.116 |
| Day 8 | 6.3±1.4 | 5.2±0.9 | 0.016 |
| Median Nocturnal pH | | | |
| Day 1 | 2.9±1.9 | 2.2±1.3 | 0.338 |
| Day 8 | 6.2±1.8 | 4.0±1.6 | 0.005 |
| % Time pH >4 | | | |
| Day 1 | 37.7±25.4 | 25.3±24.5 | 0.083 |
| Day 8 | 84.8±17.8 | 73.7±15.8 | 0.094 |
| %Time Nocturnal pH>4 | | | |
| Day 1 | 28.4±34.5 | 13.8±28.9 | 0.064 |
| Day 8 | 81.6±27.6 | 49.8±25.3 | 0.013 |

[a]Arithmetic means from untransformed data.
[b]Untransformed p-values form Wilcoxon Rank Sum Test.

In comparing Day 1 to Day 8, it was observed that median and mean gastric pH over 24 hours and nocturnal pH increased from Day 1 (predose) to Day 8 (after administration of RBP for 7 days) for both treatment cohorts. The percentage of time gastric pH was above 4 was also higher on Day 8 than on Day 1 for both cohorts.

**Safety:**

The occurrence of adverse events appeared to be higher in the hepatically impaired cohort. A statistically significant difference was found between the cohorts when comparing the number of

subjects who experienced adverse events in the body. Eighty-five percent of the subjects in the hepatically impaired cohort were reported to have had at least one adverse event compared with 58% in the healthy cohort. Fifty-four percent of the subjects in the hepatically impaired cohort and 25% of the subjects in the healthy cohort reported adverse events that were considered by the investigator to be possibly related to the study medication.

The majority of adverse events (88%) reported during the study were mild in severity. Severe asthenia was reported for Subject 2003, this was the only severe event reported. This event was considered by the investigator to have a possible relationship to the study medication; the event resolved by the end of the study. One subject (Subject 2005) discontinued the study prematurely. Subject 2005 experienced moderate hepatic encephalopathy after receiving six of the seven doses of RBP. This event was considered by the investigator to have a remote relationship to the study medication, but was probably related to the nature of her liver disease. The subject was hospitalized due to this event for 2 days and was discontinued from the study. After treatment with lactulose, the hepatic encephalopathy resolved and the subject was discharged from the hospital.

There were no apparent dose-related differences in laboratory tests, vital signs, physical examination, or ECG results. Clinically relevant low platelet count, calcium, and albumin values as well as total and free $T_4$ values were reported for subjects in the hepatically impaired cohort and were considered by the investigator to be related to the nature of their liver disease. Clinically relevant high AST, ALT, alkaline phosphatase, total bilirubin, total LDH, and total protein values were seen in the hepatically impaired cohort and were also believed by the investigator to be related to the nature of their liver disease.

**CONCLUSIONS:**

The results of this interim report show the following.

- The rate (Cmax) and extent (AUC) of absorption for RBP was greater in hepatically impaired subjects than in the healthy cohort, but the differences were not statistically significant.
- Tmax was significantly shorter in hepatically impaired subjects than in healthy subjects.
- Half-life was approximately 10 hours longer for subjects with hepatic impairment than for healthy subjects, although the difference was not statistically significant due to the high variability.
- Oral volume of distribution was also larger in the hepatically impaired subjects than in the healthy subjects. Again, these differences were not statistically significant.
- $Cl_{oral}$ was virtually the same for both cohorts.
- Despite higher plasma concentrations of RBP, hepatically impaired subjects did not derive an enhanced acid suppression effect compared with healthy subjects. Indeed, mean and median gastric pH were significantly greater in the healthy cohort on Day 8.
- Gastric pH in the hepatically impaired cohort was lower, i.e., more acidic, at baseline than in the healthy cohort. Overall, administration of 20 mg RBP, once a day for 7 days, appeared to reduce gastric acidity, i.e., increased all of the PD parameters for both groups.
- Administration of 20 mg RBP, once a day for 7 days, was generally well tolerated by both healthy and hepatically impaired subjects. However, adverse events were more frequently reported by the hepatically impaired cohort.

