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Dipyridamole Bioavailability in Subjects With Reduced Gastric Acidity

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Dipyridamole (DP) is an antiplatelet agent that shows decreased oral bioavailability with increased gastric pH that occurs with commonly prescribed antacids. An extended-release (ER) formulation of DP that employs tartaric acid to improve bioavailability of DP in the presence of elevated gastric pH was developed as a combination antiplatelet product with immediate-release aspirin. This crossover-designed study examined the relative bioavailability of DP from the composite product compared to conventional DP tablets during reduced gastric acidity. Gastric pH was increased (pH > 4.0) in 20 healthy subjects with lansoprazole (30 mg/d for 5 days). Dipyridamole systemic exposure over 12 hours was compared after oral administration of a single composite ER capsule (200 mg DP + 25 mg aspirin) versus two 100-mg conven-

tional DP tablets given 6 hours apart combined with 81 mg aspirin. DP relative bioavailability was reduced 53% with conventional tablets compared to the composite buffered ER capsule in reduced gastric acid conditions. Peak DP plasma concentrations were 57% lower with immediate-release tablets compared to the composite formulation with high stomach pH. Substituting generic DP plus low-dose aspirin may be less effective than the buffered DP composite product in patients with concomitant antacid therapies.

Keywords: Dipyridamole; elderly; gastric pH; stroke prevention; antiplatelet agents

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Dipyridamole (DP) and aspirin have antithrombotic pharmacological properties that act through different noncompeting mechanisms. Aspirin acts as an irreversible cyclooxygenase-1 inhibitor, while DP appears to act through a number of different antithrombotic systems such as cyclic guanyl-dependent nucleotide phosphodiesterase inhibition to increase platelet cGMP, scavenging of oxy- as well as peroxyradicals, and blocking uptake of adenosine.^{1,2} Pharmacokinetic studies in healthy volunteers found that plasma profiles for aspirin and DP were not changed when the drugs were given together, which supported combination

therapy.^{3,4} However, several clinical trials in patients with cardiovascular disease failed to show an additive efficacy of DP with high-dose aspirin compared to aspirin alone. In contrast, a large clinical trial that used a buffered extended-release DP (ER-DP) combined in a capsule with immediate-release aspirin showed additive effects of DP over aspirin alone in preventing stroke.^{5,6}

Pharmaceutically, DP is a poorly soluble weak base that shows pH-dependent absorption. Studies in healthy elderly patients showed that increasing gastric pH with the commonly used H₂ receptor antagonist famotidine dramatically decreased DP absorption.⁷ To mitigate the effects of gastric pH on absorption and facilitate combination antiplatelet treatment, a composite formulation was developed that combined immediate-release low-dose aspirin with buffered extended-release DP encapsulating a tartaric acid core, ER-DP. Since sustained or ER preparations depend on continued drug absorption that occurs considerably after gastric contents move into the intestine, absorption needs to be ensured in the high-pH environment of the intestine. Standard enteric coatings are not effective for compounds that are not absorbed at neutral or basic pH. The design of the composite formulation consid-

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ered that an ER formulation of DP would need to provide a sufficiently acidic local milieu within the basic pH environment of the intestine to promote absorption.

A study was designed to examine the effects of increased gastric pH on DP bioavailability from the composite aspirin plus buffered ER-DP formulation that showed additive effects of the antiplatelet agents.⁸ Bioavailability of DP from the marketed composite ER formulation was compared with an equivalent dose of immediate-release DP coadministered with low-dose aspirin in subjects with an elevated gastric pH induced by pretreatment with the widely used proton pump inhibitor lansoprazole. The dosing regimen was chosen to approximate doses of DP and aspirin that are commercially available and might be substituted for the marketed composite ER capsule formulation. Lansoprazole is widely used in the elderly population and was selected as a representative antacid that is likely to be coadministered in patients prescribed antiplatelet therapy.

