Effect of Fluconazole on the Steady-State Pharmacokinetics of Delavirdine in Human Immunodeficiency Virus-Positive Patients

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Flucnazole, an inhibitor of certain human cytochrome P-450 isozymes, is used for the prevention and treatment of a broad range of fungal infections that predominantly affect immunocompromised individuals. This study evaluated the influence of fluconazole on the steady-state pharmacokinetics of delavirdine, a nonnucleoside inhibitor of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase, in 13 HIV-1-infected patients with CD4 counts ranging from 186 to 480/mm³. Both the control group (n = 5) and the fluconazole group (n = 8) received 300 mg of delavirdine mesylate every 8 h for 30 days; subjects in the fluconazole group took a 400-mg, once-daily dose of fluconazole on study days 16 to 30. Harvested plasma from serial blood samples collected on days 15, 16, and 30 were assayed for concentrations of delavirdine and its N-desalkyl metabolite by a reversed-phase high-pressure liquid chromatography (HPLC) method. Blood samples obtained on days 16 and 30 were also assayed for fluconazole by HPLC. Delavirdine mesylate alone and in combination with fluconazole was well tolerated. There were no significant differences (P > 0.16) in delavirdine pharmacokinetic parameters between treatment groups on day 15 or day 30. After coadministration of fluconazole and delavirdine mesylate for 2 weeks (day 30), no significant differences (P > 0.058) were observed in any delavirdine pharmacokinetic parameters relative to those after receiving delavirdine mesylate alone (day 15) after in the fluconazole group. Fluconazole pharmacokinetic parameters were similar to those previously reported for healthy volunteers and HIV-positive patients. On the basis of these findings, fluconazole and delavirdine mesylate may be taken concurrently without adjustment of the dose of either drug.

Delavirdine mesylate, a nonnucleoside reverse transcriptase inhibitor, is under development as a potential therapeutic agent for the treatment of AIDS. Delavirdine belongs to a class of compounds known as bisheteroarylpiperazines which bind to human immunodeficiency virus type 1 (HIV-1) reverse transcriptase at a site different from that to which the nucleoside analogs bind (32). The anti-HIV activity of delavirdine has been investigated in several in vitro assay systems; the 50% inhibitory concentration (IC₅₀) of delavirdine is 0.26 μM (17). In 25 primary HIV-1 isolates, delavirdine blocked viral replication in peripheral blood lymphocytes with a mean 50% effective concentration of 0.066 μM (17). At a concentration of 3 μM, delavirdine totally prevented the spread of HIV in MT-4 cell cultures (17). In other in vitro studies, delavirdine has exhibited synergy with zidovudine or zalcitabine over a wide range of concentrations (10).

After administration of delavirdine mesylate at single doses ranging from 10 to 400 mg, the oral clearance of delavirdine is relatively high (40 to 140 liters/h), indicative of first-pass elimination or poor absorption, or both. The rate of drug absorption is rapid, with peak delavirdine concentrations occurring within 1.5 h after dosing (12). The steady-state pharmacokinetics of delavirdine are nonlinear for total daily doses of 60 to 1,200 mg, as evidenced by a 40-fold decrease in oral clearance, a substantial prolongation in apparent half-life (t₁/₂), and a reduction in the ratio of formation clearance to elimination clearance of the N-desalkyl metabolite of delavirdine (2, 12). As the delavirdine mesylate daily dose increases from 400 to 1,200 mg, oral clearance decreases by about 50% and t₁/₂ increases by approximately 300% (2). The absolute bioavailability of delavirdine has not been assessed; on the basis of the urinary recovery of delavirdine and its major metabolites at steady state, delavirdine absorption is estimated to be at least 45% (13).

Flucnazole is a broad-spectrum antifungal drug used for the treatment of certain superficial and systemic infections which predominantly affect immunocompromised individuals (14, 23). Findings indicate that fluconazole could be a potent inhibitor of certain cytochrome P-450 isozymes mediating drug metabolism in humans (14). Fluconazole is water soluble and is readily absorbed from the gastrointestinal tract; peak concentrations in plasma are reached 1.5 to 2 h after oral administration. The absolute bioavailability of oral fluconazole is greater than 90% (14). Steady state is reached after 6 days of dosing. The elimination t₁/₂ of fluconazole is about 30 h. Most of the drug is excreted unchanged in the urine (14, 29).

