

Absence of Clinically Relevant Drug Interactions Following Simultaneous Administration of Didanosine-encapsulated, Enteric-coated Bead Formulation with Either Itraconazole or Fluconazole

B. Damle*, H. Hess, S. Kaul and C. Knupp†

Clinical Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543, USA

ABSTRACT: This open-label, two-way crossover study was undertaken to determine whether the enteric formulation of didanosine influences the pharmacokinetics of itraconazole or fluconazole, two agents frequently used to treat fungal infections that occur with HIV infection, and whose bioavailability may be influenced by changes in gastric pH. Healthy subjects were randomized to Treatment A (200-mg itraconazole or 200-mg fluconazole) or Treatment B (same dose of itraconazole or fluconazole with 400 mg of didanosine as an encapsulated, enteric-coated bead formulation). In the itraconazole study, a lack of interaction was concluded if the 90% confidence interval (CI) of the ratio of the geometric means of log-transformed C_{\max} and AUC_{0-T} values of itraconazole and hydroxyitraconazole, the active metabolite of itraconazole, were contained entirely between 0.75 and 1.33. In the fluconazole study, the equivalence interval for C_{\max} and AUC_{0-T} was 0.80–1.25. The data showed that for itraconazole the point estimate and 90% CI of the ratios of C_{\max} and AUC_{0-T} values were 0.98 (0.79, 1.20) and 0.88 (0.71, 1.09), respectively; for hydroxyitraconazole the respective values were 0.91 (0.76, 1.08) and 0.85 (0.68, 1.06). In the fluconazole study, the point estimate and 90% CI of the ratios of C_{\max} and AUC_{0-T} values were 0.98 (0.93, 1.03) and 1.01 (0.99, 1.03), respectively. The T_{\max} for itraconazole, hydroxyitraconazole, and fluconazole were similar between treatments. Both studies indicated a lack of clinically significant interactions of the didanosine formulation with itraconazole or fluconazole. These results showed that the encapsulated, enteric-coated bead formulation of didanosine can be concomitantly administered with drugs, such as the azole antifungal agents, whose bioavailability may be influenced by interaction with antacids. Copyright © 2002 John Wiley & Sons, Ltd.

Key words: didanosine; enteric coating; antacid interaction; itraconazole; fluconazole

Introduction

Didanosine (ddI), a purine nucleoside analog, is indicated for the treatment of human immunodeficiency virus (HIV) infection. Didanosine is administered orally with antacids to protect it against acid-induced hydrolysis in the stomach

[1]. Didanosine buffered formulations that are available as marketed products include the buffered powder for oral solution, chewable/dispersible buffered tablet, and pediatric powder for oral solution. To eliminate the need for using buffers in the didanosine formulations, an enteric-coated bead formulation of didanosine was developed and approved for marketing in the United States and Europe. In a pivotal bioequivalence study, the encapsulated enteric-coated bead formulation (1 × 400-mg capsule) was found to be bioequivalent with respect to area

*Correspondence to: Clinical Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543, USA.
E-mail: bharat.damle@bms.com

†Current address: Pfizer Inc., Ann Arbor, MI 48105, USA.

under the plasma concentration curve (AUC) but not the peak plasma concentration (C_{\max}) compared to the marketed chewable/dispersible buffered tablet (2×200 mg tablets) as the reference in normal volunteers and in HIV-infected subjects [2]. Non-equivalence with respect to C_{\max} was not surprising based on the anticipated release profile of an enteric formulation.

