pH-Related Changes in the Absorption of Dipyridamole in the Elderly

Tanya L. Russell,[1,2,6] Rosemary R. Berardi,[1] Jeffrey L. Barnett,[3] Tami L. O'Sullivan,[1,4] John G. Wagner,[1,5] and Jennifer B. Dressman[1]

Received August 28, 1992; accepted June 28, 1993

The bioavailability of dipyridamole, a poorly soluble weak base, was evaluated in 11 healthy, older subjects (≥65 years), 6 with a low fasting gastric pH (control) and 5 with a fasting gastric pH > 5 (achlorhydric), in a randomized, crossover design. Subjects received 50 mg dipyridamole as a single oral dose both with and without pretreatment with 40 mg famotidine (control subjects) or 1360 mg glutamic acid HCl (achlorhydric subjects). Gastric pH was monitored by Heidelberg radiotelemetric capsule. Gastric emptying of ^{99m}Tc-radiolabeled orange juice was measured. Gastric pH appeared to be a primary determinant in dipyridamole absorption in the elderly. Elevated gastric pH resulted in compromised dipyridamole absorption compared to low-gastric pH conditions in all cases. The administration of glutamic acid hydrochloride to achlorhydric subjects prior to the dose of dipyridamole corrected for the decreased C_{max} and AUC(0–36) exhibited in achlorhydric subjects without pretreatment. T_{max} and k_a were slower in achlorhydrics, although pretreatment with glutamic acid HCl tended to normalize these parameters. Based on these results, it would be beneficial for achlorhydrics to take glutamic acid hydrochloride prior to taking dipyridamole and other medications which need a low gastric pH for complete absorption. The administration of 40 mg famotidine was successful in elevating the gastric pH to >5 in all subjects and maintained it at >5 for at least 3 hr in all subjects tested. The lack of differences in C_{max} and AUC(0–36) with significant differences in T_{max} and k_a indicated that control subjects after treatment with famotidine may serve as an adequate model for achlorhydrics with respect to the extent of absorption, but not with respect to the rate of absorption. Gastric emptying of a nutrient liquid was significantly slower in achlorhydric subjects than in control subjects. Finally, fasting serum gastrin appeared to be a relatively reliable and easy method for screening for achlorhydria in the elderly.

KEY WORDS: elderly; drug absorption; gastric pH; gastric emptying; dipyridamole; glutamic acid hydrochloride; famotidine; Heidelberg radiotelemetric capsule.

INTRODUCTION

Previous studies of upper gastrointestinal (GI) pH in the elderly indicate that there is a wide range of gastric pH behavior in the older population. Although the majority of healthy individuals over age 65 can be expected to have a low gastric pH during the fasted state, about 10% exhibit a median fasting gastric pH greater than 6. Approximately two-thirds of those with an elevated fasted gastric pH exhibit elevated pH even in response to meals, while the remaining one-third have fluctuating gastric pH or decreasing gastric pH after eating (1). Changes in gastric pH may be associated with changes in gastric emptying rate. Studies have shown that gastric emptying tends to be slower when the rate of gastric acid secretion is reduced, and vice versa (2,3). Although gastric acid secretory status appears to be a determinant of gastric emptying, previous studies of gastric emptying in the elderly reported to date did not group subjects on this basis. We hypothesized that administration of drugs with pH sensitive dissolution profiles would result in changes in the absorption profile in elderly subjects with an elevated gastric pH and that these changes might be exacerbated by alterations in gastric emptying.

Dipyridamole (Persantine, Boehringer-Ingelheim) was chosen as a model drug to determine whether absorption is altered by changes in levels of gastric acid in the elderly. Dipyridamole currently is used with aspirin or a coumarin-derivative anticoagulant to prevent postoperative thromboembolic complications following heart valve replacement, to reduce the rate of reinfarction during recovery from myocardial infarction, or to reduce the reoccurrence of transient ischemic attacks (4). A dose of 100 mg four times per day is recommended for antithrombotic therapy (5). Dipyridamole is a weak base with a reported pK_a of 6.4 (6) and is poorly soluble in water. Previous spectrophotometric studies in our laboratory (L. C. Dermentzoglou, unpublished data) established that dipyridamole exhibits additional dissociation constants between pH 2.0 and pH 3.0. The rate of dissolution of dipyridamole at pH values ranging from 4.0 to 7.0 in McIlvaine buffer was also studied, using a rotating disk method. The dissolution rate decreased by almost two orders of magnitude, from pH 4.0 to pH 6.0 (7). These observations suggest that the absorption of dipyridamole is dissolution rate limited over at least part of the usual physiological range of gastrointestinal pH. Furthermore, since achlorhydric subjects have high pH values in both the stomach and the intestine regardless of prandial phase (1), and since the dissolution rate of dipyridamole is very poor in that pH range, it was hypothesized that achlorhydrics would exhibit a slow rate and poor extent of absorption compared with elderly subjects who have a low gastric pH.

The primary aim of this study was to identify changes that occur in the rate and extent of dipyridamole absorption between elderly who are achlorhydric and those who have normal gastric acid secretion. A second aim was to investigate the use of glutamic acid hydrochloride (Acidulin, Eli Lilly) as a means of compensating for the lack of gastric acid production in achlorhydric subjects. The study also explored the effect of the H_2 receptor antagonist, famotidine (Pepcid; Merck, Sharp, and Dohme), on the absorption of dipyridamole in elderly adults with normal gastric acid secretion. Finally, this study sought to test the hypothesis that the rate of gastric emptying is reduced in those elderly who have low gastric acid secretion.

