Pharmacokinetic-Interaction Study of Didanosine and Ranitidine in Patients Seropositive for Human Immunodeficiency Virus

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The potential pharmacokinetic interactions between didanosine, an acid-labile antiretroviral agent, and ranitidine, an H2-receptor antagonist, were evaluated by a crossover study of 12 male patients seropositive for the human immunodeficiency virus. Single oral doses of 375 mg of didanosine, formulated as a citrate-phosphate-buffered sachet, or of 150 mg of ranitidine were administered alone or in combination (ranitidine was given 2 h prior to didanosine). Serial blood samples and total urinary output were collected after each treatment and analyzed for didanosine and/or ranitidine by validated high-performance liquid chromatography-UV assay methods. Pharmacokinetic parameters were calculated by noncompartmental methods. There were significant increases in mean area under the curve from time zero to infinity and mean urinary recovery for didanosine given in combination with ranitidine compared with those for didanosine alone. There were no significant differences between didanosine coadministered with ranitidine and didanosine alone in the respective mean peak concentrations in plasma, times to peak, elimination half-lives, or renal clearances. The mean area under the curve for ranitidine given with didanosine was significantly less than that for ranitidine given alone. There were no significant differences between the mean peak concentrations in plasma, times to peak, elimination half-lives, renal clearances, or urinary recovery values for ranitidine coadministered with didanosine and values for ranitidine given alone. These data demonstrate that administration of didanosine 2 h after ranitidine will result in a minor increase in the bioavailability of didanosine. A modification in the dose of didanosine or ranitidine is not necessary if the dose of ranitidine precedes that of didanosine by 2 h.

Didanosine (2',3'-dideoxyinosine; Videx) is a purine nucleoside analog with demonstrable in vivo and in vitro activity against human immunodeficiency virus (HIV) (1, 5, 13, 16). Didanosine has been approved as a therapeutic alternative for patients with AIDS who are intolerant of, or refractory to, treatment with zidovudine.

The pharmacokinetics of didanosine have been extensively evaluated during the course of safety and tolerance studies (10, 11). The kinetic profile is linear over a dose range of 0.4 to 16.5 mg/kg of body weight administered intravenously and 0.8 to 10.2 mg/kg administered orally and is invariant upon repeated dosing. Didanosine is unstable in an acidic environment and must be protected from acid-induced hydrolysis in the stomach (3). The absolute bioavailability of didanosine is approximately 43% when the compound is administered as a saline solution preceded by a dose of antacid (Maalox) (11). The formulation employed in large-scale safety and efficacy trials, consisting of a blended powder containing didanosine, citrate and phosphate buffers, and sucrose, demonstrates bioavailability comparable to that of the saline solution-Maalox combination used in the initial studies (11). The lack of 100% absolute bioavailability of didanosine may be attributable in part to degradation of the drug in the acidic stomach environment prior to absorption.

Ranitidine, a histamine H2-receptor antagonist, is a competitive inhibitor of histamine, blocking histamine’s action on specific H2 receptors in gastric parietal cells (9). As a result, ranitidine is a potent inhibitor of basal gastric acid secretion. After a single 150-mg oral dose of ranitidine, intragastric pH begins to steadily increase, reaching a pH of approximately 5 within 2 h of administration (6). The present study was conducted to determine whether the coadministration of ranitidine and subsequent inhibition of stomach acid production would improve the relative bioavailability of didanosine or influence didanosine pharmacokinetics. In addition, the effect of didanosine on the pharmacokinetics of ranitidine was also examined.

(This work was presented in part at the 31st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Ill., 29 September to 2 October 1991 [10a].)

MATERIALS AND METHODS

Study design. The study was an open, randomized, three-way crossover design. Treatment A was a single 375-mg dose of didanosine, treatment B was a single 150-mg oral dose of ranitidine, and treatment C was a single 150-mg dose of ranitidine followed 2 h later by a 375-mg dose of didanosine. All doses of study medications were administered after a minimum 10-h fast, and patients were not permitted to eat for 4 h after being dosed with didanosine or ranitidine. Standardized meals were served at appropriate times during confinement in the facility. All patients reported to the clinical facility on the evening prior to each treatment
session and were confined to the clinic until all blood and urine samples were collected. There was a 1-week recovery period between successive treatment sessions. A physical examination and final clinical laboratory assessments were performed after the final dosing session.