Delavirdine mesylate is believed to be metabolized by members of the cytochrome P-450 3A subfamily (CYP3A) (37). Because fluconazole is an inhibitor of certain cytochrome P-450 isozymes, concomitant administration of fluconazole and delavirdine mesylate may result in decreased delavirdine clearance (28). Several studies and case reports have indicated that clinically relevant drug interactions may occur between fluconazole and phenytoin, warfarin, cyclosporin, rifampin, or zidovudine. However, these drug interactions occurred after high cumulative doses of fluconazole (31). Results of a fluconazole interaction study conducted with delavirdine mesylate, a
structural analog of delavirdine mesylate, showed that flucon-
azole reduced the oral clearance of ateevidine by about 40% (4).
The present study was designed to determine if flucon-
azole, administered at the highest recommended dosage for
the treatment of superficial and systemic infections, affects the
pharmacokinetics of delavirdine mesylate. The pharmacoki-
netics of fluconazole were also studied during treatment with
delavirdine mesylate. The ratio of 6-β-hydroxy cortisol to free
cortisol, a putative endogenous marker of CYP3A activity (19),
was monitored in this study to assess the effects of both del-
avirdine and fluconazole on CYP3A activity.

MATERIALS AND METHODS

Subjects. Fifteen HIV-positive volunteers were enrolled in the study after each
signed a written informed consent approved by the Biodefense (Novum) In-
ternal Review Board. All subjects were required to have written documentation of
HIV-1 infection by serologic assay (enzyme-linked immunosorbent assay), West-
ern blotting, or HIV-1 culture and a CD4 lymphocyte subset of ≥100/mm³ and
≤500/mm³ determined at the time of screening (within 30 days of study entry).
Additionally, subjects were required to have a Karnofsky performance status
≥60. Acceptable screening test results with adequate baseline organ function
were required for all subjects.

Administration. Subjects were randomly assigned to either the control
(group A) or fluconazole group. In both groups, subjects received a 300-mg oral
dose of delavirdine mesylate every 8 h on study days 1 to 30. Subjects in the
fluconazole group received a 400-mg dose of fluconazole once daily on days
16 to 30. Delavirdine mesylate was administered as three 100-mg tablets approxi-
mately 2 h after or 1 h before meals. The fluconazole treatment was taken as two
200-mg tablets in the morning with delavirdine mesylate. Each dose was taken
at least 6 oz. of water. On blood draw days, subjects were instructed to
report to the clinic fasted, and drug was administered by clinic personnel.

Safety evaluation. Reported medical events, laboratory safety evaluations, and
vital signs at screening and during the course of the study comprised the primary
safety variables of this study. Physical examinations were conducted at the initial
screening and at the end of the study.

Drug administration. Subjects were randomly assigned to either the control
group or the fluconazole group. In both groups, subjects received a 300-mg oral
dose of delavirdine mesylate every 8 h on study days 1 to 30. Subjects in the
fluconazole group received a 400-mg dose of fluconazole once daily on days
16 to 30. Delavirdine mesylate was administered as three 100-mg tablets approxi-
mately 2 h after or 1 h before meals. The fluconazole treatment was taken as two
200-mg tablets in the morning with delavirdine mesylate. Each dose was taken
with at least 6 oz. of water. On blood draw days, subjects were instructed to
report to the clinic fasted, and drug was administered by clinic personnel.

Characteristics. Thirteen subjects (1 female [fluconazole
group] and 12 males) completed the study. The mean (range)
accuracy, expressed as the ratio (percent) of the estimated concentrations to the
technical quality control (QC) standard concentrations, averaged between 96.0
and 100% for the QC standards. Assay precision, expressed as the CVs of the
estimated concentrations of QC standards, averaged between 2.6 and 3.8%.
Between-day CVs for back-calculated concentrations of calibration standards
were 0.24 to 60 μM ranged from 0.8 to 2.8%, with mean accuracies within 9.5% of
the nominal concentrations. Assay accuracy averaged between 96.0 and 100% for
the QC standards; assay precision averaged between 2.6 and 3.4%.

Plasma samples were assayed for fluconazole concentrations by a validated,
sensitive, and specific isocratic HPLC method. Fluconazole and the internal
standard, clindamycin, were extracted into chloroform-ethyl ether (1:1) after the
addition of 0.5 M sodium hydroxide and cyclohexane, and the solvent was
 evaporated to dryness under nitrogen and reconstituted in the mobile phase, 0.01
M KH2PO4 (pH 3.8)–CH3CN (77:23, vol/vol). Chromatographic separation was
achieved with a reverse-phase guard and analytical column (DuPont Zorbax RX
C8). The analytes were detected with UV light at a wavelength of 210 nm.

RESULTS

Demographics. Thirteen subjects (1 female [fluconazole
group] and 12 males) completed the study. The mean (range)
age, weight, and CD4 count in the control group (n = 5) were 39 years (34 to 50 years), 72 kg (63 to 79 kg), and 260 cells/mm³ (192 to 402 cells/mm³), respectively. In the fluconazole group (n = 8), the mean (range) age, weight, and CD4 count were 32 years (22 to 41 years), 69 kg (53 to 81 kg), and 298 cells/mm³ (186 to 480 cells/mm³), respectively. The most common concomitant medications were zidovudine (four patients) and trimethoprim-sulfamethoxazole (Bactrim; four patients).

