

Magnitude and Duration of Elevated Gastric pH in Patients Infected with Human Immunodeficiency Virus After Administration of Chewable, Dispersible, Buffered Didanosine Tablets

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Study Objectives. To test the hypothesis that gastric pH would be elevated above pH 3.0 for at least 2 hours after administration of chewable, dispersible, buffered didanosine tablets. Doses tested were 200 mg (two 100-mg tablets) and 400 mg (two 200-mg tablets). We also sought to compare these doses with regard to maximum gastric pH (pH_{max}), time to pH_{max} ($T_{\text{pH-max}}$), time that gastric pH exceeds 3.0 ($T_{\text{pH}>3}$), and area under the gastric pH versus time curve for pH greater than 3.0 ($\text{AUC}_{\text{T}>\text{pH } 3}$).

Design. Prospective, parallel-group, dose-comparison, gastric pH study.

Setting. General Clinical Research Center, University of Michigan Hospitals, Ann Arbor, Michigan.

Patients. Nineteen patients infected with human immunodeficiency virus, aged 30–62 years, and receiving long-term didanosine therapy.

Intervention. Patients underwent continuous gastric pH monitoring, using the Heidelberg capsule radiotelemetric pH monitoring device. After documentation of a fasting baseline gastric pH below 3.0, patients were given 180 ml of water (control phase), and gastric pH was allowed to return to baseline. After administration of a single, oral dose of didanosine 200 mg or 400 mg with 180 ml of water, gastric pH was recorded until pH remained below 3.0 for 10 minutes.

Measurements and Main Results. A mean pH_{max} of 8.6 (range 6.3–9.5) was achieved with a $T_{\text{pH-max}}$ of 4.1 minutes (range 1–12.0 min). Mean $T_{\text{pH}>3}$ was 24.9 minutes (range 15–55 min), with an $\text{AUC}_{\text{T}>\text{pH } 3}$ of 2.6 $\text{pH}\cdot\text{min}^{-1}$ (range 1.2–6.9 $\text{pH}\cdot\text{min}^{-1}$). The two doses of didanosine tested did not differ significantly in mean gastric pH parameters.

Conclusions. After administration of chewable, dispersible, buffered didanosine tablets, 200 or 400 mg, the mean duration of elevated gastric pH ($T_{\text{pH}>3}$) was less than 30 minutes, with a range of 15–55 minutes. Characterization of the magnitude and duration of elevated gastric pH may allow for earlier administration of other pH-sensitive drugs. The short duration of elevated gastric pH may help explain the wide variability in didanosine bioavailability observed clinically.

Key Words: didanosine, ddI, buffered didanosine tablets, gastric pH, HIV. (Pharmacotherapy 2004;24(11):1539–1545)

Didanosine is a nucleoside analogue reverse transcriptase inhibitor recommended as a

component of combination antiretroviral therapy for patients infected with the human immuno-

deficiency virus (HIV). When administered with other antiretroviral agents, the drug has beneficial effects on key prognostic values and improves clinical outcomes.¹

Didanosine is susceptible to acid hydrolysis when administered orally; an estimated 10% of didanosine is degraded every 2 minutes at pH 3.0 or below.² Another limitation of didanosine is its poor solubility at low pH values ($pK_a = 9.1$). As a result, one oral dosage formulation contains buffers to prevent degradation of drug in the gastrointestinal tract and improve its solubility.

One commercially available formulation of didanosine is a chewable, dispersible tablet containing calcium carbonate and magnesium hydroxide buffers. In order to supply adequate buffering capacity, each dose of didanosine requires administration of two tablets. Didanosine is usually dosed either as 200 mg (two 100-mg tablets) twice/day or 400 mg (two 200-mg tablets) once/day. In general, didanosine is rapidly absorbed after oral administration, with maximum plasma concentrations occurring in 0.25–1.5 hours. The oral bioavailability of chewable, dispersible, buffered didanosine tablets is $42 \pm 12\%$; however, wide interpatient variability is observed, possibly resulting from variations in gastric degradation, gastrointestinal motility, and transit time.^{1,3}

