International Journal of Pharmaceutics, 28 (1986) 151–155
Elsevier

IJP 00947

Effect of food and antacids on the oral absorption of pirenzepine in man

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(Received May 9th, 1985)
(Modified version received July 9th, 1985)
(Accepted September 11th, 1985)

Key words: pirenzepine – Gastrozepin – antacids – food – fasted – relative bioavailability

Summary

The effect of food or an aluminum and magnesium hydroxide antacid on the bioavailability of orally administered pirenzepine was evaluated in 20 subjects in a 4-way crossover study. The extent of oral bioavailability of a 50 mg pirenzepine tablet administered following a 10 h fast was significantly (ANOVA, $P < 0.05$) greater than that of pirenzepine in the presence of either food or antacids. This was reflected by a mean reduction of 30% in area under the curve ($AUC_{0 \rightarrow 48h}$) when pirenzepine was administered either one-half hour before a meal, with a meal or with a liquid antacid preparation. It was also observed that pirenzepine peak plasma concentrations were reduced by 30% with concomitant food, or by 45% when concomitant antacids were administered. The rate of absorption, measured as the reduction in time to reach peak plasma concentration, was significantly (ANOVA, $P < 0.05$) greater when pirenzepine was given either with a meal or one-half hour before a meal, than when administered following a 10 h fast or with antacid. There was no significant difference in the biological half-life of pirenzepine among the four treatments (range 12.1 – 12.9 h).

Introduction

The rate and extent to which an orally administered drug is absorbed are a function of its chemical nature as well as various interactions between the drug and the gastrointestinal tract (Levy, 1972; Chasseaud and Taylor, 1974).

Food intake may exert a complex influence on the bioavailability of drug compounds. Potentially, food may interfere with tablet disintegration, drug dissolution and drug transit through the gastrointestinal tract. Food may influence bioavailability by decreasing the rate of gastric emptying (Chasseaud and Taylor, 1974; Koch-Weser, 1974), or by an alteration in gastrointestinal pH (Levine, 1970; Toothaker and Welling, 1980).

The result of food–drug interactions on drug absorption, being a complex function of a number of different processes, is difficult to predict (Toothaker and Welling, 1980; Welling, 1980), and valid conclusions can be derived only from direct studies on specific drugs. For a drug compound that must be administered two to four times a day, it is unlikely that drug absorption will not in some way be affected by a meal.

Antacids may also affect the absorption, dissolution, adsorption, chelation, ionization, gastric emptying and urinary excretion of many drugs (Hurwitz, 1977). The most widely used components are magnesium hydroxide and aluminum

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hydroxide, with most antacid preparations containing a combination of these two compounds (Am. Med. Ass., 1983).

Antacids have been available for the treatment of peptic ulcer disease for more than 100 years. Surveys have shown that half of American adults use antacids, with heavy proprietary antacid use most likely due to acid-related distress (Graham and Smith, 1981). Clinicians readily prescribe antacids symptomatically for relief of gastric pain, as well as in combination therapy with anticholinergics and H_2 receptor antagonists.

Pirenzepine, a selective antimuscarinic compound is being investigated for clinical efficacy in the treatment of duodenal ulcer. In contrast to the classical antimuscarinic compounds, pirenzepine exhibits selectivity at a molecular level by distinguishing between subclasses of muscarinic receptors (Hammer et al., 1980; Giachetti et al., 1982; MacIntosh, 1983). Therapeutically, for duodenal ulcer in U.S. clinical trials, pirenzepine is administered orally as a 50 mg tablet, 3 times a day. Because of its strongly hydrophilic properties, pirenzepine is incompletely absorbed following oral administration (Hammer and Koss, 1979).

The objective of this open label, four period crossover study was to identify and characterize the influence of food and antacid use on the relative oral bioavailability of pirenzepine in normal volunteers.

Materials and Methods

Twenty healthy male volunteers between the ages of 18 and 48 years and within 10% of their normal body weight participated in this study. Informed consent was obtained and clinical protocols were approved by the Institutional Review Board, using the principles set forth for human investigation (Federal Register, 1981).

Prior to enrolment in the study, a complete medical history was taken and physical examination (including ECG) performed. Subjects were accepted into the study if their clinical laboratory tests (blood and urine) were within normal limits.

No medications of any kind were taken by the subjects for 14 days prior to or during the investigation. No coffee, tea, cola or alcoholic beverages were consumed for 24 h prior to the start of each treatment or until blood sampling was completed. Smoking was not permitted from 1 h before until 24 h after pirenzepine administration.

Subjects were randomly assigned to one of four treatment sequences determined from one balanced 4×4 Latin Square. Drug administration was single dose, open label crossover with at least one week washout between administration of each treatment. A single 50 mg pirenzepine tablet (Gastrozepin, Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT), was given orally with 8 oz. of water either following a 10 h fast, as the reference treatment; with 30 ml of an antacid (Mylanta II, Stuart Pharmaceuticals, U.S.A.; aluminum hydroxide 400 mg/5 ml, magnesium hydroxide 400 mg/5 ml and simethicone 30 mg/5 ml); immediately following a standardized meal; or one-half hour prior to a standardized meal. The standardized meal provided a total of 440 kcal, as 20 g (20%) protein, 17 g (35%) fat, and 50 g (45%) carbohydrates. Four and one-half hours after drug administration, a light meal was given. For the subjects in the fasting and antacid treatment groups, this light meal was the first meal of the study period. Another light meal was given 8 h after drug administration with no further restrictions.