METHODS

Subjects

The study population consisted of 24 healthy Caucasian subjects, 12 women and 12 men. The mean and range of the demographic variables were age 52 (42-64) years, weight 75.1 (54.6-99.9) kg, and height 170.1 (151-191) cm. Four female subjects were not considered evaluable because they had vomited within 6 hours of receiving the study drug at either period 1 or period 2 of the crossover design. Therefore, data analysis was performed on a sample consisting of 12 men and 8 women.

Before participating in any study-related procedures, each subject provided written informed consent, in conformance with the principles enunciated in the Declaration of Helsinki. The study was conducted at a phase I facility operated by MDS Pharma Services in Vaudreuil, Canada, and was approved by the local Institutional Review Board. Subjects were pretreated with the proton pump inhibitor lansoprazole (30 mg daily for 5 days) prior to randomization to treatment groups. To qualify for randomization, a subject had to have reduced stomach acidity as measured by a nasogastric probe (Digrapper, Medtronic, Minneapolis, Minn) prior to being dosed with study medication (stomach pH >4.0 on 3 consecutive measurements separated by at least 5 minutes). The same qualifying criterion was required for the subject to receive his or her second treatment regimen with study medication. All subjects pretreated with lansoprazole qualified for randomization to study treatment, indicating that the pre-

treatment with lansoprazole was highly effective in elevating stomach pH to greater than 4.0.

Study Design and Treatments

This study was a randomized 2-way crossover open-label trial in subjects with an elevated gastric pH (>4.0) resulting from 5 days of pretreatment with a proton pump inhibitor (lansoprazole). The study was designed to compare the pharmacokinetics of a marketed composite ER-DP formulation (Aggrenox, 200 mg tartaric acid buffered ER DP and 25 mg immediate-release aspirin; Boehringer Ingelheim) versus a comparable dose of commercially available immediate-release DP coadministered with low-dose aspirin (100 mg DP plus 81 mg delayed-release aspirin followed 6 hours later by a second dose of 100 mg DP) in subjects with low gastric acid. Fourteen days separated the 2 treatment periods, and each period was balanced with an equal number of subjects receiving each treatment.

Subjects were pretreated with the proton pump inhibitor lansoprazole. Each subject was administered a single oral dose of one 30-mg lansoprazole delayed-release capsule (Prevacid; TAP Pharmaceuticals Inc, Lake Forest, Ill) taken with 240 mL of water at 98, 74, 50, 26, and 2 hours prior to receiving either DP treatment.

Subjects were randomized to 1 of 2 treatment sequences. Subjects received either the composite ER-DP capsule in period 1 and DP plus aspirin in period 2, or vice versa. For treatment A, a single composite ER capsule was administered as an oral dose with 240 mL water at 9:00 AM. For treatment B, a single oral dose of 2 immediate-release DP 50-mg tablets (Barr Laboratories, Inc, Pomona, NY) plus 1 low-dose delayed-release aspirin tablet (Bayer aspirin, 81 mg) was administered with 240 mL of water at 9:00 AM. Six hours later, a second oral dose of two DP 50-mg tablets was administered in treatment B. Subjects fasted on the days of study drug administration until about 2 hours after being dosed at 9:00 AM. All subjects were served the same meals and snacks beginning the evening before each study drug administration and during the day of each study drug administration. On the day of dosing, all subjects were served standardized meals that included a light snack 130 minutes postdose, a lunch at 1:00 PM, and a snack 6.5 hours after the morning dose. To minimize alteration of stomach pH, tomato juice and fruit juices were not permitted.

Study Procedures

On study days 1 and 14, subjects were awakened at about 5:30 AM, and the stomach pH measurement de-

vice (Digitrapper) was inserted via the nasogastric route. Lansoprazole 30 mg was administered at about 7:00 AM. At about 7:30 AM, a venous catheter was inserted to allow for repeated blood sampling. At about 8:30 AM, the pH of the gastric juice was measured to determine if the subject qualified for continuation in the study.

Safety assessments included a physical examination at screening and poststudy, a 12-lead electrocardiogram at screening, and recording of vital signs at screening and on study days -1, 1, 2, 14, 15, 16, and 17. Clinical laboratory assessments were carried out at screening and on study days -1, 2, 14, and 16. Subjects were monitored for adverse events throughout the study.