The manufacturer of the drug recommends the twice-daily dosing regimen because more evidence supports the effectiveness of this dosing frequency compared with the once-daily regimen. However, an enteric-coated (without buffers) formulation of didanosine that is administered once/day recently has been marketed in the United States and Europe. This formulation, as well as once-daily dosing of the chewable,

dispersible, buffered tablets, should be considered only for patients whose clinical management requires once-daily dosing (due to drug interactions, compliance, etc.). Only limited data support the long-term durability of response with a once-daily dosing regimen of didanosine.⁴ Yet, in day-to-day clinical practice, most patients receive the enteric-coated formulation due to its improved tolerance, the convenience of once-daily administration, and the ability to avoid many pH- and cation-based drug-drug interactions. The results of this study, however, may help dispel many of the assumptions regarding administration of concomitant drugs in the presence of gastric pH changes after ingestion of chewable, dispersible, buffered didanosine tablets. In addition, whereas the enteric-coated formulation is approved for clinical use in the United States and Europe, the chewable, dispersible, buffered tablet formulation is used in less developed countries.

The gastric neutralizing effect of chewable, dispersible, buffered didanosine tablets has the potential to interfere with absorption of drugs that require low gastric pH for dissolution and absorption. To our knowledge, no published studies have characterized the magnitude or duration of change in gastric pH resulting from the buffering activity of chewable, dispersible, buffered didanosine tablets. As a result, drug interactions are a frequent concern when managing complex drug regimens containing didanosine, and simultaneous administration of didanosine with food or drugs that are affected by the buffering effect of didanosine is not recommended.

The objective of our study was to characterize the magnitude and duration of elevated gastric pH in adult patients with HIV infection who received chewable, dispersible, buffered didanosine tablets. We hypothesized that baseline gastric pH would be increased above pH 3.0 for a minimum of 2 hours after administration of a single oral dose of didanosine 200 mg (two 100-mg tablets) or 400 mg (two 200-mg tablets). Since the amount of buffer contained in the chewable, dispersible, buffered tablets is the same regardless of tablet strength, we did not anticipate any differences in magnitude or duration of pH change between the two doses.

Methods

Patient Selection

Nineteen patients with HIV infection were recruited from HIV clinic populations at the

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University of Michigan Health System and the Veterans Affairs Ann Arbor Healthcare System. Patients were 14 Caucasian and five African-American men, aged 30–62 years (mean age 44 yrs), who were receiving chewable, dispersible, buffered didanosine tablets as a component of their antiretroviral therapy. We excluded patients who had a history of dysphagia or swallowing disorders, or a history of gastrointestinal pathology that could interfere with gastric pH (e.g., chronic diarrhea, recent gastrointestinal surgery, pancreatitis). We also excluded those patients taking drugs that affect gastric pH or gastric emptying (histamine₂-receptor antagonists, proton pump inhibitors, or metoclopramide).

Study Agent

Didanosine (Videx; Bristol-Myers Squibb, Princeton, NJ) was purchased from the hospital pharmacy of the University of Michigan as chewable, dispersible, buffered tablets for oral administration in strengths of 100 mg and 200 mg. Tablets were buffered with calcium carbonate and magnesium hydroxide. A single lot of didanosine was used for the entire study.

Study Design and Procedure

The study protocol was approved by institutional review boards at the Veterans Affairs Ann Arbor Healthcare System and the University of Michigan Health System, as well as the General Clinical Research Center (GCRC) at the University of Michigan Hospitals. All studies were performed at the GCRC. Written informed consent was obtained from the patients before their enrollment in the study.