Subjects remained seated until 2 h after drug administration, after which they were allowed to sit or walk around leisurely.

Blood samples were collected prior to and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36 and 48 h after administration of each treatment. Blood samples (7 ml) were drawn using an evacuated heparinized tube and inverted at least 5 times for proper mixing of heparin and blood. Blood samples were centrifuged at 2000 rpm for at least 3 min to obtain plasma. The plasma samples were immediately frozen and stored at approximately $-20°C$ until analyzed. Concentrations of pirenzepine in plasma were quantitated by a sensitive and specific radioimmunoassay (Bozler, 1978; Homon et al., 1985).

The area under the plasma concentration–time curve ($AUC_{0 \rightarrow 48h}$) for each subject and each treatment was calculated using the linear

trapezoidal method. Multiple test statistics were performed utilizing a general linear models procedure. Carryover effects, by study design, were assumed to be zero, as there was a seven day washout period between each treatment. An additive 4-period crossover analysis of variance was used to obtain the estimate of population variance for the variables analyzed. Period was added as a class variable to determine the validity of the experimental design. For each variable, using the estimate of variance from the associated analysis of variance table, the t-test was used to compare each treatment to the reference treatment. Bonferroni's inequality was used to adjust for multiple comparisons. This inequality states that in order to assure a joint significance level of 0.05, the required significance level for an individual comparison is $P = 1 - (0.95)^{1/M}$ where M is the number of comparisons made (Miller, 1981; SAS, 1982).

The model decision program AUTOAN (Sedman and Wagner, 1976) and graphical methods were utilized in the determination of biological half-life from individual data.

Results and Discussion

The relative extent of bioavailability of pirenzepine following a 10 h fast was significantly ($P < 0.05$) greater than that of pirenzepine in the presence of either food or antacids (Fig. 1). This was reflected by a mean reduction of 30% in area under the curve ($AUC_{0 \rightarrow 48h}$) when pirenzepine was administered either one-half hour before a meal, with a meal or with a liquid antacid preparation. It was also observed that the pirenzepine peak plasma concentrations were reduced by 30% when concomitant food, or by 45% when concomitant antacids were administered. The time to reach peak plasma concentration, a rough measure of absorption rate, was significantly less when pirenzepine was given either with a meal (3.1 ± 2.2 h) or one-half hour before a meal (2.4 ± 1.1 h), than when administered following a 10 h fast (5.5 ± 2.6 h) or with antacid (6.9 ± 1.7 h). Mean area under the curve, mean peak concentration and mean time to peak for each treatment are summarized in Table 1. The power of detecting a 20% difference in area under the curve between fasted administration of pirenzepine and the administration of pirenzepine one-half hour before a meal, with a meal or concomitantly with an antacid with $\alpha = 0.05$ was 0.98. The power of detecting the same difference in area under the curve between any two treatments with $\alpha = 0.05$ was 0.90. The experimental design was considered to be valid as there was no period effect ($P > 0.4$) for the treatments administered.

Due to the hydrophilic nature of pirenzepine, absolute bioavailability when compared to an intravenous standard is incomplete (Hammer et al., 1979). However, the relative bioavailability of the tablet form, relative to an oral solution given in the fasted state, is unity (Matzek et al., 1985). Because pirenzepine is a basic drug with pK_a's of 2, 8 and 11 (Perrin et al., 1974) the rate of absorption may be directly related to the pH of the stomach and the rate at which drug passes from the stomach to the intestine. Any co-administered treatment influencing the rate of gastric emptying

TABLE 1

MEAN AREA UNDER THE CURVE, MEAN PEAK CONCENTRATION, MEAN TIME TO PEAK, AND HARMONIC MEAN BIOLOGICAL HALF-LIFE FOR PIRENZEPINE IN PLASMA FOLLOWING ORAL ADMINISTRATION OF 50 mg TABLET EITHER FASTED OR IN THE PRESENCE OF FOOD AND ANTACIDS

Parameter	10 h fast	0.5 h before meal	with meal	with antacid
Area under the curve $0 \rightarrow 48$ h (ng · h/ml)	820.1 (304.1) [a]	551.6 (148.5)	559.1 (164.9)	633.1 (219.9)
Peak concentration (ng/ml)	50.7 (20.4)	35.4 (10.7)	36.9 (11.7)	27.5 (11.1)
Time to peak (h)	5.5 (2.6)	2.4 (1.1)	3.1 (2.2)	6.9 (1.7)
Harmonic mean biological half-life (h)	12.1 (3.8)	12.7 (3.4) [b]	12.9 (3.4)	12.9 (4.9)

[a] Mean of 20 subjects with standard deviations in parenthesis.
[b] Mean of 19 subjects.