Blood samples, each of 5 mL, were drawn by an indwelling catheter or venipuncture immediately prior to dose administration and 0.50, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5.92, 8, 9, 10, 12, 14, 24, and 48 hours after each dose administration. Blood was equilibrated with sodium heparin by gentle rocking, cooled in ice water, and centrifuged at >2000 rpm at +4°C within 30 minutes of collection for approximately 10 minutes to produce plasma. Plasma was frozen as soon as possible at ≤-15°C and stored until analysis.

Pharmacokinetic Calculations

Plasma DP concentrations were measured using a validated online extraction high-performance liquid chromatography fluorescence method that included an internal standard with a limit of quantification of 30 ng/mL as previously described.⁹ Lansoprazole did not interfere with chromatography of DP. Areas under the plasma DP concentration-time profiles through 12 and 48 hours (AUC_{0-12} and AUC_{0-48}) were calculated using a linear trapezoidal algorithm. Observed maximum concentrations were used directly from the data without modeling. Terminal half-lives following oral administration of the composite DP ER capsule were determined using WinNonlin Professional version 3.1 (Pharsight Corporation, Palo Alto, Calif) after identifying the log-linear portion of the terminal elimination phase using uniform weighting for each individual. Half-lives could not be estimated for the immediate-release tablet formulation given at a 6-hour interval due to the irregular shapes of the profiles.

A sample size of 20 evaluable subjects was chosen to provide approximately 90% power to demonstrate ≥20% inferiority of the test drug versus reference drug at the 5% 2-sided significance level, assuming that the residual standard deviation of $\log(AUC_{0-12})$ was 0.2. The analysis of variance model (SAS version 8, Cary,

NC) included sequence, subject nested within sequence, period, and treatment. To test whether the test drug (immediate release) was absorbed as well as the reference drug (composite ER capsule), a 95% confidence interval for the test/reference ratio of the geometric means was calculated. Inferior absorption of the test drug was inferred if the confidence interval fell entirely below 1.

RESULTS

All 24 randomized subjects completed the study protocol. However, the absorption process was considered compromised in 4 female volunteers who vomited after administration of study medication. Therefore, data from these subjects were not included in comparison between treatments.

Mean plasma profiles for the 20 evaluable subjects after each treatment are shown in Figure 1. DP bioavailability was clearly dampened with the immediate-release generic DP compared to the composite ER formulation in subjects with elevated gastric pH. Corresponding mean pharmacokinetic parameters are summarized in Table I for the 2 treatments. The extent of DP exposure that is reflected by the AUC_{0-12} with the immediate-release formulation was only 50% of the mean value after the composite buffered ER formulation. Total DP exposure was estimated from AUC_{0-48} values that were consistently higher from the buffered ER formulation 200-mg dose compared to the same dose given at the recommended 6-hour dosing interval as conventional tablets. The ratio of AUC_{0-48} values for conventional DP tablets compared to the buffered ER formulation ranged from 0.65 to 0.88 for the 20 individuals. Peak DP concentrations (C_{max}) measured with the immediate-release formulation were less than half those measured after the composite ER formulation, with a geometric mean ratio of 43% for individuals.

Table I lists the mean ratios of the immediate-release formulation (test) versus the composite buffered ER (reference) product along with the 95% confidence interval for the ratio of parameters calculated for each of the 20 subjects in the crossover study. The difference between treatments was statistically significant, with P values less than .001 for all parameters except the time to peak concentration (t_{max}). The entire 95% confidence interval for the ratios was less than 1.0 for all parameters except t_{max} and trough concentrations measured at the end of the dosing interval (C_{12}). The concentration of DP at 12 hours, which is the end of the dosing interval for the composite ER formulation, was significantly higher for immediate-release DP.