Patients were instructed to fast for at least 8 hours before arriving in the morning at the GCRC, as well as for the duration of the study period. All prescription and nonprescription drugs, herbal and nutritional supplements, and beverages that could alter gastric pH or gastric motility (e.g., citrus juices, caffeinated and carbonated beverages) were withheld starting the night before the morning of the study and for the duration of gastric pH monitoring. Subjects received oral didanosine doses of either 200 mg (two 100-mg tablets) or 400 mg (two 200-mg tablets). Subjects were instructed to thoroughly chew and swallow two tablets, then rinse their mouth with 180 ml of water, and swallow. If subjects preferred, they could disperse the two tablets in 120 ml of water and swallow, rinsing

with the remaining 60 ml of water.

The Heidelberg capsule pH monitoring system (Heidelberg International, Inc., Blairsville, GA) was employed for continuous gastric pH monitoring. The Heidelberg capsule is a small, consumable, nondigestible, radiotelemetric unit that measures hydrogen ion concentrations in the gastrointestinal tract. The Heidelberg capsule was activated by immersion in a solution of 0.9% sodium chloride and calibrated with standard pH solutions at pH 1.0 and pH 7.0 at 35°C. Once activated, the device transmits a continuous radio signal to an antenna located in a belt worn by the subject. The output of the device is a graph of pH versus time.

The Heidelberg capsule was administered with 180 ml of water, and baseline gastric pH was obtained for each patient. The Heidelberg capsule was maintained in the stomach at approximately 50 cm by tethering the capsule with silk surgical thread and taping the tethered thread to the patient's cheek. The position of the capsule in the stomach was indicated by a combination of tether length (measured for each patient) and continuous monitoring of gastric pH (approximately $\text{pH} \leq 3.0$). Capsule placement was verified by abdominal radiograph in patients who had an elevated gastric pH ($\text{pH} > 3.0$) at baseline. After verifying capsule placement, patients whose baseline pH exceeded 3.0 were excluded from further participation.

Once baseline pH was established and was stable for 10 minutes, the patient consumed 180 ml of water, which served as a control phase, as ingestion of water can elevate gastric pH. Gastric pH was monitored continuously until it returned to baseline and was stable for 10 minutes. Once the control phase was completed, the patient received two tablets of didanosine either 100 mg (for a total dose of 200 mg) or 200 mg (for a total dose of 400 mg). Each patient's gastric pH was continuously monitored until it returned to baseline (or was reduced to < 3.0) and remained stable for 10 minutes. The capsule was recovered at the end of the study and recalibrated to ensure accuracy.

If the investigator suspected that the capsule had entered the small intestine, which often is marked by tugging on the tether along with a rapid, unreversed elevation of pH, the tether was pulled back in an attempt to return the capsule to the stomach. In the event that pulling back on the tether failed to relocate the capsule, an abdominal radiograph was performed to verify the position of the capsule.

Table 1. Gastric pH Parameters After Oral Administration of Didanosine

Measurement	Didanosine Dose		p Value	Overall (N=18)
	200 mg (n=9)	400 mg (n=9)		
Baseline gastric pH				
Mean	1.8	2.2	0.04	2.0
Range	1.2–2.4	1.6–2.6		1.2–2.6
pH _{max}				
Mean	8.7	8.6	0.80	8.6
Range	7–9.5	6.3–9.5		6.3–9.5
T _{pH-max} (min)				
Mean	4.2	4.0	0.88	4.1
Range	2.0–10.0	1.0–12.0		1.0–12.0
T _{pH>3} (min)				
Mean	22.7	27.2	0.37	24.9
Range	15.0–36.0	15.0–55.0		15.0–55.0
AUC _{T>pH 3} (pH•min ⁻¹)				
Mean	2.4	2.8	0.53	2.6
Range	1.2–4.0	1.5–6.9		1.2–6.9

pH_{max} = maximum pH; T_{pH-max} = time to maximum pH; T_{pH>3} = time zero (administration of didanosine) to the time of the last pH > 3.0; AUC_{T>pH 3} = area under the pH-time curve for pH > 3.0.

