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Effect of Fluconazole on Pharmacokinetics of 2′,3′-Dideoxyinosine in Persons Seropositive for Human Immunodeficiency Virus

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Fluconazole inhibits cytochrome P-450-mediated enzymatic metabolism of several drugs. Since hepatic metabolism is partially responsible for 2′,3′-dideoxyinosine (didanosine or ddI) elimination, fluconazole therapy may lead to increased ddI concentrations in serum and subsequent concentration-dependent adverse effects. The purpose of this study was to determine if ddI pharmacokinetics are influenced by a 7-day course of oral fluconazole. Twelve adults with human immunodeficiency virus (HIV) who had received a constant dosage of ddI for at least 2 weeks were investigated. On study day 1, multiple serum samples for determination of ddI concentrations were obtained over 12 h. Then subjects received a 7-day course of oral fluconazole (200 mg every 12 h for two doses and then 200 mg once daily for 6 days) while ddI therapy continued. Following the last dose of fluconazole, serum samples for determination of ddI concentrations were again obtained over 12 h. ddI concentrations in serum were analyzed by radioimmunoassay. In contrast to previously published data, there was marked between-subject variability in ddI areas under the concentration-time curve, even when the dose was normalized for weight. No significant differences were found between mean ddI areas under the concentration-time curve from 0 to 12 h on study day 1 (1,528 ± 902 ng · hr/ml) and following fluconazole treatment (1,486 ± 649 ng · hr/ml). There were no significant differences in other pharmacokinetic parameters, such as ddI peak concentrations in serum (971 ± 509 and 942 ± 442 ng/ml) or half-lives (80 ± 32 and 85 ± 21 min.) before and after fluconazole treatment, respectively. We conclude that a 7-day course of oral fluconazole does not significantly alter ddI pharmacokinetics in adults that are infected with human immunodeficiency virus.

Patients infected with human immunodeficiency virus (HIV) are commonly treated with multiple medications concurrently. Fluconazole is well absorbed in the HIV population and is frequently prescribed for prophylaxis and treatment of fungal infections (6). However, fluconazole inhibits a number of hepatic P-450 enzymes that are responsible for the metabolism of many drugs, such as theophylline, phenytoin, cyclosporin, and rifabutin (9, 16, 21). In addition, fluconazole has recently been shown to decrease clearance of zidovudine (ZDV), a drug which is metabolized primarily by glucuronidation (19). The mechanism for this latter interaction is unknown, but it demonstrates that the full spectrum of metabolic enzymes which are inhibited by fluconazole remains unknown.

The antiretroviral agent 2′,3′-dideoxyinosine (didanosine or ddI) is used to treat persons infected with HIV (1, 10). Approximately 50 to 70% of the absorbed dose of ddI appears in urine as various metabolites, although the full metabolic profile is unknown (3a, 11a, 14). Dose-related toxicities of ddI include peripheral neuropathy and pancreatitis (5, 15, 22). Since fluconazole and ddI are commonly coadministered, fluconazole has the potential to inhibit the metabolism of ddI, leading to higher levels in serum and an increase in toxicities or intolerance. This study was conducted to evaluate the effect of multiple oral doses of fluconazole on the pharmacokinetics of ddI.

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MATERIALS AND METHODS

Subjects. Thirteen HIV-infected adults (aged 26 to 51 years) who had received a constant dosage of ddI taken twice daily (BID) for at least 2 weeks were recruited from the Infectious Diseases Clinic population of the Medical College of Virginia Hospitals at Virginia Commonwealth University (MCV/VCU). One subject developed bacterial pneumonia and did not complete the study; results for the remaining 12 subjects are reported. The characteristics of the three women and nine men who made up the final study sample are shown in Table 1. All subjects had previously received ZDV; one was taking ZDV and ddI concurrently. Nine of the subjects were classified as having AIDS on the basis of histories of opportunistic infection.