Table I Pharmacokinetic Parameters for Dipyridamole in Subjects With Low Gastric Acidity (pH > 4.0) After a Single Composite Capsule Containing 200 mg Extended-Release Dipyridamole, Tartaric Acid, and 25 mg Aspirin or After 2 Immediate-Release Dipyridamole 100-mg Doses That Were Separated by 6 Hours Combined With an 81-mg Aspirin Tablet Given With the First Dose

Parameter	Composite Extended-Release Dipyridamole Capsule With Aspirin	Immediate-Release Dipyridamole Plus Aspirin	Ratio Immediate Release Versus Buffered Extended-Release Composite	95% Confidence Interval
AUC ₀₋₁₂ , ng•h/mL				
Mean	7883	3943	0.50 ^a	0.41, 0.59
Range	3976-12 341	994-7709		
AUC ₀₋₄₈ , ng•h/mL				
Mean	11 896	9051	0.76 ^a	0.65, 0.88
Range	4753-21 188	1389-25 159		
C _{max} , ng/mL				
Mean	1842	848	0.46 ^a	0.31, 0.61
Range	1000-3302	202-1643		
C ₁₂ , ng/mL				
Mean	237	362	1.53 ^a	1.19, 1.87
Range	66-621	78-909		
t _{max} , h				
Mean	2.2	2.8	1.28	0.86, 1.69
Range	1.5-3.0	0.75-8.0		

a. Immediate release significantly different than extended-release composite, $P < .01$.

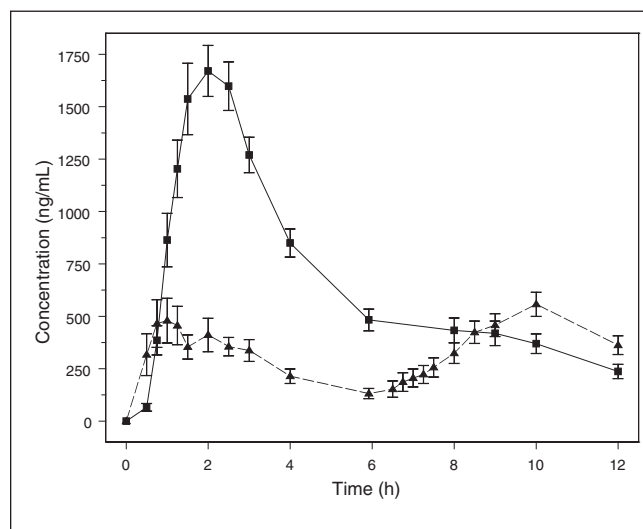


Figure 1. Mean plasma dipyridamole profiles in 20 subjects with elevated gastric pH (> 4.0) who were given a composite capsule containing 200 mg dipyridamole buffered extended-release and 25 mg immediate-release aspirin (squares, solid line) or given an immediate release dipyridamole 100-mg dose at 0 and 6 hours, where the first dose was coadministered with an 81-mg delayed-release aspirin tablet (triangles, broken line). Error bars represent the SEM for 20 evaluable subjects who participated in the crossover study.

DISCUSSION

Results of this study showed that DP bioavailability from a commercially available ER plus low-dose aspirin combination product is approximately twice the bioavailability from immediate-release DP tablets for subjects with increased gastric pH. In this study, DP profiles under conditions of increased gastric pH were remarkably similar to previous pharmacokinetic evaluation of the tartaric acid buffered ER-DP composite formulation in controls.¹⁰ Under steady-state conditions, peak plasma levels of DP were achieved 2 hours (range, 1-6 hours) after administration of a daily dose of 400 mg (given as 200 mg twice daily). The peak plasma concentration in steady-state dosing was 2.0 $\mu\text{g/mL}$ (1.0-4.0 $\mu\text{g/mL}$), with trough concentrations that were approximately 0.5 $\mu\text{g/mL}$ (0.2-1.0 $\mu\text{g/mL}$).¹⁰

DP and aspirin formulations selected for comparison in this study were based on available marketed products in the United States that might be considered as an alternative to the brand-composite ER capsule. Low-dose aspirin is available without prescription as 81-mg delayed-release tablets, while DP is available as 50-mg immediate-release tablets. Since the pharmaco-

kinetics of aspirin and DP were shown to be unaltered by each other in the range of doses used in this study, commercially available formulations of aspirin and DP were chosen. A dosing schedule was designed to administer an equal amount of DP (200 mg).