[1] College of Pharmacy, The University of Michigan, Ann Arbor, Michigan 48109-1065.
[2] Current address: Marion Merrell Dow Inc., Marion Park Drive, P.O. Box 9627, Kansas City, Missouri 64134.
[3] School of Medicine, The University of Michigan Hospital, Ann Arbor, Michigan 48109.
[4] Current address: Detroit Receiving Hospital, Department of Pharmacy, 4201 St. Antoine, Detroit, Michigan 48201.
[5] Professor Emeritus, The University of Michigan.
[6] To whom correspondence should be addressed.

0724-8741/94/0100-0136$07.00/0

MATERIALS AND METHODS

Subject Selection

The study was conducted in the Clinical Research Center of The University of Michigan Hospitals on an inpatient basis, with the approval of the Institutional Review Board for studies involving human subjects. All participants gave written informed consent. Eleven healthy, older (≥65 years) men and women participated in the study. All subjects were in good health as determined by medical history, physical examination, and blood and urine laboratory screens. None had a history of GI disease or were receiving medications which may affect GI physiology. Administration of medications, consumption of alcohol and caffeine, and smoking were restricted during the study.

The subjects were classified into two groups according to their gastric acid secretory status. The control group (n = 6) consisted of subjects with pH profiles similar to that of young adults (8), while the achlorhydric group (n = 5) consisted of subjects with elevated gastric pH in both fasted and fed conditions. The control group consisted of three men and three women with a mean age of 71 (range, 66–80) and the achlorhydric group consisted of four men and one woman with a mean age of 70 (range, 66–79).

Study Methods

The study was conducted as a randomized, two-period, complete crossover design. Each subject received both Treatment A and Treatment B in a randomized order, with at least a 1-week washout between treatments. The chart in Fig. 1 describes the procedures for GI pH monitoring and treatment dosing.

Treatment A consisted of a single oral dose of 50 mg dipyridamole.

Treatment B was divided into two groups. *Control subjects* received a single oral dose of a 40-mg famotidine tablet (crushed prior to administration) followed by a single oral dose of two 25-mg dipyridamole tablets. *Achlorhydric subjects* received two consecutive doses of two 340-mg glutamic acid hydrochloride capsules, the first dose 10 min prior to and the second dose concurrently with a single oral dose of two 25-mg dipyridamole tablets.

The intent of Treatment A was to compare dipyridamole absorption in those elderly who are achlorhydric with that in elderly who have a low gastric pH. Gastric emptying was also assessed in Treatment A in both subject groups.

In Treatment B, the gastric pH of each subject group was adjusted to a gastric pH typical of the other group. The control subjects were given famotidine to raise their gastric pH similar to the achlorhydric subjects, while the achlorhydric subjects were given glutamic acid hydrochloride (HCl) to lower their gastric pH similar to the controls. The intent of Treatment B was to allow each subject to act as his or her own control to assess differences in absorption which occur primarily due to the differences in gastric pH. Famotidine was chosen over the other H_2 receptor antagonists because it was less likely to interfere with the cytochrome P450 oxidase system. At the time the study was designed, omeprazole, a gastric acid pump inhibitor, was not yet readily available and its ability to elevate gastric pH had not been thoroughly investigated. Previous work in our laboratory indicated that famotidine would be successful in consistently elevating gastric pH to >4.5 in those with a normal gastric pH and that glutamic acid hydrochloride would be successful in lowering gastric pH to <3 in subjects with an elevated pH (9).

Day 1 admit to the clinic, collect vital signs
7pm - begin fasting (water only)

6am - calibrate Heidelberg capsule
7am - predose blood sample for dipyridamole and serum gastrin
- vital signs
- administer Heidelberg capsule with 150 ml water

Treatment A	Treatment B	
	Control Subjects	Achlorhydric Subjects
7:20am - 120 ml water	7:15am - 40 mg famotidine tablet with 120 ml water	7:20am - 2x340 mg glutamic acid HCl capsules with 120 ml water
7:30am - 2x25 mg dipyridamole tablets with 120 ml water	7:30am - 60 ml water every 15 min until pH>5 for at least 10 min	7:30am - 2x340 mg glutamic acid HCl capsules and 2x25 mg dipyridamole tablets with 120 ml water
	10 min following last water - 2x25 mg dipyridamole tablets with 120 ml water	

Blood samples - 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post dose
Vital signs - one hour post dose and as needed
Heidelberg capsule - retrieve capsule at 4 hours post dose and check calibration
Meals - lunch at 4 hours post dose, dinner at 9 hours post dose and snack at 8 pm
9pm - Treatment A only, begin fasting (water only)

Day 2 Blood sample - 24 hours post dose

Treatment A	Treatment B
Gastric emptying procedure	Breakfast
Breakfast	Vital signs and Release from clinic
Vital signs and Release from clinic	

Return to the clinic 1/2 hour before blood sample
Blood sample - 36 hours post dose
Release from clinic

Fig. 1. Study event schedule.

Gastric Emptying Procedure

Gastric emptying procedures were conducted in the Nuclear Medicine Department. A reference marker was located on the skin below the right clavicle within the field of view, but not overlying the stomach or esophagus, so that the region of interest could be accurately located in each scan. A liquid meal consisting of 300 mL of orange juice labeled with 3.7×10^{13} dps of ^{99m}Tc-DPTA was given. The subject drank the labeled juice through a straw over a period not exceeding 2 min, then sat facing a wide-field-of-view gamma camera with a low-energy, parallel-hole collimator coupled to a computer. Scintiscans were acquired on computer dynamic 30-sec frames for the first 30 min and then 30-sec frames once every 15 min until 75% of the liquid emptied from the stomach or until 3 hr elapsed.