Criteria for exclusion from the study included intolerance to fluconazole; azole therapy in the 2 weeks prior to initiation of this study; concurrent treatment with agents known to induce or inhibit P-450 enzymes; drugs whose metabolism is altered by fluconazole, such as phenytoin or cyclosporin; elevated liver function test (bilirubin, alkaline phosphatase, aspartate aminotransferase, or alanine aminotransferase) results that were greater than three times the upper limits of normal; and creatinine levels that were greater than 2.0 mg/dl. Subjects were instructed not to take drugs which could alter gastric pH and ddI absorption, such as antacids or histamine-2 receptor antagonists. Women who were pregnant or were not using an accepted means of birth control were also excluded. The study was approved by the Committee for Conduct on Human Research at MCV/VCU, and informed consent was obtained from all subjects.

Study design. The study period for each subject consisted of 8 days. Collection of blood samples for pharmacokinetic analysis of ddI was done on days 1 (pretreatment) and 8 (posttreatment) in the Clinical Research Center at MCV/VCU. All subjects except one were taking the commercially available tablet formulation that contained antacid (dihydroxyaluminum sodium carbonate, magnesium hydroxide, and sodium citrate). The exception was one person who continued to use the sachet formulation (powdered ddI with sodium citrate USP dihydrate, dibasic sodium phosphate USP anhydrous citric acid, and sucrose). Subjects were instructed to take ddI on an empty stomach (1 h before a meal or 2 h after) each morning and night at the previously prescribed dose (range, 3.2 to 7.8 mg/kg/day) throughout the study. On the first day of the study, subjects were admitted to the Clinical Research Center and took the usual morning dose of ddI with 8 oz (1 oz

TABLE 1. Characteristics of subjects at entry into study

Characteristic	Value for group
Male/female	9/3
Age (yr)	
Median	35
Range	26–51
Race	
African-American	7
Caucasian	5
Wt (kg)	
Mean	63
Range	51.6–76.6
$CD4^+$ count (cells/mm^3)	
Median	23
Range	9–627
Current use of:	
Tobacco	6
Alcohol	6
Past intravenous drug use	4
ddI dose (mg/kg/day)	
Mean	5.8
Range	3.2–7.8
Daily dosage (mg BID)	
100	2
125	1
200	8
250 (powder)	1
Time on ddI (mo)	
Median	5.5
Range	0.5–20
Time on ZDV (mo)	
Median	5.5
Range	0.5–37

= 29.573 ml) of water after fasting for at least 7 h. They continued to fast for 4 h following that dose of ddI. During study days 2 through 7, subjects continued ddI therapy in the usual outpatient setting and took oral fluconazole (Diflucan [lot no. 2406A]; Roerig-Pfizer, New York, N.Y.) on the following schedule: 200 mg every 12 h on day 2 and then 200 mg each morning for six additional days. On study day 8, subjects again fasted for at least 7 h before and 4 h after the usual morning dose of ddI, which was taken simultaneously with the last dose of fluconazole after readmission to the Clinical Research Center.

Evidence of adverse effects during this study was monitored by history, physical examination on days 1 and 8, and laboratory evaluation when indicated by abnormal signs or symptoms. Compliance with the fluconazole regimen was assessed on day 8 by questioning subjects and counting remaining tablets.

Collection of blood samples. Blood samples (5 ml per sample) for analysis of ddI concentrations were obtained through an indwelling catheter on the following schedule: immediately before ddI administration (time zero) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 10, and 12 h after the ddI dose. Each sample was permitted to clot for 20 to 30 min at room temperature before centrifugation at 1,000 × *g* for 10 min at 4°C. In vitro metabolism of ddI by erythrocytes under these conditions is negligible (3). Separated serum was transferred to labeled polypropylene tubes, which were then sealed. These tubes were dipped in 10% bleach solution and then stored at −70°F.