**Patients.** Twelve male volunteers seropositive for HIV but free of any evidence of HIV-related disease were enrolled in the study after having met the inclusion criteria and passed the exclusion criteria. Key inclusion criteria included an age of between 18 and 50 years and a body weight within 15% of the desirable weight for the patient’s height and frame. Patients were excluded from the study if they had any evidence of acute or chronic infectious disease (other than a positive HIV test), renal or hepatic insufficiency, or a recent history of drug or alcohol abuse. Patients were not allowed to receive zidovudine within 1 month prior to the first treatment session. All patients signed the appropriate informed consent documents, approved by the Institutional Review Boards of the University of Wisconsin—Madison and Hazleton Laboratories, prior to study initiation. The patients had a mean (standard deviation) of 31 (4.0) years, an average height of 180.9 (6.9) cm, and a mean body weight of 74.4 (9.4) kg. All the patients were Caucasian, and the majority were homosexual.

**Drug formulation and administration.** Didanosine was supplied by the Pharmaceutical Product Development Department of Bristol-Myers Squibb Co., Syracuse, N.Y. Each sachet contained 375 mg of didanosine, buffered agents (sodium citrate USP dihydrate, dibasic sodium phosphate USP anhydrous, and citric acid), and sucrose packaged in a sealed foil packet. The contents of the packet were reconstituted with 120 ml of room-temperature drinking water and then ingested.

**Blood and urine sampling.** Serial heparinized blood samples (5 ml) were collected predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 h after didanosine administration. After the administration of ranitidine, heparinized samples (5 ml) were collected predose and at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 h. When didanosine and ranitidine were administered in the same treatment session, the ranitidine tablet was taken 2 h prior to the didanosine dose.

**Pharmacokinetics and analysis.** Didanosine was analyzed by a validated high-performance liquid chromatography-mass spectrometry method (8). Plasma samples were analyzed for intact didanosine by an established high-performance liquid chromatography method (12). The urine samples were analyzed by a validated modification of the plasma assay, in which 50 μl of buffered urine was mixed with 450 μl of plasma and extracted and chromatographed by using the plasma method conditions. QC samples were included in each analytical sequence in order to verify the stability of study samples during shipment and handling and the accuracy and precision of the analyses.

**Analysis of plasma and urine samples.** Plasma samples were analyzed for intact didanosine by an established high-performance liquid chromatography (HPLC)–UV method (12). The urine samples were analyzed by a validated modification of the plasma assay, in which 50 μl of buffered urine was mixed with 450 μl of plasma and extracted and chromatographed by using the plasma method conditions. QC samples were included in each analytical sequence in order to verify the stability of study samples during shipment and storage and the accuracy and precision of the analyses.

The standard deviations for didanosine in plasma (25 to 10,000 ng/ml) and urine (1 to 400 μg/ml) were linear. The between-day and within-day errors for two different concentration pools (65 and 9,482 ng/ml) of plasma QC samples were no greater than 2.5 and 3.6% relative standard deviation (RSD), respectively, with an average deviation from the nominal values of no more than 16.1%. The between-day and within-day errors for the urine QC samples (3.0 and 377 μg/ml) did not exceed 4.7 and 2.1% RSD, respectively. The mean predicted urine concentrations were within 3.8% of the nominal values. These data indicate that the assays were accurate, precise, and reproducible and demonstrate that didanosine was stable during sample storage and shipment.

Ranitidine in plasma and urine samples was quantitated by validated methods. Briefly, an aliquot of plasma was mixed with an internal standard (propranolol), alkalized with sodium hydroxide, and then extracted with methylene chloride. The aqueous layer was removed, and the methylene chloride was evaporated to dryness. After reconstitution of the extract in mobile phase, the sample was chromatographed by using a reverse-phase HPLC system with a UV detector. For urine samples, an aliquot of each specimen was mixed with plasma and then processed and analyzed by the plasma method. Appropriate QC samples were included in each analytical sequence.