Sample Analysis

Plasma. An ion-pairing, reverse-phase HPLC assay with fluorescence detection was used to determine the con-

centration of dipyridamole in each plasma sample according to procedures developed by Wolfram *et al.* (10).

Radioactivity. The cine was reviewed to detect changes in the volunteer's position. A region of interest was then flagged over the stomach and marker, and a time–activity curve was generated. Corrections were made for decay of the isotope, then the time to 10, 25, 50, and 75% emptied was calculated to generate a percentage emptied-versus-time profile.

Pharmacokinetic Analysis

Median plasma concentrations at each collection time were determined. The maximum median dipyridamole concentration and time of occurrence of the maximum concentration (C_{max}, ng/mL; and T_{max}, hr) were estimated from the data. The AUC(0–T), where T is the time of the final sample, was calculated for each subject using a combination of the regular trapezoidal rule and the logarithmic trapezoidal rule. AUC(0–∞) was calculated from the sum of AUC(0–T) plus the estimated concentration at the final sample time, T, divided by the terminal rate constant, λ_1.

The disposition phase of the oral concentration versus time curve was first fit using nonlinear least squares to determine the most likely model for each. Six of 22 dipyridamole concentration-versus-time curves more closely fit a one-compartment open model than the two-compartment open model. For these subjects, the Wagner–Nelson method (11) was subsequently used to calculate the fraction absorbed and the absorption rate constant.

For curves more closely fitting a biexponential disposition, the absorption rate constants were determined using a method described by Wagner *et al.* (12). This method eliminates the need for intravenous disposition data when using the exact Loo–Riegelman method (13,14) with the Proost modification (15) to estimate the absorption rate constant.

For subject AL (Treatment A) and subject AW (Treatment B), the disposition data were first fit to a biexponential equation. Use of the exact Loo–Riegelman equation, however, resulted in poor estimates of the fraction absorbed and a poor fit of the overall concentration curve. For these subjects the final reconstruction equation (2) was used to estimate k_{10}, k_a, and t_0, which resulted in a better fit of the data.

The equation used to reconstruct the estimated concentration-versus-time curve for the subjects with monoexponential disposition was

$$C_T = C_0 \frac{k_a}{(k_a - \lambda_1)} [e^{(-\lambda_1)(t-t_0)} + e^{(-k_a)(t-t_0)}] \quad (1)$$

For subjects fitting a biexponential disposition, the following equation was used to reconstruct the estimated curve:

$$C_T = C_0 k_a \frac{(k_{21} - \lambda_1) e^{(-\lambda_1)(t-t_0)}}{(k_a - \lambda_1)(\lambda_2 - \lambda_1)} + \frac{(k_{21} - \lambda_2) e^{(-\lambda_2)(t-t_0)}}{(k_a - \lambda_2)(\lambda_1 - \lambda_2)} + \frac{(k_{21} - k_a) e^{(-k_a)(t-t_0)}}{(\lambda_1 - k_a)(\lambda_2 - k_a)} \quad (2)$$

All nonlinear least-squares curve fitting was accomplished with the statistical package SAS (v5.16, 1986, SAS Institute, Inc., Cary, NC).

Statistical Analysis

The pharmacokinetic parameters of maximum plasma concentration (C_{max}), area under the concentration-versus-time curve to 36 hr [AUC(0–36)], time to reach maximum concentration (T_{max}), and estimated absorption rate constant (k_a) were analyzed. Pharmacokinetic parameters were transformed by first taking logarithms of the values before applying statistical tests. A schematic of comparisons is given in Fig. 2. The following Treatment and Subject group comparisons were examined.

- Control subjects, Treatment B/Control subjects, Treatment A
- Achlorhydric subjects, Treatment A/Achlorhydric subjects, Treatment B
- Achlorhydric subjects, Treatment A/Control subjects, Treatment A
- Control subjects, Treatment B/Achlorhydric subjects, Treatment A
- Achlorhydric subjects, Treatment B/Control subjects, Treatment A

Within each group, Treatment A was compared to Treatment B using the method for analysis of crossover design studies described by Fleiss (16). All comparisons between subject groups were made using a two-tailed unpaired t test. Statistical significance was based on a significance level of $\alpha = 0.05$.

pH data were analyzed for each 1-hr period following the dose of dipyridamole. Medians within each subject group and treatment phase were then calculated for each 1-hr period (n = 240 pH values) following the dipyridamole dose based on the individual pH medians. Correlation between individual median pH during the first hour after the dose of dipyridamole and each of the pharmacokinetic parameters, C_{max}, T_{max}, AUC(0–36), and k_a, was determined by linear regression analysis.

Systolic and diastolic blood pressures were monitored for each patient. Baseline readings obtained prior to the dose of dipyridamole and readings obtained approximately 1 hr following the dose of dipyridamole were reported. Differences between the baseline and the 1-hr postdose values are reported as percentage change from the baseline. The percentage change in systolic and diastolic blood pressures was compared between subjects who reported adverse reactions and subjects without adverse reactions using a two-tailed unpaired t test.

For the gastric emptying procedure, the radioactivity at

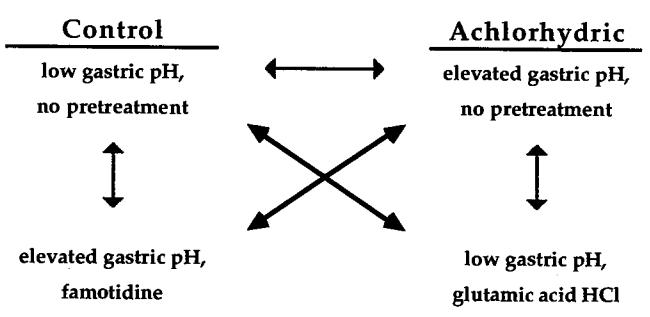

Fig. 2. Diagram of statistical comparisons of interest for the dipyridamole pharmacokinetic parameters.