Drug analysis. Prior to analysis, all serum samples were incubated at 58 to 60°C for 30 min in order to inactivate HIV. Incubation at 56°C for up to 3 h does not alter ddI concentrations (14). Concentrations of ddI were determined by validated radioimmunoassay with commercially available reagents (Sigma Chemical Co., St. Louis, Mo.). All samples were run in duplicate, and means are reported. Radioimmunoassays were performed as follows: 100 μl of a serum sample or standard was dispensed into tubes, and then 100 μL of ddI-3H (D-8914; Sigma Chemical Co.) followed by 100 μL of ddI antiserum (D-9039; Sigma Chemical Co.) was placed into each tube. The contents of these tubes were gently mixed and allowed to incubate at room temperature for 1 h. One milliliter of rabbit immunoprecipitation reagent (R-8633; Sigma Chemical Co.) was placed into each tube, and then tubes were centrifuged at 8,000 rpm (model GP8; International Equipment Co.) for 36 min at 4°C. The supernatant from each tube was removed, and 0.5 ml of 0.5 N HCl was placed into each tube with the remaining pellet. After vortexing, the contents of each tube were transferred into liquid scintillation vials with 15 ml of scintillation solution (Insta-Gel XL; Packard, Downers Grove, Ill.). Each vial was counted for 4 min in a scintillation counter. Radioimmunoassay sensitivity was 0.3 ng/ml and was linear from 0.3 to 10 ng/ml. Samples presumed to have ddI concentrations that were greater than 10 ng/ml were diluted prior to analysis. The between-day coefficients of variation for controls of 2.5 and 7.0 ng/ml were 8.4 and 5.6%, respectively. Control samples were assayed along with subject samples to confirm the stability of ddI under these storage conditions. In common with most radioimmunoassays, this ddI assay is not known to significantly cross-react with other compounds, including ddA, inosine, adenosine, uric acid, and caffeine (D-8914; Sigma Chemical Co.). Baseline ddI concentrations in serum prior to days 1 and 8 in this study revealed either no drug or low concentrations of ddI, suggesting that there is no cross-reactivity between ddI and the other drugs these subjects received.

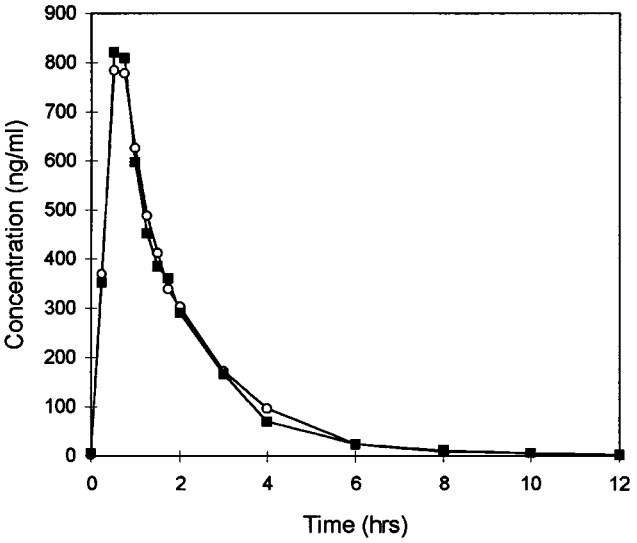

FIG. 1. Mean ddI concentrations in serum over time before and after fluconazole treatment. ■, ddI alone; ○, ddI with fluconazole.

Pharmacokinetic analysis. ddI concentrations in serum versus time were analyzed by compartmental and noncompartmental pharmacokinetic methods. The nonlinear least-squares regression curve-fitting program RSTRIP (17) was used to generate model-dependent parameter estimates, including the terminal elimination rate. A two-compartment model (exponential terms for absorption and elimination), weighted by $1/C^2$, was found to provide the best fit to the data, assessed by the model selection criterion, a modification of the Akaike information criterion (2, 17). Minimum and maximum (C_{max}) ddI concentrations in serum and the time at which C_{max} occurred (T_{max}) were determined by visual inspection of the data. The parameter of primary interest, the area under the concentration-time curve from 0 to 12 h (AUC_{0-12}), was calculated by the trapezoidal rule.

Statistical analysis. A sample size of 12 was calculated to yield 88% power to detect a 20% difference in AUC, assuming a standard deviation of 20% and a two-sided alpha of 5%. Differences in the pharmacokinetic parameters of ddI (AUC_{0-12}, C_{max}, T_{max}, and half-life [$t_{1/2}$]) before and after fluconazole treatment were compared by using the Wilcoxon signed-rank test with the Bonferroni correction. A significant difference was defined as $P < 0.01$. Linear regression was used to assess the relationship between weight-normalized dose and baseline ddI AUC_{0-12} (prior to fluconazole administration).

