GTC-45-808: Effect of Phosphate Binders on Supplemental Iron Absorption in Healthy Subjects

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Name of Sponsor/Company

Genzyme Corporation, 500 Kendall Street, Cambridge, MA 02142
Geltex Pharmaceuticals, Inc., Waltham, MA 02451, (Geltex Pharmaceuticals, Inc. was acquired by Genzyme Corporation December 2000)

Investigators and Study Center(s)

This was a single-center study conducted in the United States.

Studied Period

First patient enrolled: 17 May 2000
Last subject completed: 09 December 2000

Phase of Development

Phase I

Objectives

To test the hypothesis that calcium-based phosphate binders [e.g. calcium carbonate (Tums®) and calcium acetate (PhosLo®)] significantly decrease the absorption of oral iron while sevelamer HCl (Renagel®) does not.

Methodology

This was an open-label, single-dose, prospective, randomized, four-treatment, four-period, crossover study. On each treatment day, subjects randomly received one of four possible drug regimens (iron alone, iron plus calcium carbonate, iron plus calcium acetate, and iron plus sevelamer hydrochloride). Plasma iron levels were observed for six hours following each dosing occasion. There was a one-week washout period between all treatments.

Number of Patients (Planned and Analyzed)

A sample size of 23 subjects was planned. Twenty-three patients were enrolled and completed the study.

Diagnosis and Main Criteria For Inclusion:

Healthy male and female volunteers at least 18 years of age who were normal with respect to iron status.

Test Product, Dose, and Mode of Administration

The following test regimens were administered orally. In all cases, iron was administered as Feosole® 1 tablet containing 65 mg of elemental iron.

Calcium carbonate/iron: calcium carbonate (Tums®) 4 x 750 mg tablets (3000 mg) plus iron 1 x 65 mg tablet (65 mg)

Calcium acetate/iron: calcium acetate (PhosLo®) 4 x 667 mg tablets (2668 mg) plus iron 1 x 65 mg tablet (65 mg)

Sevelamer HCl/iron: sevelamer HCl (Renagel®) 7 x 403 capsules (2821 mg) plus iron 1 x 65 mg tablet (65 mg)

Reference Therapy, Dose and Mode of Administration

Iron alone: iron (FeosoleÒ) 1 x 65 mg tablet administered orally

Duration of Treatment

The total study duration for a subject was a minimum of four weeks including 4 dosing sessions separated by at least one week.

Criteria for Evaluation – Pharmacokinetics

The effect of phosphate binders on the absorption of iron was assessed by measuring the iron concentration in serial plasma samples (predose, 0.5, 1, 1.5, 2, 3, 4, 5, and 6 hours postdose). Change in plasma iron concentrations was calculated for each non-predose sample. Area under the change in plasma iron concentration versus time curve from predose to six hours was the primary measure of iron absorption.

Criteria for Evaluation – Safety

Safety was assessed based on adverse events and laboratory measures (clinical chemistry, iron indices, and plasma iron concentrations).

Statistical Methods – Subjects

Demographic data were summarized using means and standard deviations for continuous variables and proportions for discrete variables.

Statistical Methods – Pharmacokinetics

Area under the curve (AUC) was calculated using the standard trapezoidal method. AUC data were summarized using geometric means with 95% confidence intervals and were log-transformed prior to further statistical analysis due to their expected log-normal distribution.

Analysis of variance (ANOVA) was used to compare iron absorption in the four treatment groups after controlling for potential differences in absorption due to sequence, period and subject effects. The possibility of a carryover effect was assessed during the initial analysis and excluded, as expected with a 1-week washout period. If ANOVA revealed a statistically significant treatment effect ($p< 0.05$), least square mean log AUC differences in iron absorption were calculated for iron plus each phosphate binder versus iron alone. The null hypotheses that each of these differences was not significantly different from zero were tested, with $p < 0.017$ defined as statistically significant. A critical p-value < 0.017 was used to accommodate the multiple comparisons in the analysis (n=3 Bonferroni's correction) providing an experiment-wise error rate of 0.05.

The relative bioavailability of iron was estimated as the antilog of the mean log difference in AUC for iron administered with a given phosphate binder compared with iron administered alone. The 95% confidence intervals for the relative bioavailabilities were also calculated. A relative bioavailability of 1 represents the expected bioavailability if a given phosphate binder had no impact on iron absorption.

Statistical Methods – Safety

The total number of adverse events (AE), the total number of subjects with AEs, and the proportion of subjects with AEs by treatment were summarized. Chi-square tests were used to determine if there was a statistically significant difference in the proportion of subjects with AEs by treatment group.

Blood chemistry results, iron indices, and plasma iron concentrations were listed by subject.

Summary – Conclusions (Subjects)

Twenty-three subjects were enrolled and completed the 4 treatments according to the protocol.

The mean age of the subjects was 26 years, and 52% of the subjects were male. The subjects were Caucasian (74%), Asian (22%), and African-American (4%). Mean iron indices at the time of screening were hemoglobin 14.2 ± 1.2 g/dL, hematocrit 41.5 ± 3.2%, plasma iron 95.2 ± 34.6 ug/dL, ferritin 45.4 ± 28.5 ng/mL, and transferring saturation 24.5 ± 8.6%.

Summary – Conclusions (Pharmacokinetics)

All subjects were included in the pharmacokinetic analyses (n=23).

The extent of iron absorption was significantly decreased by both calcium carbonate and calcium acetate; it was not significantly decreased by selevamer HCl. The relative bioavailability of iron when administered with calcium carbonate, calcium acetate, and sevelamer HCl was estimated to be 0.81, 0.73, and 0.90, respectively. The rate of iron absorption appeared to be decreased by calcium acetate as T_{max} was significantly longer for it (4.26 ± 0.90 hours) compared to iron alone (3.35 ± 1.08). T_{max} was not significantly different for either calcium carbonate (3.48 ± 1.14 hours) or sevelamer (3.76 ± 1.51 hours).

Summary – Conclusions (Safety)

All subjects were included in the safety analyses (n=23).

No serious adverse events occurred during the study. Thirteen of 23 subjects (57%) experienced 14 adverse events judged by the investigator to be related to study medication. Subjects cited nausea and gastrointestinal discomfort as the most frequent complaint; one subject reported dizziness as an additional side effect. All events were assessed as mild or moderate in intensity. None of the adverse events were serious or severe, and no patients required medical intervention. No subject discontinued participation in the study.

The difference in frequency of adverse events among the four treatments was statistically significant ($p<0.0001$). The incidence of gastrointestinal adverse events was substantially higher when the subject received iron plus calcium acetate (57%) compared to iron alone (4%), iron plus calcium carbonate (0%) and iron plus sevelamer (0%).

Small but statistically significant decreases in all iron indices occurred over the study period, but all subjects maintained normal iron status throughout the study. There were no clinically significant laboratory abnormalities.

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