The standard curves for ranitidine in plasma (50 to 5,000 ng/ml) and urine (2.5 to 250 μg/ml) were linear. The between-day and within-day errors for the QC samples in plasma (60 and 4,850 ng/ml) were no greater than 1.0 and 1.5% RSD, respectively, with a deviation from the nominal values of no more than 11.7%. The between-day and within-day errors for the QC samples in urine (7.5 and 190 μg/ml) did not exceed 4.7 and 2.7% RSD, respectively, with mean predicted concentrations of QC samples within 11.8% of the nominal values. These data indicate that the assays were accurate, precise, and reproducible and demonstrate that ranitidine was stable during sample storage and shipment.

**Pharmacokinetic analyses.** Data for concentration in plasma (C) versus time (t) were analyzed by noncompartmental methods and moment analysis (8, 17). The highest observed concentration in plasma and the corresponding sampling time were defined as Cmax and Tmax, respectively. For treatment C, the analysis interval for didanosine was adjusted to begin with the 2-h sample to account for the 2-h delay prior to the administration of didanosine. The terminal log-linear period was defined by the last n (>3) datum points (ln C, t), where n was selected to minimize the mean square error. The absolute value of the slope of the terminal log-linear phase, β, was used to estimate the apparent elimination half-life, t1/2, by the equation 0.693/β.

The area under the C versus t curve (AUC) and the area
under the first moment of the concentration-time curve (AUMC) were calculated by using the trapezoidal rule from \( t_0 \) to \( t_m \), where \( t_m \) is the time at which the drug concentration appeared to decline in a log-linear manner. From \( t_m \) to the last nonzero datum point at \( t_n \), the log trapezoidal method was used (17). AUC and AUMC were then extrapolated to infinity and reported as AUC\(_{0 \rightarrow \infty} \) and AUMC\(_{0 \rightarrow \infty} \). Mean residence time (MRT), total urinary recovery (UR), and renal clearance (CL\(_R \)) were estimated by standard methods (8).

**Statistical analyses.** The sample size of 12 patients yielded 80% power to detect a 20% difference in treatment means for parameters of interest. Analysis of variance, appropriate for a three-way crossover study, was used to compare pharmacokinetic parameters for didanosine or ranitidine given alone with those obtained for the drugs after coadministration. Separate analyses were conducted for didanosine and ranitidine pharmacokinetic parameters. Treatment groups were compared with respect to \( C_{\text{max}} \), AUC\(_{0 \rightarrow \infty} \), \( t_{1/2} \), MRT, CL\(_R \), and UR. An analysis of variance model with sequence, subject within sequence, treatment, period, and residual error taken into consideration was used. \( T_{\text{max}} \) values for the drugs administered together and alone were compared by using the Wilcoxon signed rank test (4). A significance level of 0.05 (\( \alpha = 0.05 \)) was used for all tests.

**RESULTS**

**Safety and tolerance.** Didanosine and ranitidine, given alone or in combination, were well tolerated by all patients participating in the study. Mild to moderate gastrointestinal symptoms and/or headache were reported by one patient in each treatment session with didanosine alone or ranitidine alone and by two patients during the combination treatment phase. None of these events required treatment, and all complaints were resolved prior to time of discharge from the study.