As the encapsulated enteric-coated formulation of didanosine lacks antacids, it does not decrease the bioavailability of compounds that are dependent on acidic gastric pH for absorption (e.g. indinavir) and compounds that are chelated by calcium or aluminum cations in the antacids (e.g. ciprofloxacin) [3]. Another class of compounds whose bioavailability is decreased by changes in gastric pH are the azole antifungal agents. In a previous interaction study with ketoconazole, an apparent increase of approximately 30% in the systemic exposure to ketoconazole was observed upon coadministration with the enteric formulation of didanosine [3]. This was surprising as an interaction was not anticipated, and more importantly, the concern was a decrease in the exposure of ketoconazole after coadministration with didanosine enteric formulation. It was identified that the apparent increase was a manifestation of the anomalous nature of absorption of ketoconazole when given alone in three out of the 24 subjects in Study (3). The authors concluded, upon reanalyzing the data after excluding these three subjects, that the encapsulated, enteric-coated formulation of didanosine has no drug interactions with ketoconazole [3]. Therefore, the present study was undertaken to confirm the lack of interaction of the didanosine encapsulated enteric formulation with azole antifungal agents. The azole antifungal compounds evaluated in this study were itraconazole and fluconazole.

Itraconazole (Sporanox[®]) and fluconazole (Diflucan[®]) are triazole compounds effective after oral administration for the treatment of superficial and systemic fungal infections. Itraconazole is indicated for the treatment of blastomycosis, aspergillosis, and histoplasmosis in both immunocompromised and non-compromised patients. Fluconazole is useful in the treatment of oral candidiasis, a frequent opportunistic infection in immunocompromised patients. Itraconazole is

soluble only under acidic conditions [4]. Therefore, in the presence of ranitidine, the oral absorption of itraconazole is markedly reduced [5]. The chewable tablet formulation of didanosine which contains antacids has been shown to significantly reduce itraconazole absorption when the two drugs are given simultaneously [6]. Unlike itraconazole, fluconazole is highly water soluble under both acidic and neutral conditions [4]. Hence, the oral absorption of fluconazole is not markedly influenced by concomitant administration of cimetidine or antacids [7,8].

Itraconazole and fluconazole may be administered for the treatment of fungal infections in HIV-infected persons who may also be receiving treatment with didanosine for HIV infection. Administration of the enteric-coated bead formulation of didanosine, which does not contain antacids, is not likely to change gastric pH and influence the absorption of itraconazole or fluconazole. In addition, since the bioavailability of fluconazole is not markedly influenced by changes in gastric pH, an interaction study between didanosine and fluconazole would be able to identify if any other potential mechanisms of interaction exist between the enteric formulation of didanosine and azole antifungal agents. Therefore, the objective of the two studies reported here was to evaluate the influence of didanosine, administered as an encapsulated, enteric-coated bead formulation, on the single-dose oral pharmacokinetics of itraconazole and fluconazole.

Materials and Methods

Study design

Two separate, open-label, single-dose, randomized, balanced, two-way crossover studies were conducted to determine the effect of concomitant administration of didanosine, as an encapsulated, enteric-coated bead formulation, on the pharmacokinetics of itraconazole and fluconazole in normal healthy subjects. Male or female subjects, 18–50 years of age, and a minimum body weight of 60 kg were enrolled in both studies. Female subjects of child bearing

potential had a confirmed negative pregnancy test 72 h prior to study start and used an effective, non-hormonal method of birth control during the course of the study. Written informed consent was obtained from all subjects before the start of each study. A summary of subject demography parameters enrolled in both studies is presented in Table 1.

Study 1: A total of 27 subjects were randomized to receive Treatment A consisting of 200 mg of itraconazole (2 × 100-mg Sporanox[®] capsules) or Treatment B consisting of 200 mg of itraconazole (2 × 100-mg Sporanox[®] capsules) plus 400 mg of didanosine (1 × 400-mg capsule) as an enteric-coated bead formulation. Two subjects withdrew from the study due to withdrawal of consent after receiving one treatment; pharmacokinetic data from these subjects were not included for statistical analyses. Based on the variability in the pharmacokinetics of itraconazole reported by Barone *et al.* [9], the study provided at least 84 and 89% power to conclude absence of effect of didanosine enteric-coated bead formulation on C_{max} and AUC of itraconazole.