Results from this study in subjects with depressed gastric acid are in marked contrast to an early bioavailability study comparing immediate-release and ER-DP formulations.⁹ In volunteers with normal gastric acidity, peak to trough fluctuation was similar at steady state with a 200-mg ER formulation administered twice daily compared to a 100-mg immediate-release formulation administered every 6 hours.⁹ Interestingly, DP profiles were remarkably similar for the 200-mg buffered ER composite capsule evaluated in the present study in subjects with elevated gastric pH compared with the early report examining the same dose given as an ER formulation in controls. Peak DP concentrations were approximately 1800 to 2300 ng/mL in both studies after the ER formulations.

Prescribing information for many combination therapies and especially newer agents normally includes interactions for products that are likely to be coadministered. Accordingly, development for new medications requires assessment for drug interactions as well as recommended dosing guidelines for special user populations, including the elderly. Potential drug interactions that are associated with enzyme-mediated metabolism have been successfully screened using *in vitro* and *in vivo* probe approaches.¹¹ However, identifying clinically significant drug and food interactions often remains a major challenge in elderly patients with multiple chronic medical conditions. Therapy with H₂-receptor blockers and proton pump inhibitors to manage gastrointestinal disorders is common in the general population as well as among elderly subjects who are more likely to be treated with antiplatelet medications. Chronic treatment with proton pump inhibitors is common, with lansoprazole among the 10 most prescribed drugs in the United States.¹²

Absorption of pH-dependent drugs and nutrients represents an important but often underrecognized pharmacokinetic topic. The effects of gastric pH on ketoconazole and itraconazole are generally included in reviews that note reduced bioavailability by drugs that increase gastric pH, such as H₂ receptor antagonists, proton pump inhibitors, sucralfate, and didanosine.¹³ Ketoconazole prescribing information recommends dissolving tablets in acidic solutions for patients with achlorhydria. Early studies examining tetracycline and ampicillin absorption led to formulations that were less dependent on gastric pH.^{14,15} A

pharmaceutical approach to improve pH-dependent absorption was also employed for didanosine, which uses a high-pH buffer included in the tablet formulation. Cautions note that drugs such as ketoconazole, itraconazole, and drugs that can be chelated by the ions of the buffer (quinolones and tetracyclines) should be administered 2 hours before or 6 hours after didanosine. Coadministration of other antiviral agents with the antacid Maalox results in decreased drug absorption that is considered clinically significant.¹⁶

Although studies showed no substantive effect of achlorhydria or H₂ antagonists on drug absorption,^{17,18} several literature reports indicate that a low gastric pH is required for DP absorption.^{7,19} However, the clinical significance of reduced absorption is not well characterized, and interactions with antacids generally are not listed in prescribing information for standard DP formulations. Equivocal results of clinical trials that evaluated the efficacy of DP in combination with aspirin may be explained in part by impaired absorption of the nonbuffered formulation. The striking difference in outcome of a large stroke-prevention study (European Stroke Prevention Study II [ESPS-2]) contrasts with previous reports indicating little added benefit of DP compared to aspirin alone. The ESPS-2 study, which used a buffered formulation, showed additive effects of aspirin and DP to reduce the risk of stroke 37% compared to placebo and 23% when compared to aspirin alone in 6600 patients at risk for stroke.³ In contrast to decreased DP that would be expected from age-associated increases in gastric pH, pharmacokinetic data from the ESPS-2 trial indicated that elderly subjects had higher DP exposure compared to younger study subjects.¹⁰ The increased AUC in elderly subjects was attributed to decreased DP clearance.

In conclusion, DP bioavailability from the composite buffered ER-DP formulation combined with low-dose aspirin was not diminished with high gastric pH in contrast to nonbuffered tablets. Since use of antacids is widespread among patients at risk for stroke, it is possible that improved absorption with the buffered ER-DP formulation may be associated with efficacy in preventing stroke.

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