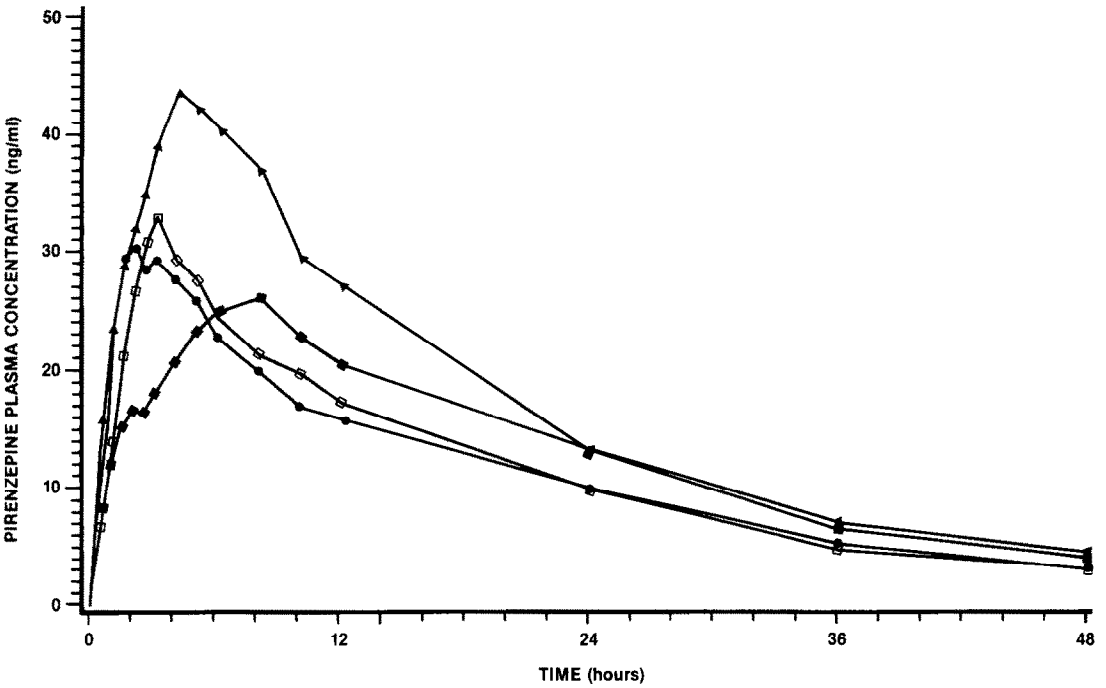

Fig. 1. Mean pirenzepine plasma concentrations for 20 subjects following a single 50 mg dose and co-administration of an antacid (■), or a meal (□), or 0.5 h prior to a meal (●), or following a 10 h fast (▲).

should be considered as potentially influencing the rate of absorption of the orally administered drug. Aluminum hydroxide-containing antacids have been reported to delay gastric emptying (Hurwitz, 1977), and the administration of an aluminum hydroxide/magnesium hydroxide antacid concomitantly with pirenzepine may have contributed to the increased time to peak concentration that was seen in this study. Although food has been identified as a factor modifying drug absorption by delaying the gastric emptying rate (Melander, 1978), food also alters the pH and diffusional barrier the drug molecule must interact with to be absorbed (Mayersohn, 1979). Food may increase the rate of absorption by changing the pH of the environment of the dissolved drug and by effectively increasing the surface area of absorption by increasing the volume of the gastrointestinal contents, despite diluting the drug concentration (Henderson et al., 1966). Food is a powerful stimulator of intestinal blood flow (Nelson et al., 1979), also contributing to an increase in absorption rate at mealtime.

It has been reported that oral administration of pirenzepine at therapeutic dosages does not inhibit gastrointestinal, interdigestive motility in man (Lederer et al., 1982), and has no effect on gastric emptying (Corinaldesi et al., 1982).

The harmonic mean terminal half-life following oral administration (Table 1) was approximately 12 hours (range 6.9 to 27.7 h), in agreement with previous studies (Hammer et al., 1979; Matzek et al., 1985). The plasma concentration time curves for orally administered pirenzepine suggest complete distribution within the time frame of absorption. The lack of change in elimination rate with various co-administered treatments is consistent with the hypothesis that food or antacids alter only the absorption process of pirenzepine.

The proposed dosage regimen from clinical trials for pirenzepine is 50 mg 3 times a day. For consistent, rapid absorption of pirenzepine the results of this study would suggest dosing at mealtime. The data would also suggest that the extent of drug absorption will be reduced by 30% from a fasted standard. However, because food remains

an obvious and convenient daily ritual with which to associate the administration of drugs (George, 1984), compliance may be improved by giving pirenzepine with meals.

Acknowledgements

The authors would like to acknowledge Dr. John Arnold, M.D., Quincy Research Center, Kansas City, MO, U.S.A., for supervision of the clinical portion of this study.

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