Study 2: A total of 14 subjects were randomized to receive Treatment A consisting of 200 mg of fluconazole (1 × 200-mg Diflucan[®] tablet) or Treatment B consisting of 200 mg of fluconazole (1 × 200-mg Diflucan[®] tablet) plus 400 mg didanosine (1 × 400-mg capsule) as an enteric-coated bead formulation. All enrolled subjects com-

pleted the study. Based on the variability in the pharmacokinetics of fluconazole reported by Zimmermann *et al.* [10], the study provided at least 84 and 89% power to conclude absence of the effect of didanosine enteric-coated bead formulation on C_{max} and AUC of fluconazole.

For both studies, the washout period between treatments was at least two weeks. Each treatment was given with 240 ml of room-temperature tap water, and subjects were confined to the clinical facility until 72 h postdose. Plasma samples were collected for pharmacokinetics prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 24, 48, and 72 h postdose. Clinical evaluations, including laboratory tests, physical examinations, vital signs, and electrocardiograms were performed during screening, at selected times, and prior to discharge to assess safety and tolerance. A safety assessment was done by closely monitoring the occurrence of adverse events (AEs), physical examinations, vital signs, clinical laboratory results, and electrocardiograms from the prestudy screening through discharge.

Sample analysis

Quantitation of the plasma concentrations of itraconazole, and its active metabolite hydroxyitraconazole, was based on a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method for the simultaneous measurement of both compounds, similar to that reported elsewhere [11]. The plasma concentration of fluconazole was determined by using a validated high-performance liquid chromatography (HPLC) method similar to that previously reported [12]. Didanosine concentrations were measured using a validated radioimmunoassay (RIA) method [2].

For itraconazole, hydroxyitraconazole, and fluconazole, the standard curves were linear over the concentration ranges of 1–1000, 1–1000 ng/ml, and 0.1–20 µg/ml, respectively. For itraconazole, hydroxyitraconazole, and fluconazole assays, mean predicted concentrations of the quality control (QC) samples were within 10.8, 14.6, and 6.9% of their nominal values, respectively; between- and within-day variabilities were within 13, 7.9, and 9.9% of the coefficient of

Table 1. Key demographic parameters for enrolled subjects

Parameter	Study 1 (<i>n</i> = 27)	Study 2 (<i>n</i> = 14)
Age (years)		
Mean	31	33
S.D.	9	10
Range	18–48	18–49
Gender, <i>n</i> (%)		
Male	24 (89)	11 (79)
Female	3 (11)	3 (21)
Race, <i>n</i> (%)		
White	4 (15)	4 (29)
Black	22 (81)	10 (71)
Hispanic/Latino	1(4)	—
Weight (kg)		
Mean	78.4	81.3
S.D.	10.9	8.8
Range	60.0–96.0	69.0–101.0

variation (CV), respectively. For didanosine, the standard curves were described by a four-parameter logistic regression model in the range of 3–200 ng/ml. Mean predicted concentrations of the QCs were within 6% of their nominal values; between- and within-day variabilities were within 16% CV. These analytical data indicate that the assays used for all analyses were precise and accurate.

Pharmacokinetic analysis

The plasma concentration–time data were analyzed by a non-compartmental method [13]. The C_{\max} and the time to peak plasma concentration (T_{\max}) were obtained from experimental observations. Using no weighting factor, the terminal log-linear phase of the serum concentration–time curve was identified by least-squares linear regression of at least three data points, which yielded a minimum mean square error. The half-life of the terminal log-linear phase ($t_{1/2}$) was calculated as $0.693/K$, where K is the absolute value of the slope of the terminal log-linear phase. The area under the plasma concentration–time curve from zero to infinity ($AUC_{0-\infty}$) was determined by summing the areas from time zero to the time of last measured concentration, calculated by using conventional trapezoidal and log-trapezoidal methods and the extrapolated area. The extrapolated area was determined by dividing the final concentration by the slope of the terminal log-linear phase. The area under the plasma concentration versus time curve (AUC_{0-T}) was calculated by the trapezoidal rule from time zero to the time of the last measurable concentration. Parameters determined for itraconazole, hydroxyitraconazole, and fluconazole were C_{\max} , T_{\max} and AUC_{0-T} . Those determined for didanosine were C_{\max} , T_{\max} , $AUC_{0-\infty}$, and $t_{1/2}$.