**REVIEWER'S COMMENTS:**

1. Fourteen subjects (4 healthy and 10 impaired) took a variety of concomitant medications during the study.
2. Subjects were not enrolled nor dosed on the same dates in this study.

**RECOMMENDATION:**

Although the comparison of the PK parameters between the two cohorts was not statistically significant, there were some differences. The Medical Officer will be requested to evaluate whether adjustment in the administration of RBP will be necessary for this population.

**Child-Pugh Classification of Severity of Hepatic Impairment***

| Clinical and Laboratory Measurements | Points Scored for Increasing Abnormality | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Encephalopathy Grade[a,b] | 0 | 1 to 2 | 3 to 4 |
| Ascites | None | Slight | Moderate |
| Bilirubin (mg/dL) | <2 | 2-3 | >3 |
| Albumin (g/dL) | >3.5 | 2.5-3.5 | <2.5 |
| Prothrombin Time (seconds prolonged) | 1-4 | 4-6 | >6 |

[a] Grade 3 or 4 encephalopathy, or severe ascites/edema, not eligible for this study

[b] Portal-systemic encephalopathy is staged 0 to 4 as shown in the following table. Stage 1 to 2 encephalopathy is assumed if the subject is in need of continuous therapy with lactulose and neomycin

* Slight modification of grading of severity of liver disease as stated in Pugh RN et.al[10]

The hepatic impairment grade categories are as follows:

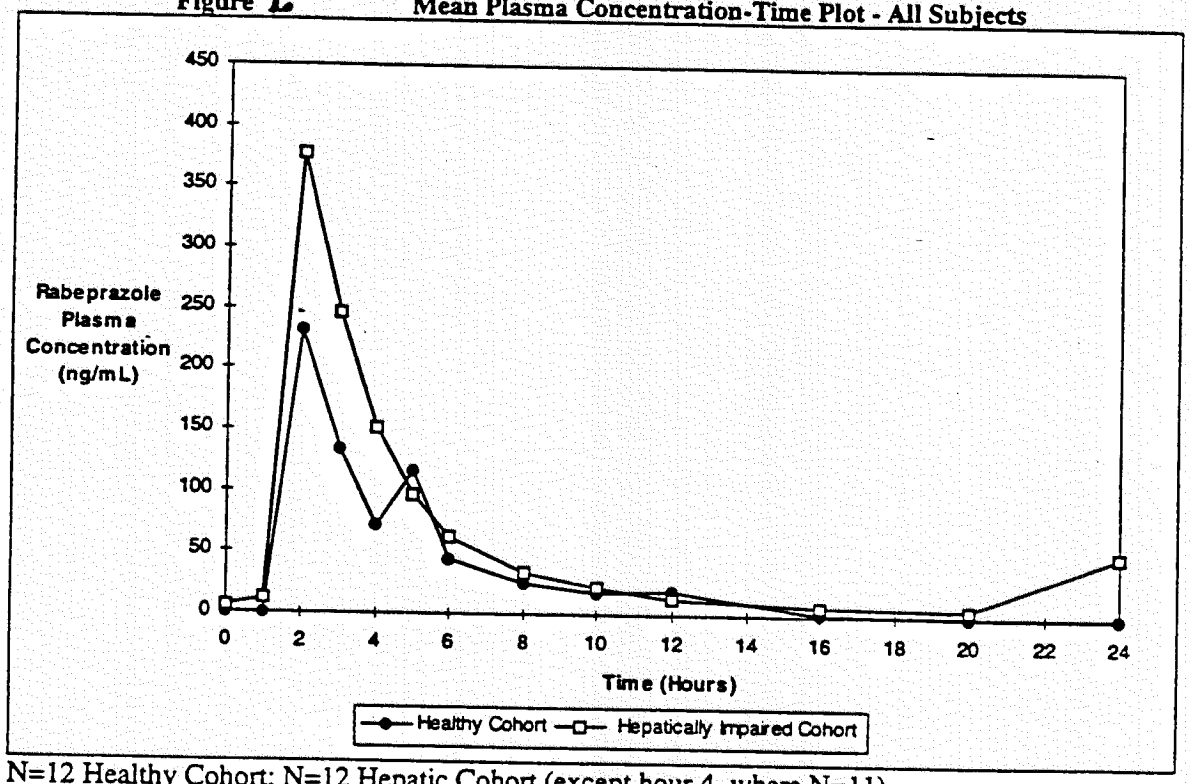
Grade A = 5 or 6 points
Grade B = 7, 8, or 9 points
Grade C = 10 to 15 points