75, 50, 25, and 10% of maximum radioactivity was determined for each subject. The time to empty 10, 25, 50, and 75% of the ^{99m}Tc was then determined from each plot of radioactivity versus time, and comparisons were made between control subjects and achlorhydric subjects using a two-tailed unpaired t test.

RESULTS

Fasting Serum Gastrin

Fasting serum gastrin levels collected for the subjects in this and other studies in which these subjects participated are shown in Table I. All samples were assayed at the University of Michigan Hospital. Fasting serum gastrin levels in all control subjects were less than 65 pg/mL, whereas levels in the achlorhydric subjects were consistently greater than or equal to 100 pg/mL.

pH Measurements

Table II lists the individual median pH and interquartile ranges for each control subject during both treatment phases. Table III gives similar results for the achlorhydric group. The maximum plasma dipyridamole concentration (C_{max}) was inversely correlated to pH, while the time to reach maximum plasma concentration (T_{max}) was directly correlated with pH as shown in Figs. 3A and B. The absorption rate constant and pH were not strongly correlated, perhaps because of the large intersubject variability in k_a when dipyridamole was administered under low-median pH conditions. Finally, the area under the plasma concentration–time curve was not strongly correlated with pH.

Dipyridamole Pharmacokinetics

Median plasma dipyridamole concentrations over time for both treatments are plotted in Fig. 4A (control subjects) and Fig. 4B (achlorhydric subjects). Mean pharmacokinetic parameters with statistical results are listed in Table IV. Figure 5 is a representative plot of the goodness of fit of the theoretical plasma concentration over time estimated using the method of Wagner *et al.* (12).

Table I. Fasting Serum Gastrin Levels for Control Subjects and Achlorhydric Subjects Compiled from the Gastrointestinal pH Study, the Dipyridamole Absorption Study, and a Pilot Study of Changes in Gastrointestinal Physiology with Aging

Control		Achlorhydric	
Subject	FSG (pg/mL)	Subject	FSG (pg/mL)
MN	34[a]	RS	143[a]
	45[c]		100[b]
AL	35[a]	AM	1681[a]
	45[c]		2160[a]
			1791[b]
EH	50[a]	SB	209[a]
	53[c]		190[b]
HW	34[a]	AW	1415[b]
	63[c]		465[a]
MM	47[a]	FS	158[b]
			244[a]
FS	37[a]		
	43[c]		

[a] Collected during dipyridamole absorption study.
[b] Collected during GI pH study.
[c] Collected during related gastrointestinal physiology study.

Gastric Emptying

Figure 6 is a graph of the mean time to empty 10, 25, 50, and 75% of the radioactivity from the stomach for both the controls and the achlorhydrics. Time to empty 25, 50, and 75% of the radiolabeled drink was significantly slower in the achlorhydric group than in the control group (P values are indicated in Fig. 6).

Adverse Reactions

In general, blood pressure changed in a random manner in response to dipyridamole administration except for the three subjects who exhibited adverse reactions to the dipyridamole. In these subjects, both systolic and diastolic blood pressure dropped quite dramatically when dipyridamole was given under low-gastric pH conditions. At the time of symptom onset, blood pressure in subject EH dropped from a baseline value of 142/75 to 89/57, subject MN dropped from 131/83 to 72/44, and subject FS dropped from 143/86 to 68/37. These three subjects complained of sudden and severe dizziness and a rapid onset of nausea without vomiting. In a comparison of the percent change at 1 hr following the dipyridamole dose, the symptomatic subjects (n = 3) exhibited a significantly greater decrease in systolic blood pressure than did the asymptomatic subjects (P = 0.022). The adverse reactions disappeared as the blood pressure returned toward baseline values. The three subjects, all control subjects, exhibited adverse effects during Treatment A only. They had three of the four highest observed maximum plasma concentrations, at 2317, 2220, and 1986 ng/mL, suggesting that adverse effects may be related to serum dipyridamole levels.

DISCUSSION

Fasting Serum Gastrin

Fasting serum gastrin appears to be a reasonable indicator of gastric pH conditions. If the results can be confirmed in a larger number of subjects, this test might prove useful as a quick, easy, and relatively inexpensive method for screening elderly patients for elevated gastric pH.

pH Measurements

Median fasted gastric pH values observed during Treatment A were similar to previously recorded pH profiles for each subject. Control subjects had median fasted gastric pH values <2, whereas achlorhydric subjects had median fasted gastric pH values >6.

The pretreatments administered during Treatment B were successful in raising and lowering gastric pH to the desired value during the first hour following the dose of dipyridamole. The median pH for the control subjects after administration of 40 mg famotidine was greater than 5 in all subjects for the first 3 hr following the dose of dipyridamole.