Statistical analysis

The 90% confidence interval approach was used to assess drug interaction [14]. To demonstrate the effect of coadministration of didanosine on the pharmacokinetics of itraconazole, hydroxyitraconazole, and fluconazole, an analysis of variance model appropriate for a two-period, two-treatment, crossover design was used for the C_{\max} and AUC_{0-T} values. Both parameters were

log-transformed prior to analysis. The factors in the analysis were sequence group, subject within sequence, period, and treatment. Point estimates and 90% confidence intervals (CI) for the means and differences between means on the log scale were exponentiated to obtain estimates for geometric means and ratios of geometric means on the original scale. Absence of an effect on C_{\max} or AUC_{0-T} was concluded if the corresponding 90% CI was contained within the equivalence interval. The presence of an effect on C_{\max} or AUC_{0-T} was concluded if the 90% CI was entirely outside the corresponding equivalence interval. Otherwise, the effect was considered 'indeterminate'. For itraconazole and hydroxyitraconazole, the equivalence interval was 0.75–1.33 while that for fluconazole was 0.80–1.25. The wider CI for itraconazole and hydroxyitraconazole were based on the findings of Boelaert *et al.* who evaluated the single-dose pharmacokinetics of itraconazole (200 mg) in uremic patients and examined whether hemodialysis would influence the pharmacokinetics of itraconazole [15]. Compared to uremic patients without dialysis, the C_{\max} and AUC_{0-8h} values for patients on dialysis were reduced by 47% and 51%, respectively. The reduction in exposure was not considered to be of clinical consequence; thus, the authors concluded that the dose of itraconazole for uremic patients, whether dialyzed or not, need not be adjusted. Furthermore, there is no dose adjustment specified in the package insert for itraconazole for patients with renal dysfunction. Therefore, in the present study, the equivalence interval for itraconazole was set at 0.75–1.33.

Results

Pharmacokinetics

The mean plasma concentration–time profiles for itraconazole, hydroxyitraconazole, and fluconazole, given as single agents and concomitantly with didanosine, are depicted in Figures 1, 2 and 3, respectively. The geometric means, ratios of geometric means, and 90% CIs for C_{\max} and AUC_{0-T} are summarized in Table 2.

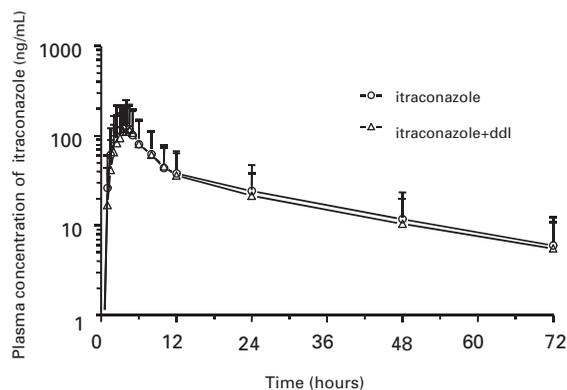


Figure 1. Mean (S.D.) plasma concentration–time profile for itraconazole ($n = 25$) administered alone and concomitantly with the encapsulated, enteric-coated bead formulation of didanosine