RESULTS

Safety. Prior to beginning this study, three subjects had reported symptoms that could have been related to the use of ddI (two with intermittent abdominal pain without nausea and one with intermittent lower extremity paresthesias). Despite these symptoms and after consultations with their health care providers, these subjects had continued ddI therapy without interruption and without apparent adverse effects. The symptoms of none of these persons worsened while they were taking both ddI and fluconazole. Another subject reported odynophagia that was neither aggravated nor improved by fluconazole. The following symptoms occurred while subjects were taking fluconazole and required no treatment: mild diarrhea in one subject and apparent vaginitis in another. None of the subjects dropped out of this study because of toxicities related to the study medications.

TABLE 2. Pharmacokinetic parameters of ddI before and after fluconazole treatment

Treatment	Mean AUC_{0-12} ± SD (ng · h/ml)	Mean C_{max} ± SD (ng)	T_{max} (min)		Mean $t_{1/2}$ + SD (min)
			Median	Range	
ddI alone	1,528 ± 902	971 ± 509	45	30–75	80 ± 32
ddI + fluconazole	1,486 ± 649	942 ± 442	37.5	30–120	85 ± 21

Pharmacokinetics. Mean ddI concentrations in serum plotted against time for the two regimens are displayed in Fig. 1. A summary of the pharmacokinetic data is presented in Table 2. There were no significant differences between the AUC_{0-12}, C_{max}, T_{max}, or $t_{1/2}$ values for ddI before and after fluconazole treatment. Four subjects had higher AUCs while they were receiving ddI alone (range, 11 to 41%), seven had higher AUCs while they were receiving fluconazole (range, 9 to 120%), and one had essentially the same results (4% higher with fluconazole).

The AUC_{0-12} (ddI baseline) correlated poorly with the dose normalized for body weight ($r = 0.10$) (Fig. 2A). However, there was good correlation ($r = 0.66$; $P < 0.05$) between the AUCs for these two regimens within subjects (Fig. 2B).

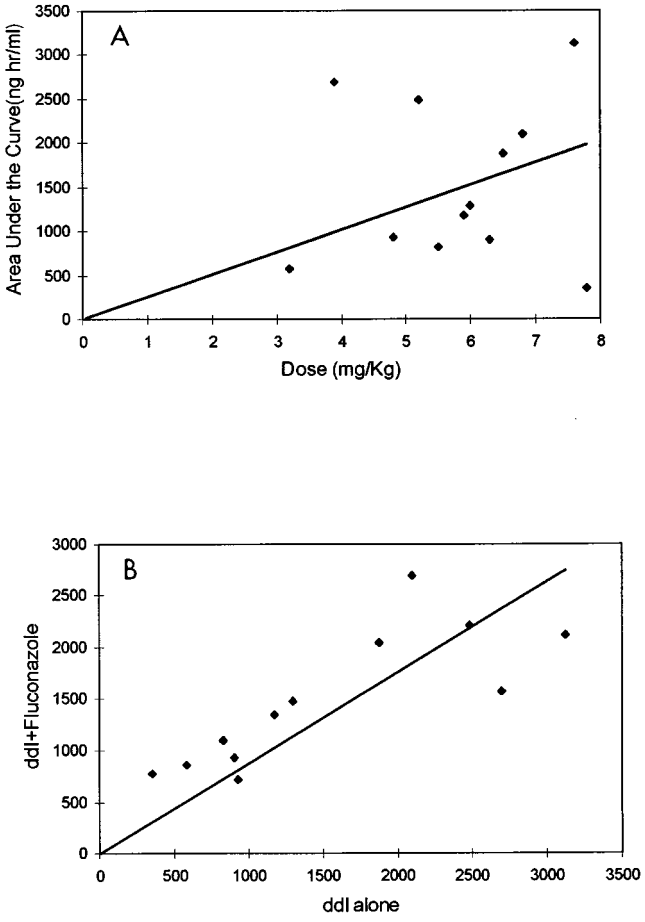

FIG. 2. (A) Regression analysis of weight-normalized ddI dose and AUC (baseline). The regression line is forced through the origin ($r = 0.10$; $P > 0.05$). (B) Correlation between AUCs of ddI with and without fluconazole. The regression line is forced through the origin ($r = 0.66$; $P < 0.05$).