Table II. Median Gastric pH (with Interquartile Range in Parentheses) for Each Control Subject Within Each 1-hr Period Following the Dose of Dipyridamole for Both Treatment A and Treatment B

	Treatment A				Treatment B (famotidine pretreatment)			
Subject	1 hr[a]	2 hr	3 hr	4 hr	1 hr	2 hr	3 hr	4 hr
EH	1.2	1.3	1.2	1.2	5.9	5.8	5.7	5.3
	(1.1–1.4)	(1.2–1.3)	(1.1–1.2)	(1.2–1.3)	(5.9–6.0)	(5.7–5.8)	(5.7–5.8)	(5.2–5.6)
AL	1.0	1.0	1.1	0.9	5.9	5.9	5.9	6.0
	(0.9–1.1)	(0.9–1.0)	(0.9–1.8)	(0.87–1.23)	(5.0–6.3)	(5.8–6.0)	(5.8–6.0)	(5.9–6.2)
MM	1.2	1.3	1.3	1.1	6.1	5.9	5.7	5.6
	(1.2–1.6)	(1.2–1.4)	(1.2–1.4)	(1.1–1.2)	(5.9–6.3)	(5.6–6.1)	(5.7–5.8)	(5.4–5.7)
MN	0.7	0.7	0.7	1.2	5.1	5.4	5.4	4.6
	(0.6–0.8)	(0.6–0.8)	(0.6–0.8)	(0.8–1.8)	(4.4–5.4)	(4.9–5.5)	(5.4–5.5)	(3.5–5.0)
FSN	0.9	1.2	0.9	1.1	5.9	5.8	5.8	6.0
	(0.8–1.0)	(1.0–1.7)	(0.9–1.0)	(1.0–1.2)	(5.6–6.1)	(5.7–5.9)	(5.8–5.9)	(5.9–6.3)
HW	1.1	1.1	1.6	1.0	6.5	6.6	6.3	6.4
	(1.0–1.2)	(0.9–1.2)	(1.3–2.1)	(0.9–1.3)	(6.4–6.6)	(6.4–6.6)	(6.2–6.4)	(6.3–6.4)
Overall	1.0	1.1	1.1	1.1	5.9	5.8	5.8	5.8
	(0.9–1.2)	(1.0–1.3)	(0.9–1.3)	(1.0–1.2)	(5.9–6.1)	(5.8–5.9)	(5.7–5.9)	(5.3–6.0)

[a] Each 1-hr median represents $n = 240$ pH values and each overall median is the median of the individual subject median.

After administration of 1360 mg glutamic acid hydrochloride, the median pH fell to below the target of 3 in all achlorhydric subjects for the first hour following the dose of dipyridamole. The pH had risen above 3 in almost all achlorhydric subjects by the third hour. However, the crucial period for maintaining a lowered gastric pH is during the first hour postdose, when the drug is most likely to be in the stomach.

Dipyridamole Pharmacokinetics

Treatment A Versus Treatment B Within Each Subject Group. In all *control subjects,* the pharmacokinetics of dipyridamole were compromised when control subjects were pretreated with famotidine, compared to administration of dipyridamole alone. The C_{max} and k_a were significantly decreased. T_{max} was significantly longer in Treatment B, with an average of 2 hr, compared to an average of 0.6 hr in Treatment A. The mean AUC(0–36) was decreased by 37% when gastric pH was elevated, however, this change was not statistically significant. These data indicate compromised absorption when the control subjects were pretreated with famotidine to raise the gastric pH, most likely as a result of a decreased dissolution rate of dipyridamole under elevated-pH conditions. These results concur with a study recently published by Kohri *et al.* (17), who investigated the administration of dipyridamole powder to rabbits under high- and low-gastric acidity conditions and found a profound reduction in the bioavailability of dipyridamole in the low-acidity group.

Within the *achlorhydric group,* the maximum concentration was significantly higher in Treatment B than in Treatment A. The average time to reach maximum concentration was three times longer in Treatment A than in Treatment B. The mean AUC(0–36) in the achlorhydrics without pretreat-

Table III. Median Gastric pH (with Interquartile Range in Parentheses) for Each Achlorhydric Subject Within Each 1-hr Period Following the Dose of Dipyridamole for Both Treatment A and Treatment B

	Treatment B (glutamic acid hydrochloride pretreatment)				Treatment A			
Subject	1 hr[a]	2 hr	3 hr	4 hr	1 hr	2 hr	3 hr	4 hr
SB	2.2	4.3	7.1	6.9	6.5	6.8	6.9	7.4
	(1.9–3.4)	(3.8–6.2)	(7.0–7.2)	(6.7–7.1)	(6.4–6.6)	(6.7–6.9)	(6.8–7.0)	(7.2–7.4)
AM	1.4	2.5	3.3	6.5	6.4	7.2	7.2	7.4
	(1.4–1.5)	(2.3–2.7)	(3.0–3.8)	(4.7–7.1)	(6.3–6.6)	(7.1–7.3)	(6.9–7.3)	(7.4–7.5)
RS	1.4	2.4	6.2	6.6	6.6	6.8	6.7	6.9
	(1.2–1.6)	(1.9–4.0)	(6.1–6.3)	(6.5–6.6)	(6.4–6.8)	(6.7–6.8)	(6.4–6.8)	(6.7–7.0)
FSA	1.6	1.9	2.2	3.2	6.6	6.6	6.1	6.2
	(1.5–1.6)	(1.7–2.0)	(2.2–2.4)	(3.1–3.4)	(6.6–6.6)	(6.4–6.6)	(6.0–6.1)	(6.1–6.2)
AW	1.7	6.4	6.6	6.6	6.6	6.5	6.8	6.6
	(1.5–2.2)	(6.2–6.5)	(6.4–6.6)	(6.4–6.7)	(6.4–6.7)	(6.4–6.7)	(6.8–6.9)	(6.5–6.7)
Overall	1.6	2.5	6.2	6.6	6.6	6.8	6.8	6.9
	(1.4–1.8)	(2.3–4.8)	(3.0–6.7)	(5.7–6.7)	(6.5–6.6)	(6.6–6.9)	(6.5–6.9)	(6.5–7.4)

[a] Each 1-hr median represents $n = 240$ pH values and each overall median is the median of the individual subject median.