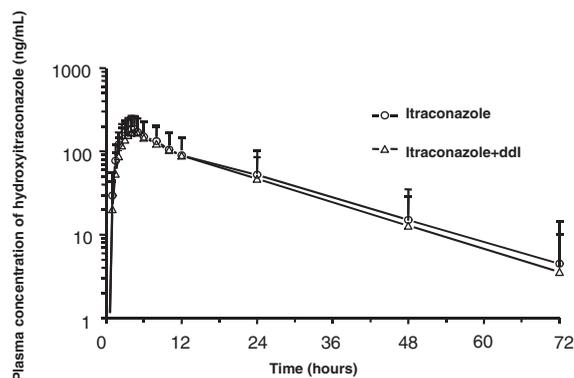


Figure 2. Mean (S.D.) plasma concentration–time profile for hydroxyitraconazole ($n = 25$) administered alone and concomitantly with the encapsulated, enteric-coated bead formulation of didanosine

The C_{\max} of itraconazole and hydroxyitraconazole was similar when given as a single agent or concomitantly with didanosine. Statistical analysis indicated that the C_{\max} of itraconazole and hydroxyitraconazole satisfied the no effect criteria. The geometric mean AUC_{0-T} for itraconazole and hydroxyitraconazole when itraconazole was given in combination with didanosine were lower by 12 and 15%, respectively, than that of itraconazole given alone. The upper bound of the 90% CI for AUC_{0-T} was within the equivalence interval of 0.75–1.33 but the lower bound was slightly lower than the prespecified limit of 0.75

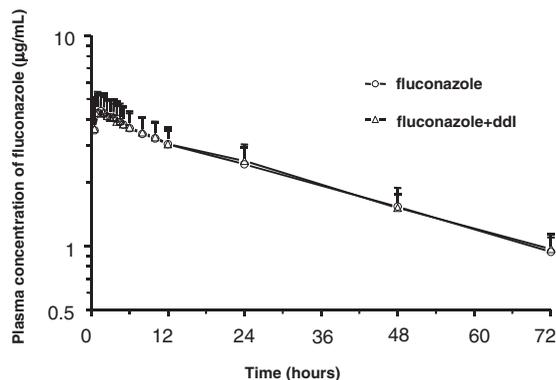


Figure 3. Mean (S.D.) plasma concentration–time profile for fluconazole ($n = 14$) administered alone and concomitantly with the encapsulated, enteric-coated bead formulation of didanosine

for both analytes, indicating an indeterminate effect on AUC (Table 2). The median T_{\max} was 3.0 h for itraconazole given alone and 3.5 h for itraconazole coadministered with didanosine. For hydroxyitraconazole, the median T_{\max} was 4.0 h for both treatment groups.

The C_{\max} and AUC_{0-T} values of fluconazole given as a single agent or in combination with didanosine were similar. Statistical analysis indicated that both the C_{\max} and AUC_{0-T} of fluconazole satisfied the criteria for a lack of drug interaction (Table 2). The median T_{\max} was 1.5 h when fluconazole was given alone and 1.25 h when fluconazole was coadministered with didanosine.

The mean concentration–time profiles of didanosine in the two studies are shown in Figure 4. The mean pharmacokinetic parameters for didanosine were similar when didanosine was coadministered with either itraconazole or fluconazole; the C_{\max} values were 857 and 854 ng/mL, respectively, and the $AUC_{0-\infty}$ values were 2606 and 2703 h ng/mL, respectively (Table 3).

Safety and tolerability

Study treatments in both studies were well tolerated by healthy subjects. In the itraconazole study, a total of eight adverse events were experienced by six (23%) subjects in each treatment period (i.e. after administration of

Table 2. Point estimates and 90% CI for log-transformed C_{\max} and AUC_{0-T} values for itraconazole, hydroxyitraconazole, and fluconazole