**Staging of Hepatic Encephalopathy[a]**

| Stage | Mental State | Asterixis | EEG |
|---|---|---|---|
| 0 | Normal | None | Normal |
| 1 | Euphoria: occasional depression; fluctuating, mild confusion; slowness of mentation and affect; slurred speech; sleep rhythm disturbance | None or slight | Usually normal |
| 2 | Impending coma; drowsiness; inappropriate behavior; has ability to maintain sphincter control | Easily elicited | Abnormal: Generalized slowing |
| 3 | Stupor; subject sleeps most of the time; confusion is marked; speech is incoherent | Usually present | Always abnormal |
| 4 | Deep coma; subject may or may not respond to painful stimuli | Usually absent | Always abnormal |

[a] Trey et al. New Eng J Med. 274:473, 1966. [11]

Figure 1 Mean Plasma Concentration-Time Plot - All Subjects




N=12 Healthy Cohort; N=12 Hepatic Cohort (except hour 4, where N=11)

APPEARS THIS WAY
ON ORIGINAL

**TITLE:** An Open-Label, Multidose Pharmacokinetic Comparison of 20 mg Rabeprazole Sodium in Normal, Healthy Elderly and Young Volunteers

**Protocol Number:** E3810-A001-112

**Study Dates:** May-June 1996

**OBJECTIVE:** To compare the pharmacokinetic characteristics of 20 mg RBP in normal, healthy elderly and young volunteers

**METHODS:**
**Study Design:** open-label, single-center, parallel-group, two-cohort study

**Study Population:**
Subjects in the young cohort were healthy male or females between the ages of 19 and 30 years, while subjects in the elderly cohort were male or females over 65 years of age. Subjects within the two groups were matched for gender. In the elderly cohort, certain chronic medications were permitted if the dose regimen had been constant for one month and the drug was not anticipated to alter RBP PKs.

**Treatment and Drug Administration:**
20 mg RBP was given under fasting conditions as single, daily, oral doses for 7 days.
All doses were administered with 240 ml water after an overnight fast, and were followed by an additional 3 hours of fasting.

**Study Drug Supplies:**
20 mg enteric-coated RBP tablet; #K48007ZZD. ***This is the to-be-marketed formulation.***

**Biological Sampling:**
Blood was sampled for the determination of plasma RBP concentrations on Days 1, 5, and 6 prior to dosing. On the morning of Day 7, following the last dose of RBP, blood was collected prior to dosing and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 24, 36, and at 48 hours post-dose.

**Pharmacokinetic Analysis:**
$AUC_{0\text{-}T}$, $AUC_{0\text{-}\infty}$, Cmax, Cmin, Tmax, kel, and half-life were determined using SAS Release 6.08.

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

**Statistical Methods:**
Differences between cohorts in the mean values for all the PK parameters except Tmax were compared for statistical significance using the Student's t-Test. Tmax was compared using the Wilcoxon Signed-Ranked Test. Treatment effects were considered statistically significant at a p-value of $<0.05$.