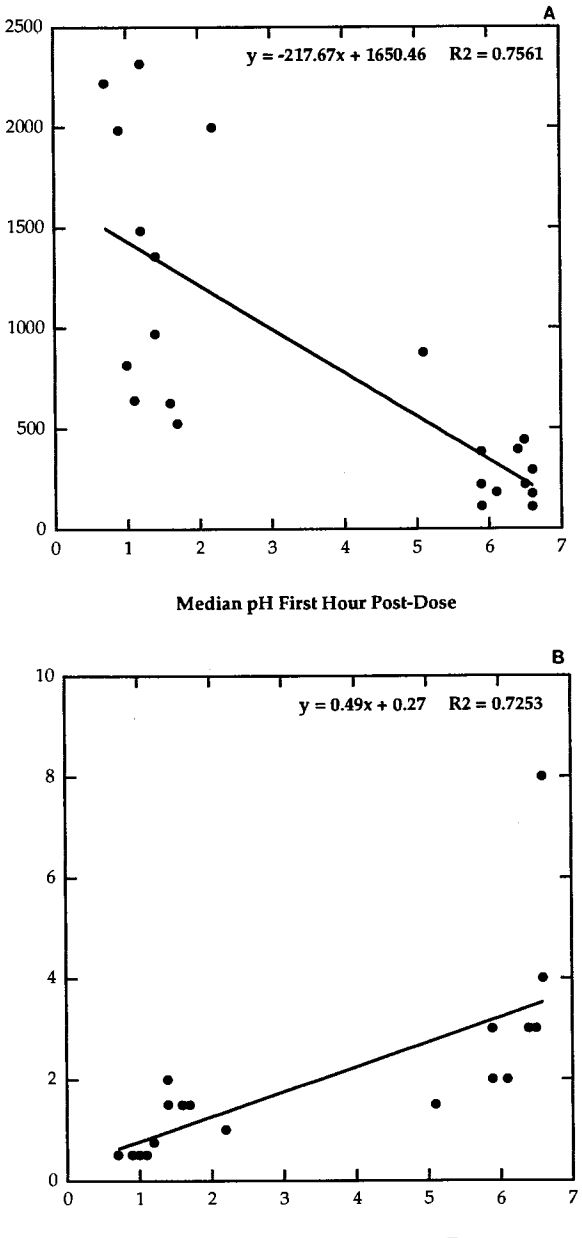

Fig. 3. Correlation between median pH for each subject during the first hour following the single oral dose of dipyridamole and maximum plasma dipyridamole concentration, C_{max} (ng/mL) (A), and time to reach maximum plasma dipyridamole concentration, T_{max} (hr) (B).

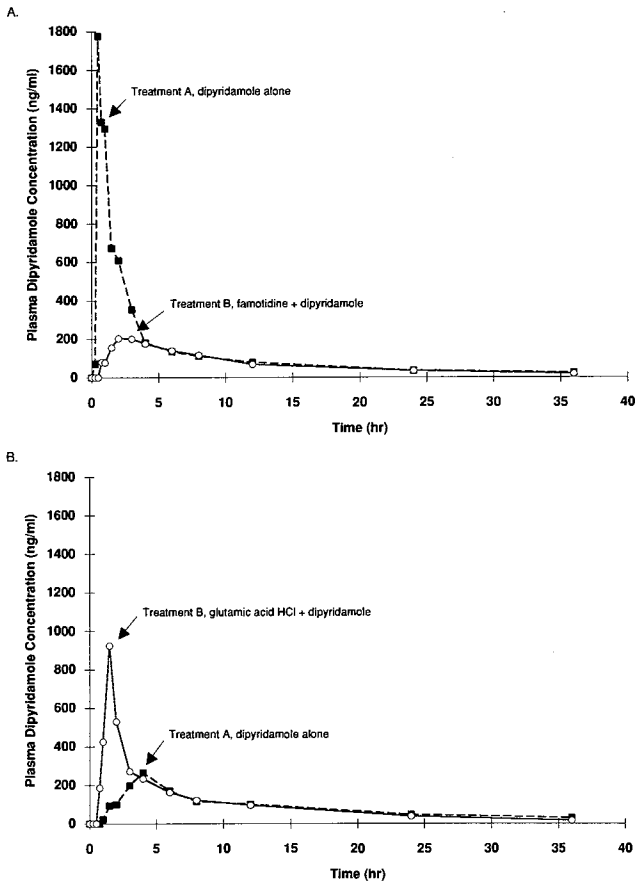

Fig. 4. Plot of median plasma dipyridamole concentration over the 36-hr sampling period for control subjects (A) and achlorhydric subjects (B). Filled squares represent Treatment A (no pretreatment) and open circles represents Treatment B (pretreatment).

ment compared to achlorhydrics after pretreatment with glutamic acid was significantly decreased, by 30%, suggesting that the extent of absorption was compromised under elevated-gastric pH conditions. The mean rate of absorption was significantly decreased, by 74%. These effects on dipyridamole pharmacokinetics most likely result from the inability of dipyridamole to dissolve under elevated-pH conditions.

Achlorhydric Subjects, Treatment A, Versus Control Subjects, Treatment A. The maximum plasma concentration and the absorption rate constant were significantly decreased in the achlorhydric group compared to the control group. The average time to reach maximum plasma concentration was 7.6 times longer in the achlorhydrics. The mean AUC(0–36) was decreased by 24%, but this decrease was not statistically significant. These data indicated that the absorption occurred more slowly and, possibly, to a lesser extent in the achlorhydric subjects studied compared to the controls. The lack of statistically significant differences in AUC(0–36) could be the result of one or more of the following factors: (i) a short absorption phase in comparison to the elimination and distribution phases; (ii) larger intersubject variability in the AUC combined with the small number of subjects (i.e., inadequate power); (iii) a longer gastric emptying time in the achlorhydrics, allowing more time for dissolution to occur than in the controls; and/or (iv) enhancement of the dissolution rate in the small intestine by bile salts.