Analyte	Parameter	Geometric means		Ratios of geometric means	
		Treatment A ^a	Treatment B ^b	Point estimate	90% CI
Itraconazole (<i>n</i> = 25)	C_{\max} (ng/ml)	111	108	0.98	(0.79, 1.20)
	AUC_{0-T} (h ng/ml)	1425	1250	0.88	(0.71, 1.09)
Hydroxy-itraconazole (<i>n</i> = 25)	C_{\max} (ng/ml)	182	166	0.91	(0.76, 1.08)
	AUC_{0-T} (h ng/ml)	2707	2300	0.85	(0.68, 1.06)
Fluconazole (<i>n</i> = 14)	C_{\max} (μ g/ml)	4.7	4.6	0.98	(0.93, 1.03)
	AUC_{0-T} (h μ g/ml)	152	153	1.01	(0.99, 1.03)

^aTreatment A: Study 1, itraconazole 200 mg; Study 2: fluconazole 200 mg.

^bTreatment B: Study 1, itraconazole 200 mg plus didanosine 400 mg; Study 2: fluconazole 200 mg plus didanosine 400 mg.

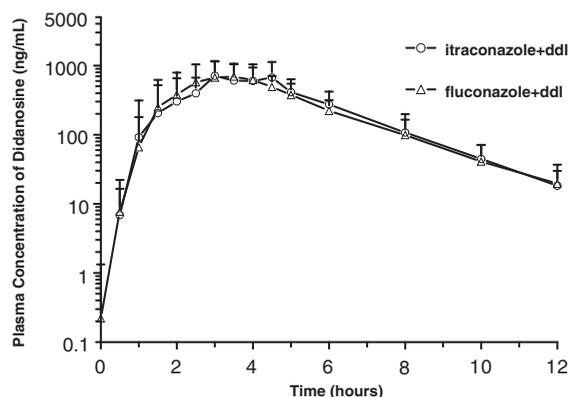


Figure 4. Mean (S.D.) plasma concentration–time profiles of didanosine administered as an encapsulated, enteric-coated bead formulation concomitantly with itraconazole (*n* = 25) and fluconazole (*n* = 14)

itraconazole alone and itraconazole plus didanosine). In the fluconazole study, a total of two adverse events were reported by two (14%) subjects in each treatment period. All AEs were mild or moderate in intensity. AEs that were rated as probably or possibly related to the study medication included abnormal clinical laboratory values (alanine aminotransferase increase, aspartate aminotransferase increase, lipase increase), arthralgia, constipation, diarrhea, headache, nausea, and vesiculobullous rash. Headache was the most frequently reported AE in both studies.

Most AEs resolved during the study or at follow-up after discharge. There were no serious AEs or deaths in either study.

Discussion

The encapsulated, enteric-coated bead formulation of didanosine does not contain antacids and thus does not decrease the bioavailability of drugs that depend on gastric acidity for absorption or are chelated by cations in the antacids. This lack of interaction of the enteric formulation of didanosine has been confirmed with indinavir and ciprofloxacin [3].

The results from the itraconazole study show that the C_{\max} of itraconazole and hydroxyitraconazole was unchanged, but the AUC was reduced by about 12% for itraconazole and 15% for hydroxyitraconazole when given in combination with didanosine enteric formulation relative to the administration of itraconazole alone. This is in sharp contrast to the more than 80% decrease in itraconazole exposure seen with the chewable/dispersible buffered tablet formulation of didanosine that contains antacids [6]. The pharmacokinetics of itraconazole have been reported to be quiet variable. For example, the % CV for the AUC values of itraconazole

Table 3. Pharmacokinetic parameters of didanosine after administration of the encapsulated, enteric-coated bead formulation (400 mg) simultaneously with itraconazole (200 mg) or fluconazole (200 mg)