DISCUSSION

The kinetics of ddI in this study were generally similar to those previously reported (4, 8, 11a–15, 18), although the different doses and formulations used in previous studies make comparisons difficult. One of the striking observations in this trial was the marked between-subject variability in AUC even after doses were weight normalized. Although each dose varied less than threefold (1.6 to 3.9 mg/kg per dose), AUCs demonstrated a nearly ninefold range (354 to 3,124 ng · hr/ml). Although a previous study reported dose proportionality for the ddI AUCs of 17 HIV-positive subjects over the dose range of 0.8 to 10.2 mg/kg (14), when we studied the more narrow dose range used clinically (100 to 250 mg BID), there was little correlation between weight-normalized dose and AUC. In this study, dose normalized for weight explains only 7% of the variability in steady-state AUC_{0-12}. This observation raises questions as to whether the recommendation that doses be adjusted for weight, such as a 125-mg tablet BID for a <60-kg patient and a 200-mg tablet BID for a >60-kg patient, has a firm pharmacokinetic basis (3a). A NONMEM analysis of ddI pharmacokinetics in patients from phase I trials reported a 22% between-subject coefficient of variation for clearance and a 50% within-subject coefficient of variation (18). In contrast, this study reports high between-subject variability and relatively low within-subject variability. Possible explanations for this variability include patient differences in gastric pH, gastrointestinal motility, and concomitant medications used by study subjects (although subjects were taking no medications known to alter ddI pharmacokinetics).

Didanosine has a number of characteristics which are expected to contribute to greater variability in systemic exposure than that of most drugs. It is labile to gastric acid degradation, and between-subject differences in gastric pH (common in patients with AIDS) may lead to differences in absolute bioavailability (18). The commercial formulations of ddI (tablets and buffered powder) differ in bioavailability (3a, 14, 20), and all dosage forms include buffers to increase stability in gastric fluids. Systemic availability appears to be further compromised by a rate-limited absorption step (8, 12, 14), leading to recommendations that ddI be taken BID instead of once a day (3a, 8). With the ddI formulations used in this trial (taken BID under fasting conditions), mean systemic bioavailability has been reported to range from 33 to 41% (8, 14, 15, 18, 22). Since the AUC of ddI has been shown to correlate with both suppression of p24 antigen and the frequency of adverse effects (7, 8, 22), a prospective study to evaluate whether monitoring concentrations in serum improves response or reduces toxicity may be beneficial.

The metabolic fate of ddI in humans is incompletely characterized. Of the quantity that reaches systemic circulation, 30 to 50% appears in urine as an unchanged drug; the remainder is excreted as various metabolites, which appear to be products of xanthine oxidase or other purine metabolic pathways (11, 14). In dogs that receive ddI under conditions that mimic those in humans, the bioavailability and $t_{1/2}$ of ddI are similar to

those in humans (10a). Additionally, in these animals, metabolites via xanthine oxidase appear in plasma and/or urine and consist primarily of allantoin and lesser quantities of uric acid, hypoxanthine, and xanthine. Since the pharmacokinetics of ddI in dogs are similar to those from limited observations in humans, similarities in metabolic profiles of these two species (i.e., xanthine oxidase) may explain the lack of interaction found in this trial (see below).

Like other azoles, fluconazole is an inhibitor of multiple hepatic P-450 enzymes; it also appears to inhibit some non-P-450 enzymes, such as uridine diphosphate-glucurosyl transferase, which is responsible for the metabolism of ZDV (6, 9, 19). However, we found that the pharmacokinetics of ddI are not altered by fluconazole when both are given at commonly prescribed dosages. Consistent with these observations, a recent investigation found that ketoconazole did not alter the pharmacokinetics of ddI in 12 subjects with HIV (11a). These data argue that the metabolism of ddI is not rate limited by P-450 enzymes or other non-P-450 enzymes which are inhibited by azoles. We conclude that fluconazole may be safely given to HIV-infected patients who receive ddI.

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