Control Subjects, Treatment B, Versus Achlorhydric Subjects, Treatment A. The measures of extent of dipyridamole absorption, C_{max} and AUC (0–36), did not differ significantly between control subjects after famotidine pretreatment and achlorhydric subjects with no pretreatment. The measures of rate, namely, T_{max} and k_a, were significantly slower in the achlorhydrics compared to the controls after famotidine pretreatment. These data suggest that pre-

Table IV. Mean (% CV) Dipyridamole Pharmacokinetic Parameters for Control and Achlorhydric Subjects and Results of Statistical Comparisons Between Groups and Treatments (Given as *P* Values)

	Low gastric pH	Elevated gastric pH	Control elevated pH vs control low pH
Controls			
C_{max} (ng/mL)	1577.50 (46)	332.83 (84)	0.0030
AUC(0–36) (hr * ng/mL)	4258 (41)	2692 (67)	0.0570
T_{max} (hr)	0.58 (22)	2.25 (27)	0.0010
K_a (hr^{-1})	47.6 (118)	1.7 (47)	0.0220
			Achlorhydric elevated pH vs achlorhydric low pH
Achlorhydrics			
C_{max} (ng/mL)	1095.20 (55)	282.80 (50)	0.0004
AUC(0–36) (hr * ng/mL)	4613 (32)	3222 (39)	0.0180
T_{max} (hr)	1.50 (24)	4.40 (47)	0.0230
K_a (hr^{-1})	3.1 (35)	0.8 (55)	0.0020
	Achlorhydric low pH vs control low pH	Control elevated pH vs achlorhydric elevated pH	Achlorhydric elevated pH vs control low pH
C_{max} (ng/mL)	0.2700	0.8900	0.0006
AUC(0–36) (hr * ng/mL)	0.6400	0.4100	0.3900
T_{max} (hr)	0.0001	0.0130	0.0001
K_a (hr^{-1})	0.0050	0.0360	0.0002

treatment with famotidine in healthy, control subjects is a reasonable model for the extent of absorption seen in achlorhydria. The failure to simulate the rate of absorption closely appears to be attributable to the slower gastric emptying rate associated with achlorhydria. Because of the difficulty in identifying and recruiting asymptomatic achlorhydric subjects, the famotidine pretreatment method may have some utility in future studies seeking to predict changes in the extent of drug absorption in the achlorhydric patient population.

Achlorhydric Subjects, Treatment B, Versus Control Subjects, Treatment A. Administration of glutamic acid hydrochloride to achlorhydric subjects appeared to compensate for the decreased plasma concentration resulting from the elevated gastric pH but did not totally compensate for differences in rate of absorption between control subjects and achlorhydrics. The C_{max} and AUC(0–36) did not differ significantly between control subjects and achlorhydric subjects who had been pretreated with glutamic acid hydrochloride. The T_{max} and k_a, however, were still significantly slower in the achlorhydric subjects even when the gastric pH was lowered prior to dosing with dipyridamole. The use of glutamic acid hydrochloride would be beneficial for subjects who are known achlorhydrics when taking medications such as dipyridamole, ketoconazole (18), calcium products (19), and other products which are dependent on an acidic gastric pH for adequate absorption. These data suggest that other changes in gastrointestinal physiology, which affect the rate of drug absorption, may occur in achlorhydria.

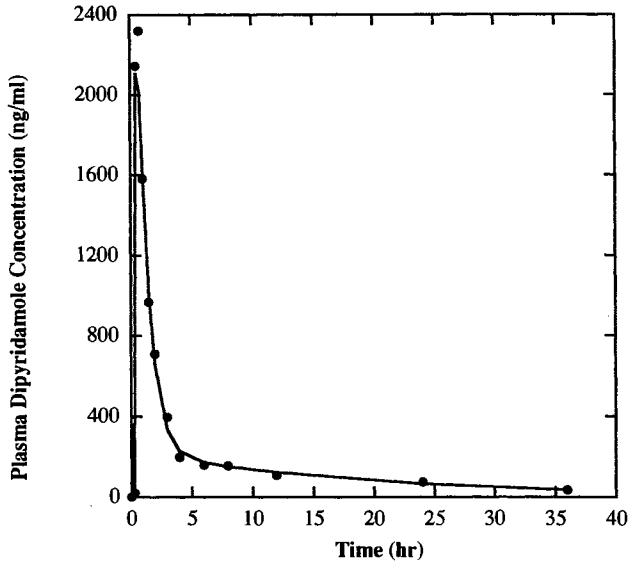

Fig. 5. Reconstruction of the fit of the original data from subject EH, Treatment A, after a single oral dose of 50 mg dipyridamole.

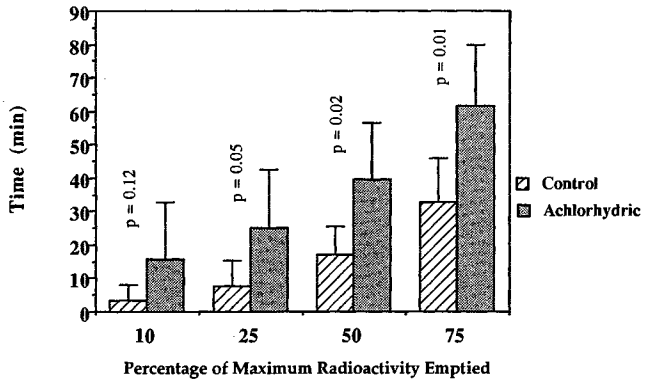

Fig. 6. Pooled means with standard deviation error bars for time to empty 10, 25, 50, and 75% of ^{99m}Technetium radiolabeled orange juice meal within each subject group. *P* values for unpaired *t* tests between control subjects and achlorhydric subjects are given.