Pharmacokinetic parameter	Itraconazole plus didanosine (<i>n</i> = 25)	Fluconazole plus didanosine (<i>n</i> = 14)
C_{\max} (ng/ml)		
Geometric Mean (CV%)	857 (45)	854 (46)
$AUC_{0-\infty}$ (h ng/ml)		
Geometric mean (CV%)	2606 (37)	2703 (38)
$T_{1/2}$ (h)		
Mean (S.D.)	1.62 (0.21)	1.64 (0.27)
T_{\max} (h)		
Median (min, max)	3.0 (1.5, 6.0)	3.25 (1.5, 4.5)

following a 200 mg dose are reported to be about 43–70% [5, 10, 16]. Hence reductions in itraconazole AUC values of about 51% in uremic patients on dialysis compared to those not dialyzed, and an AUC reduction of about 41% on coadministration with orange juice have been deemed clinically insignificant [15,17]. Thus, it appears that the slight decrease in the AUC of itraconazole and hydroxyitraconazole observed in this study is not likely to significantly influence its antifungal activity. Results from the fluconazole treatment clearly indicated a lack of any interaction with the encapsulated, enteric-coated formulation of didanosine.

It should be noted that the terminal elimination phase for itraconazole, hydroxyitraconazole, and fluconazole was similar between treatments. This suggests that didanosine does not interfere with the clearance mechanisms of these compounds. Furthermore, the mean C_{\max} and $AUC_{0-\infty}$ values of didanosine obtained after concomitant administration with itraconazole and fluconazole in the present study were reasonably comparable to the values reported in healthy volunteers (1241 ng/ml and 3380 h ng/ml, respectively) and in HIV-infected subjects (830 ng/ml and 2247 h ng/ml, respectively) [2]. These data suggest that itraconazole and fluconazole do not affect the pharmacokinetics of concomitantly administered didanosine. This is not surprising since didanosine is partly metabolized by non-cytochrome P450-mediated nucleoside salvage pathways and

is partly eliminated in the urine as unchanged drug, whereas the metabolism of azole antifungal agents is cytochrome P450-mediated [18,19].

As the concern for interaction between didanosine and itraconazole or fluconazole was not related to metabolism of these compounds but was rather due to changes in gastric pH, the results from this single-dose assessment should be applicable to steady state conditions. Furthermore, there appears to be no evidence that the pharmacokinetics of itraconazole and fluconazole may be different between normal or HIV-infected subjects [16,20], and hence the results from this study can be extended to HIV-infected population.

In conclusion, the absence of pharmacokinetic drug interaction with fluconazole, and the lack of clinical relevant interaction with itraconazole suggest that the enteric-coated bead formulation of didanosine can be coadministered with fluconazole or itraconazole. In conjunction with published results with ketoconazole indicating a lack of interaction, the encapsulated, enteric-coated bead formulation of didanosine can be coadministered with azole antifungal agents whose bioavailability is likely to be influenced with changes in gastric pH.

Acknowledgements

We sincerely thank the personnel of MDS Pharma Services Inc., Sunnyvale, CA, for plasma

sample analyses and Peter Nichola, Department of Biostatistics and Data Management, Bristol-Myers Squibb, Princeton, NJ, for the statistical analyses.

These studies were conducted in accordance with the following codes and guidelines: Title 21, Part 56 CFR (Institutional Review Board Approval); Title 21, Part 50 CFR (Protection of Human Subjects); the principles of the Declaration of Helsinki and its amendments; and Good Clinical Practice.