Data Analysis

A plot of gastric pH versus time was made for each patient. Maximum gastric pH (pH_{max}) and time to maximum pH (T_{pH>3}) were estimated by visual inspection of the data. Area under the pH-time curve from time zero (administration of didanosine) to the time of the last pH greater than 3.0 (AUC_{T>pH 3}) was calculated using the linear trapezoidal rule. We determined minimum, mean, and maximum time in which pH exceeded 3.0 for each patient.

Statistical Analysis

A nonpaired *t* test comparing the results of the two dosing groups (200 mg vs 400 mg) was performed using Statview 5.0.1 (SAS Institute Inc., Cary, NC). A *p* value of 0.05 or less was considered statistically significant. Our goal was to measure a difference in pH of 2 units with a standard error of 0.5 or confidence interval of ± 1. Earlier studies of gastric pH in patients with HIV infection showed a standard deviation of approximately 1.5.⁵⁻⁷ Based on this information, we determined that a sample size of nine patients in each group was needed to yield an 80% chance of detecting a pH difference of 2 units. In addition, a regression model was performed using SAS for Windows, version 8.02 (SAS Institute Inc.) to detect any differences in gastric pH parameters when controlling for baseline gastric pH.

Results

Eighteen of 19 enrolled patients completed the study, yielding nine evaluable patients in each group. One (5.3%) of the 19 patients was excluded after demonstrating an elevated fasting baseline gastric pH (> 3) that was consistent with decreased acid secretion, as has been reported in patients with HIV and acquired immunodeficiency syndrome.⁸⁻¹² In this patient, the position of the Heidelberg capsule in the stomach was verified by abdominal radiograph, and pH calibration of the capsule was validated before and after placement. All 19 patients tolerated the Heidelberg capsule without complaints, and no clinically significant adverse events were noted during the conduct of the study. At the end of each subject's study period the Heidelberg capsule was retrieved and recalibrated with 100% accuracy.

Table 1 summarizes overall gastric pH parameters for the 18 patients and for the two dosing groups separately. Gastric pH versus time profiles for all 18 patients during baseline monitoring and after administration of 200-mg or 400-mg oral doses of chewable, dispersible, buffered didanosine tablets are presented in Figure 1. Mean baseline gastric pH values were statistically different between the 200-mg and 400-mg groups: 1.8 and 2.2, respectively (*p*=0.04). Because a statistical difference in baseline gastric pH was noted, a statistical regression model was used to determine if any differences existed in pH parameters when

controlling for baseline gastric pH. No such differences were detected ($p>0.05$).

After ingestion of 180 ml of water during the control phase, the magnitude of pH change was minimal and was similar in each group: 0.7 for both dose groups. The 200-mg and 400-mg groups showed similar results for pH_{max} (8.7 and 8.6), T_{pH-max} (4.2 min and 4.0 min), and $AUC_{T>pH\ 3}$ (2.4 $pH\cdot min^{-1}$ and 2.8 $pH\cdot min^{-1}$), respectively. Mean values for the time that gastric pH exceeds 3.0 ($T_{pH>3}$) were similar between the 200-mg and 400-mg groups (22.7 and 27.2 min, respectively) and demonstrated a wide range of variability, from 15–55 minutes.

Discussion

The advent of highly active antiretroviral therapy (HAART) has significantly reduced the morbidity and mortality associated with HIV infection. However, HAART regimens are often complex to manage in terms of the number of drugs, drug interactions, and adverse effects. Often, patients receiving HAART are taking drugs

for comorbid conditions, as well as drugs for prophylaxis and treatment of opportunistic infections. Consequently, drug scheduling and adherence are likely to be problematic for clinicians and patients. Coadministration of chewable, dispersible, buffered didanosine tablets with certain other drugs has the potential to result in clinically significant drug-drug interactions due to chelation interactions or alterations of gastric pH. For example, the calcium and magnesium cations contained in the buffer formulation of didanosine result in major chelation interactions with several types of drugs, including quinolone antibiotics.^{13, 14} Currently, the manufacturer recommends that didanosine be administered at least 2 hours after or 6 hours before a quinolone antibiotic, due to decreased quinolone plasma concentrations during concomitant administration with didanosine. These buffers are also responsible for drug interactions due to elevations in gastric pH, as can occur when didanosine is administered orally with indinavir,¹⁵ itraconazole,¹⁶ ketoconazole,¹⁷