Gastric Emptying

Comparison of gastric emptying in our elderly subjects provides strong evidence that gastric emptying of nutrient liquids is slower in elderly with an elevated gastric pH (n = 5) than in elderly with a normal gastric pH (n = 6). On the average, the subjects with an elevated pH emptied more slowly than control subjects, with the time to empty 50% of the liquid meal being more than twice as long as in the subjects with a low gastric pH. These results provide an explanation for the longer time to reach maximum concentration observed in the achlorhydrics.

Adverse Reactions

Adverse effects occurred only when the gastric pH was low and were accompanied by high maximum dipyridamole plasma concentrations.

ACKNOWLEDGMENTS

The authors would like to thank the staff of the Clinical Research Center Staff at The University of Michigan Hospitals, whose cooperative participation was essential to this study.

The study was supported by National Institutes of Health Grant GM 38888 and Clinical Research Center at The University of Michigan Hospital Grant MO1-RR-00042. Tanya Russell was partially supported by Pfizer, Inc. Results from this study were previously presented in part as abstracts at the American Association of Pharmaceutical Scientists Midwest Regional Meeting (1991) and the American College of Gastroenterology Annual Meeting (1991).

REFERENCES

1. T. L. Russell, R. R. Berardi, J. L. Barnett, L. C. Dermentzoglou, K. M. Jarvenpaa, S. P. Schmaltz, and J. B. Dressman. Upper gastrointestinal pH in seventy-nine healthy, elderly, North American men and women. *Pharm. Res.* 10(2):187–196 (1993).
2. W. T. Davies and J. R. Kirkpatrick. Gastric emptying in atrophic gastritis and carcinoma of the stomach. *Scand. J. Gastroenterol.* 6:297 (1971).
3. J. S. Fordtran and J. H. Walsh. Gastric acid secretion rate and buffer content of the stomach after eating. *J. Clin. Invest.* 52:645–657 (1973).
4. *USP-DI Drug Information for the Health Care Professional,* United States Pharmacopeial Convention, Inc., Rockville, MD, 1991, pp. 1171–1173.
5. *Facts and Comparisons,* J. B. Lippincott, St. Louis, MO, 1990, pp. 85a–85b.
6. W. O. Foye. *Principles of Medicinal Chemistry,* Lea and Febiger, Philadelphia, 1981.
7. L. C. Dermentzoglou. *Changes in Upper Gastrointestinal pH with Aging: Implications for Drug Absorption,* Doctoral thesis, University of Michigan, Ann Arbor, 1989.
8. J. B. Dressman, R. R. Berardi, L. C. Dermentzoglou, T. L. Russell, S. P. Schmaltz, J. L. Barnett, and K. M. Jarvenpaa. Upper gastrointestinal (GI) pH in young, healthy men and women. *Pharm. Res.* 7(7):756–761 (1990).
9. M. J. Knapp, R. R. Berardi, J. B. Dressman, J. M. Rider, and P. L. Carver. Modification of gastric pH with oral glutamic acid hydrochloride. *Clin. Pharm.* 10:866–870 (1991).
10. K. M. Wolfram and T. D. Bjornsson. High-performance liquid chromatographic analysis of dipyridamole in plasma and whole blood. *J. Chromatogr.* 183:57–64 (1980).
11. J. G. Wagner and E. Nelson. Percent absorbed time plots derived from blood level and/or urinary excretion data. *J. Pharm. Sci.* 52:610–611 (1963).
12. J. G. Wagner, D. A. Ganes, K. K. Midha, I. Gonzalez-Younes, J. C. Sackellares, L. D. Olsen, M. B. Affrime, and J. E. Patrick. Stepwise determination of multicompartment disposition and absorption parameters from extravascular concentration-time data. Application to mesoridazine, flurbiprofen, flunarizine, labetalol, digoxin and diazepam. *J. Pharmacokin. Biopharm.* 19(4):413–455 (1991).
13. J. C. K. Loo and S. Riegelman. New method for calculating the intrinsic absorption rate of drugs. *J. Pharm. Sci.* 57(6):918–927 (1968).
14. J. G. Wagner. Pharmacokinetic absorption plots from oral data alone or oral/intravenous data and an exact Loo-Riegelman equation. *J. Pharm. Sci.* 72(7):838–842 (1983).
15. J. H. Proost. Wagner's exact Loo-Riegelman equation: The need for a criterion to choose between the linear and logarithmic trapezoidal rule. *J. Pharm. Sci.* 74(7):793–794 (1985).
16. J. L. Fleiss. The crossover study. In *The Design and Analysis of Clinical Experiments,* John Wiley and Sons, New York, 1986, pp. 263–290.
17. N. Kohri, N. Miyata, M. Takahashi, H. Endo, K. Iseki, K. Miyazaki, S. Takechi, and A. Nomura. Evaluation of pH-independent sustained-release granules of dipyridamole by using gastric-acidity-controlled rabbits and human subjects. *Int. J. Pharm.* 81:49–58 (1992).
18. P. Lelawongs, J. A. Barone, J. L. Colaizzi, A. T. M. Hsuan, W. Mechlinski, R. Legendre, and J. Guarnieri. Effect of food and gastric acidity on absorption of orally administered ketoconazole. *Clin. Pharm.* 7:228–235 (1988).
19. R. R. Recker. Calcium absorption and achlorhydria. *N. Engl. J. Med.* 313(2):70–73 (1985).