References

- Anderson BD, Wygant MB, Xiang TX, Waugh WA, Stella VJ. Preformulation solubility and kinetic studies of 2',3'-dideoxypurine nucleosides: potential anti-AIDS agents. *Int J Pharm* 1988; **45**: 27–37.
- Knupp C, Damle B, Nichola P, Kaul S. Bioequivalence of two formulations of didanosine (ddI), enteric coated and the chewable tablet, in healthy volunteers and subjects infected with HIV. Presented at the *40th Interscience Conference on Antimicrobial Agents and Chemotherapy*; Toronto, Ont. September 17–20, 2000; Abstract 1664.
- Mummaneni V, Damle B, Kaul S, Knupp C. Lack of effect of didanosine encapsulated enteric-coated bead formulation on the pharmacokinetics of indinavir, ketoconazole, ciprofloxacin in healthy subjects. Presented at the *40th Interscience Conference on Antimicrobial Agents and Chemotherapy*, Toronto, Ont. September 17–20, 2000. Abstract 1629.
- Lin SG, Sawyerr AM, Hudson M, Secombe J, Pounder RB. Short report: the absorption of fluconazole and itraconazole under conditions of low intragastric acidity. *Aliment Pharmacol Ther* 1993; **7**: 317–321.
- Lange D, Pavao JH, Wu J, Klausner M. Effect of a cola beverage on the bioavailability of itraconazole in presence of H₂ blockers. *J Clin Pharmacol* 1997; **37**: 535–540.
- May DB, Drew RH, Yedinak KC, Bartlett JA. Effect of simultaneous didanosine administration on itraconazole absorption in healthy volunteers. *Pharmacotherapy* 1994; **14**: 509–513.
- Bluma RA, D'Andrea DT, Florentino BM, et al. Increased gastric pH and the bioavailability of fluconazole and ketoconazole. *Ann Int Med* 1991; **9**: 755–737.
- Thorpe JE, Baker N, Bromet-Peit M. Effect of oral antacid administration on the pharmacokinetics of oral fluconazole. *Antimicrob Agents Chemother* 1990; **34**: 2032–2033.
- Barone JA, Koh JG, Bierman RH, et al. Food interaction and steady-state pharmacokinetics of itraconazole capsules in healthy male volunteers. *Antimicrob Agents Chemother* 1993; **37**(4): 778–784.
- Zimmermann T, Yeates RA, Laufen H, Pfaff G, Wildfeuer A. Influence of concomitant food intake on the oral absorption of two triazole antifungal agents, itraconazole and fluconazole. *Eur J Clin Pharmacol* 1994; **46**: 147–150.
- Carrier A, Parent J. Liquid chromatographic-mass spectrometric determination of itraconazole and its major metabolite, hydroxyitraconazole, in dog plasma. *J Chromatogr Biomed Appl* 2000; **745**: 413–420.
- Wallace JE, Harris SC, Gallegos J, Foulds G, Chen TJ, Rinaldi MG. Assay of fluconazole by high-performance liquid chromatography with a mixed-phase column. *Antimicrob Agents Chemother* 1992; **36**: 603–606.
- Gibaldi M, Perrier D. Noncompartmental analyses based on statistical moment theory. In *Pharmacokinetics*, 2nd edn, Gibaldi M, Perrier D (eds). Marcel Dekker: New York, 1982; 409–418.
- Schuurmann DJ. A comparison of two one-sided test, procedures and the power approach for assessing the bioequivalence of average bioavailability. *J Pharmacokinetics Biopharm* 1987; **15**: 657–680.
- Boelaert J, Schurgers M, Matthys E, et al. Itraconazole pharmacokinetics in patients with renal dysfunction. *Antimicrob Agents Chemother* 1988; **32**: 1595–1597.
- Itraconazole [package insert]. Titusville, NJ: Janssen Pharmaceutica Inc; January 2000.
- Kawakami M, Suzuki K, Ishizuka T, Hidaka T, Matsuki Y, Nakamura H. Effect of grapefruit juice on pharmacokinetics of itraconazole in healthy subjects. *Int J Clin Pharmacol Ther* 1998; **36**: 306–308.
- Knupp CA, Shyu WC, Dolin R, et al. Pharmacokinetics of didanosine in patients with acquired immunodeficiency syndrome-related complex. *Clin Pharmacol Ther* 1991; **49**: 523–535.
- Lomaestro BM, Piatek MA. Update on drug interactions with azole antifungal agents. *Ann Pharmacother* 1998; **32**: 915–928.
- Fluconazole [package insert]. New York, NY: Pfizer Inc; June 1998.