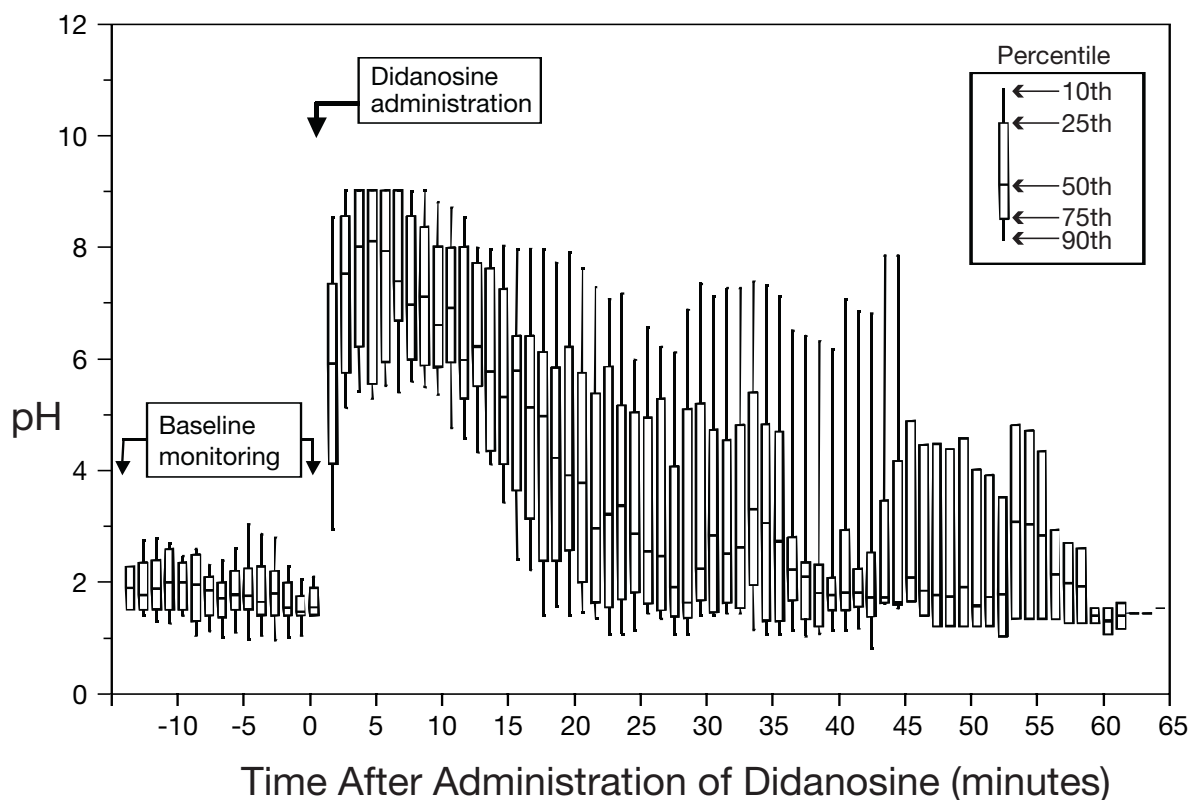


Figure 1. Baseline gastric pH values in 18 patients infected with human immunodeficiency virus and their respective pH values after administration of oral didanosine 200 mg or 400 mg in the form of chewable, dispersible, buffered tablets. Data are presented in box-whisker plots; horizontal lines within each box display the 25th, 50th, and 75th percentiles, and vertical lines display the 10th and 90th percentiles of gastric pH at each time point.

delavirdine,⁸ and atevirdine.¹⁸ In addition, didanosine must be ingested on an empty stomach, as its bioavailability is decreased by approximately 50% when taken with food.^{1, 19, 20}