**Pharmacokinetic analyses.** The mean (±SD) pharmacokinetic parameters for didanosine, calculated after the administration of didanosine alone or in combination with ranitidine, are summarized in Table 1. The profiles of mean concentration in plasma versus time for each treatment are presented in Fig. 1. Mean \( C_{\text{max}} \) values for didanosine given alone (1,617 ng/ml) were not significantly different from those obtained for didanosine given 2 h after ranitidine (1,825 ng/ml). \( T_{\text{max}} \) values averaged 0.67 h and 0.69 h after didanosine was given alone and in combination with ranitidine, respectively. Half-life and MRT values for ranitidine alone averaged 1.47 and 2.12 h, respectively. Corresponding mean \( t_{1/2} \) and MRT values (1.49 and 2.17 h, respectively) were observed during the combination phase. There were no significant differences among \( T_{\text{max}} \), \( t_{1/2} \), and MRT for didanosine between the two treatments. The AUC\(_{0 \rightarrow \infty} \) averaged 2,953 and 3,359 ng ∙ h/ml for the single and combination treatment sessions, respectively. The AUC\(_{0 \rightarrow \infty} \) for the combination treatment was significantly greater than that for didanosine administered alone, although the difference was only 14%. The extrapolated AUC represented less than 2% of the AUC\(_{0 \rightarrow \infty} \). The average UR for the combination (22%) was significantly greater than that for administration of only didanosine (17%). The mean CL\(_R \) for didanosine given alone (368 ml/min) was not significantly affected by the administration of didanosine with ranitidine (CL\(_R \), 426 ml/min).

The mean (±SD) pharmacokinetic parameters for ranitidine, calculated after the administration of ranitidine alone or in combination with didanosine, are also summarized in Table 1. Peak concentrations of ranitidine in plasma averaged 325 ng/ml for ranitidine given alone and 333 ng/ml for the combination treatment. These \( C_{\text{max}} \) values were not significantly different. The AUC\(_{0 \rightarrow \infty} \) for ranitidine coadministered with didanosine (1,483 ng ∙ h/ml) was significantly less than that for ranitidine given alone (1,771 ng ∙ h/ml). The magnitude of this decrease was 16%. The extrapolated AUC represented less than 15% of the AUC\(_{0 \rightarrow \infty} \). A second peak in the plasma ranitidine concentration occurred at approximately 2 to 3 h after dosing in 9 and 6 of the 12 patients when ranitidine was given alone and when it was coadministered

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**TABLE 1. Pharmacokinetic parameters for orally administered didanosine and ranitidine***

<table>
<thead>
<tr>
<th>Treatment*</th>
<th>( C_{\text{max}} ) (ng/ml)</th>
<th>( T_{\text{max}} ) (h)</th>
<th>( t_{1/2} ) (h)</th>
<th>MRT (h)</th>
<th>AUC(_{0 \rightarrow \infty} ) (ng ∙ h/ml)</th>
<th>CL(_R ) (ml/min)</th>
<th>UR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Didanosine alone</td>
<td>1,617 ± 715</td>
<td>0.67 ± 0.19</td>
<td>1.47 ± 0.17</td>
<td>2.12 ± 0.26</td>
<td>2,953 ± 851</td>
<td>368 ± 149</td>
<td>17 ± 8</td>
</tr>
<tr>
<td>Didanosine with ranitidine</td>
<td>1,825 ± 644</td>
<td>0.69 ± 0.19</td>
<td>1.49 ± 0.28</td>
<td>2.17 ± 0.21</td>
<td>3,359 ± 754</td>
<td>426 ± 119</td>
<td>22 ± 7</td>
</tr>
<tr>
<td>Ranitidine alone</td>
<td>325 ± 73</td>
<td>2.88 ± 0.86</td>
<td>2.79 ± 0.64</td>
<td>5.27 ± 0.78</td>
<td>1,771 ± 495</td>
<td>455 ± 89</td>
<td>28 ± 7</td>
</tr>
<tr>
<td>Ranitidine with didanosine</td>
<td>333 ± 74</td>
<td>2.42 ± 0.53</td>
<td>2.68 ± 0.43</td>
<td>4.79 ± 0.59</td>
<td>1,483 ± 251</td>
<td>476 ± 131</td>
<td>24 ± 7</td>
</tr>
</tbody>
</table>

* Values are means ± SD. Doses: didanosine, 375 mg; ranitidine, 150 mg.  
* Ranitidine was administered 2 h prior to didanosine during the combination phase of the study.  
* Not significantly different from value for drug alone (P > 0.05).  
* Value for combination is significantly different from value for single agent.