**Analytical Methods:**
Blood samples were analyzed for RBP concentrations in June, 1996, by [redacted] using [redacted] Assay validation data is provided below.

| *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** | <11% CV | <9% CV |
| **Interday Accuracy** | 95-105% at 5.5-444 ng/ml | 102-103% |
| **Intraday Precision** | Not provided | <6% CV |
| **Intraday Accuracy** | Not provided | 88-101% |
| **Specificity:** RBP [redacted] well-resolved 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 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** | <8% CV | <7% CV |
| **Interday Accuracy** | 97-106% at 5.5-444 ng/ml | 102-103% |
| **Intraday Precision** | Not provided | Not provided |
| **Intraday Accuracy** | Not provided | Not provided |
| **Specificity:** RBP [redacted] poorly formed at lower concentrations in [redacted] QC, and study sample [redacted] There also appears to be a [redacted] interfering with that of RBP at higher concentrations in some of the [redacted] | | |

**RESULTS:**

**Demographic:**

All subjects completed the study. There were 20 subjects in each cohort (young and elderly). The mean age, height, and weight for the young subjects was 23.3 years, 175.3 cm, 68.1 kg, respectively, and 71 years, 172.6 cm, and 73.5 kg, respectively, for the elderly subjects. Of the 40 subjects, 31 were Caucasian, 6 were Hispanic, 2 were of African descent, and 1 was Western Asian.

**Pharmacokinetics:**

The table below presents the mean±SD values from Day 7 and p-values from the statistical analysis for each PK parameter by cohort. Figure 1 is attached to the study report and provides the RBP plasma concentration vs time profile for both young and elderly cohorts.

**Table 1. Mean±SD PK Parameters by Cohort.**

| Parameter | Young Cohort (N=20) | Elderly Cohort (N=20) | p-value* |
|---|---|---|---|
| $AUC_{0-T}$ (ng*hr/ml) | 631.2±273.8 | 1194.6±398.8 | <0.0001 |
| $AUC_{0-\infty}$ (ng*hr/ml) | 645.1±276.8 | 1210.8±403.8 | <0.0001 |
| Cmax (ng/ml) | 426.9±144.0 | 668.9±215.6 | 0.0002 |
| Cmin (ng/ml) | 0±0 | 0±0 | - |
| Tmax (hr) | 3.5±0.9 | 2.9±0.8 | 0.0163 |
| kel (1/hr) | 0.86±0.30 | 0.62±0.19 | 0.0055 |
| Half-life (hr) | 0.9±0.4 | 1.2±0.3 | 0.0228 |

*p-values obtained from Student's t-test for all PK parameters except Tmax (Wilcoxen signed-rank test)

The half-life of RBP was short in both the young and elderly cohorts, although was increased in the elderly by about 30%. Mean values for the PK parameters and the results of the statistical analysis indicated that the subjects in the elderly cohort exhibited significantly greater AUC (approximately double) and Cmax values, and shorter Tmax values, than did the subjects in the younger cohort. There were no detectable quantities of RBP in the plasma of the young subjects prior to dosing on Days 5, 6, or 7. There were measurable levels of RBP in two of the elderly subjects prior to the Day 6 dose, however, the two subsequent 24-hour post-dose concentrations (Time 0 hr, Day 7 and Time 24 hr, Day 7) were below the LOQ. Therefore, it was concluded that there was no evidence of accumulation following daily dosing of RBP for 7 days.

**Safety:**
All adverse events were either mild or moderate in nature and there did not appear to be an increased incidence in the elderly when compared to the young population. There were no clinically significant abnormal lab values nor out-of-range vital signs recorded during the study.

**CONCLUSIONS:**
There were statistically significant differences in the PKs of RBP after 7 daily doses when young subjects were compared to elderly subjects. However, since the elderly did not demonstrate any additional risk of adverse effects nor accumulation of RBP, an adjustment in dose is probably not required.