The primary objective of our study was to characterize the magnitude and duration of elevated gastric pH in adult patients with HIV infection after administration of chewable, dispersible, buffered didanosine tablets. We chose pH 3.0 as our critical value because average gastric pH in humans ranges from 1.0–3.0, and at pH below 3.0, didanosine degrades approximately 10% every 2 minutes.² In addition, many drugs are optimally absorbed at low pH values and are insoluble or degraded at pH values greater than 3.0. For example, delavirdine solubility *in vitro* decreases approximately 200-fold when pH increases from 2.0 to 7.5, possibly accounting for the decrease in the delavirdine area under the concentration-time curve observed *in vivo* when concomitantly administered with antacids.⁸

Caution should be employed in extrapolating data from our study to other buffered formulations of didanosine or to children. Different didanosine formulations contain different buffers than the formulation used in our study. Our study was conducted with chewable, dispersible, buffered tablets for oral administration in strengths of 100 mg or 200 mg. These tablets are buffered with calcium carbonate and magnesium hydroxide. Each dose must be taken as two tablets (two 100-mg tablets or two 200-mg tablets) to provide an adequate amount of buffer. The buffered powder for the didanosine oral solution contains a citrate-phosphate buffer composed of dibasic sodium phosphate, sodium citrate, and citric acid.

The pediatric powder for didanosine oral solution is mixed with Extra Strength Mylanta Liquid (Johnson & Johnson-Merck Consumer Pharmaceuticals Co., Fort Washington, PA) or Extra Strength Maalox Plus Suspension (Novartis Consumer Health, Inc., Parsippany, NJ), both of which contain aluminum hydroxide and magnesium hydroxide buffers. Children under the age of 18 years were excluded from our study. The pharmacokinetics of didanosine in pediatric patients have been found to differ from those in adults, perhaps due to differences in pediatric gastrointestinal physiology or to the buffers used in the pediatric formulation of didanosine.²¹ Future studies designed specifically to assess the pediatric formulation of didanosine would be necessary to assess alterations in gastric pH in

children.

Characterization of the magnitude and duration of elevated pH may allow for earlier administration of other pH-sensitive agents. Our study characterized the short duration but highly variable magnitude of change in gastric pH observed after administration of chewable, dispersible, buffered tablets. These data support the findings of a previous study, which suggested that administration of indinavir, a pH-sensitive antiretroviral agent, could be recommended within 1 hour after ingestion of chewable, dispersible, buffered didanosine tablets, due to the short duration of elevated gastric pH after administration of didanosine.²² However, as previously reported, it is important to note that drug interactions due to chelation with polyvalent (e.g., magnesium, calcium) cations in the buffer are likely to persist longer than the effect on gastric pH.^{13, 14}

The short duration of elevated pH after administration of chewable, dispersible, buffered didanosine tablets may partly explain the wide variability in bioavailability observed clinically. A single dose of ranitidine 150 mg steadily increases gastric pH, reaching a pH of approximately 5.0 within 2 hours of administration.² When ranitidine is administered orally 2 hours before didanosine, the bioavailability of didanosine is increased by 14%.² Other causes of the wide range of oral bioavailability may be differences in gastrointestinal motility and transit time between patients.¹ In our study, one patient demonstrated a gastric pH greater than 3.0 for 55 minutes, perhaps due to altered gastrointestinal transit.

Conclusion

We hypothesized that gastric pH would be elevated (pH > 3.0) for at least 2 hours after administration of chewable, dispersible, buffered didanosine 200 mg (two 100-mg tablets) or 400 mg (two 200-mg tablets). We also anticipated that gastric pH parameters would not differ between the two doses. Our results showed that the mean duration of elevated gastric pH ($T_{pH>3}$) was shorter than hypothesized, with a wide range of variability. Our initial hypothesis was based on didanosine's rapid absorption after oral administration, with maximum plasma concentrations occurring within 0.25–1.5 hours. The wide variability and short duration of gastric $T_{pH>3}$ demonstrated in our study may help explain the variability in didanosine bioavailability observed clinically.

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