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![FIG. 1. Profiles of mean concentrations in plasma versus time for didanosine (375 mg) and ranitidine (150 mg) after oral administration alone or in combination to 12 patients seropositive for HIV.](http://aac.asm.org/)
with didanosine, respectively. There were no significant differences between mean respective values for $T_{\text{max}}$ (2.88 and 2.42 h), $t_{1/2}$ (2.79 and 2.68 h), or CLR (455 and 476 ml/min) for ranitidine given alone and coadministered with didanosine. The mean MRT after ranitidine was given alone (5.27 h) was significantly greater than when ranitidine was given in combination with didanosine (4.79 h). The mean UR for the combination (24%) was not significantly different from the mean UR for ranitidine given alone (28%).

**DISCUSSION**

Didanosine hydrolyzes rapidly under the pH conditions that are generally present in the human stomach. The average gastric pH in humans ranges from 1 to 3; in this pH range, didanosine degrades at a rate of approximately 10% every 2 min (3, 14). To protect didanosine, an antacid (such as aluminum or magnesium hydroxide) or other buffering agent is given either prior to or in combination with the drug. The average absolute bioavailability of didanosine given orally in this manner is approximately 43% (11). Observed variability among individuals with respect to bioavailability may be reflective of variable degradation prior to absorption or the effect of concomitant disease states which alter gastrointestinal motility. The presence of food in the stomach results in a significant decrease in the bioavailability of didanosine (18).

The primary objective of this study was to determine whether the administration of didanosine with an agent capable of inhibiting gastric acid production would result in improved bioavailability of didanosine relative to that in a nontreated condition. Ranitidine, an H$_2$-receptor antagonist, was chosen because it is a more potent inhibitor of gastric acid secretion than cimetidine and does not act as a competitive inhibitor of mixed-function oxidases to the same extent as cimetidine (9). Ranitidine is actively secreted by the renal tubules and could potentially affect the CLR of didanosine upon coadministration (9). Ranitidine is also one of the most frequently prescribed agents in this class and may be given to patients who are recipients of therapy with didanosine.

The pharmacokinetic parameters for didanosine obtained in this study are in agreement with previously reported data for the citrate-phosphate buffer formulation (11). After administration with ranitidine, the AUC$_{\text{in}}$ is significantly increased, although the magnitude of the change is only 14%. This increase in AUC is probably not clinically significant and suggests that the citrate-phosphate buffer formulation is providing adequate protection of didanosine from degradation in the stomach. Coadministration of single doses of didanosine with ranitidine does not significantly alter the CLR or apparent $t_{1/2}$ of didanosine. Additional multiple-dose studies may be necessary to confirm that repeated administration of ranitidine with didanosine does not result in significant alterations in the disposition of didanosine.

The mean values for $C_{\text{max}}$, $T_{\text{max}}$, $t_{1/2}$, AUC$_{\text{in}}$, and UR for the 150-mg dose of ranitidine given in this study are in excellent agreement with previously published values (7, 9). Consistent with other studies, a biphasic peak in concentration in plasma in many patients given ranitidine alone or in combination with didanosine was noted. A reduction of 16% in the AUC$_{\text{in}}$ of ranitidine when given 2 h prior to didanosine may be a result of decreased absorption of ranitidine in the presence of antacid (2). The AUC$_{\text{in}}$ of ranitidine has been reported to decrease by as much as one-third when it is given with an aluminum-magnesium hydroxide mixture such as Mylanta (15). Although the citrate-phosphate buffer formulation of didanosine used in this study resulted in only a 16% decrease in the AUC of ranitidine, this effect may be more pronounced if the compounds are given simultaneously or if ranitidine is given with other formulations of didanosine which contain an aluminum or magnesium hydroxide-based antacid. This lack of a clinically significant interaction between didanosine and ranitidine should not be extrapolated to other H$_2$-receptor antagonists such as cimetidine, which may have different effects on mixed-function oxidase activity or renal tubular secretion. The results of this study suggest that a modification in the dose of didanosine or ranitidine is not necessary if the dose of ranitidine precedes that of didanosine by 2 h.

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**REFERENCES**