**Safety evaluation.** There were no serious medical events. The most frequently reported events were headache, rash, and pruritus. Headache and rash were equally reported in each treatment group. Pruritus occurred in one subject in the control group and in six subjects in the fluconazole group. Thirteen patients completed all aspects of the study. Six patients experienced a rash that was possibly attributed to delavirdine mesylate. In five of these patients, onset of the rash varied between day 5 and day 10 of the study. All five of these patients were dosed through the rash, with resolution of the rash occurring between day 9 and day 23. One patient reported an episode of rash on day 1 which resolved on day 5 but then recurred on days 13 through 22; the patient was dosed through both episodes. One patient voluntarily dropped from the study on day 15 because he wanted to take noninvestigational medications disallowed by the protocol. Another patient dropped from the study prior to day 15 due to protocol noncompliance (the subject took an excluded medication, fluconazole).

There were no clinically meaningful changes in vital signs (systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, respiration, temperature) in either treatment group. Laboratory safety data (hematology, clinical chemistries, urinalysis) were unremarkable, with no clinically meaningful or drug-attributed changes occurring following drug administration.

**Delavirdine and desalkyl delavirdine pharmacokinetics.** Visual examination of trough delavirdine levels showed that steady state was reached for each subject by day 11 of dosing. Mean steady-state morning trough plasma delavirdine levels averaged between 15.2 and 22.7 μM in the control group. In the fluconazole group, the average steady-state trough delavirdine concentration ranged from 12.4 to 18.0 μM through day 16; the mean trough concentration was unchanged after initiating fluconazole treatment (range, 13.3 to 18.4 μM). Mean trough levels of desalkyl delavirdine were below 3.1 μM throughout the 30-day study period in both treatment groups. Average metabolite concentrations were unaltered in the fluconazole group after delavirdine mesylate was administered with fluconazole.

Plasma delavirdine concentration-time profiles for morning dosing intervals on days 15, 16, and 30 are depicted in Fig. 1. In the control group, average drug concentrations were similar for all 3 days. Fluconazole had no apparent effect on delavirdine concentrations. Mean steady-state plasma delavirdine concentrations did not differ on days 15, 16, and 30 in the fluconazole group.

As was observed for delavirdine, average levels of desalkyl delavirdine on days 15, 16, and 30 were similar in the control group (Fig. 2A). In the fluconazole group, there was no difference in desalkyl delavirdine concentrations between days 15 and 30; the metabolite concentration-time profile was slightly lower on day 16 than on days 15 and 30 (Fig. 2B).

**FIG. 1.** Mean ± standard deviation steady-state plasma delavirdine concentrations in control group (n = 5) on delavirdine mesylate at 300 mg every 8 h for 30 days (A) and fluconazole group (n = 8) on delavirdine mesylate at 300 mg every 8 h (days 1 to 30) and fluconazole at 400 mg once daily (days 16 to 30) (B).

Median values of desalkyl delavirdine pharmacokinetic parameters for the control and fluconazole groups are provided in Tables 1 and 2, respectively. There were no significant differences in pharmacokinetic parameters between treatment groups on day 15, day 16, or day 30 (P > 0.21). Within-group comparisons showed no significant differences in parameters between study days 15 and 16 or between study days 15 and 30 for the control group (P ≥ 0.059). Significant differences in the Fluc and CLp/CLm were observed between study days 15 and 16 in the fluconazole group; however, these differences were small (<22%). After coadministration of fluconazole and delavirdine mesylate for 2 weeks (day 30), no significant differences (P ≥ 0.059) were found in any pharmacokinetic parameters relative to those after receiving delavirdine mesylate alone (day 15) in the fluconazole group.

Median values of desalkyl delavirdine pharmacokinetic parameters for the control and fluconazole groups are presented in Tables 1 and 2, respectively. No significant between-group differences in pharmacokinetic parameters were observed on day 15, day 16, or day 30 (P > 0.15). Metabolite parameters did not differ significantly between study days 15 and 16 or between days 15 and 30 for the control group (P ≥ 0.059). In the fluconazole group, significant differences in the values of Cmin, Cmax, and t1/2 were observed after 1 day of coadministration of fluconazole and delavirdine mesylate (day 16) relative to the values after the administration of delavirdine mesylate alone (day 15). However, these differences were all small (<30%). As was found with the parent drug, metabolite pa-
rameters on day 30, 2 weeks after initiating the concurrent administration of fluconazole and delavirdine mesylate, did not differ significantly from those observed on day 15 (delavirdine mesylate alone ($P = 0.059$)).

**Fluconazole pharmacokinetics.** For fluconazole, visual examination of trough concentrations in individual subjects indicated that steady state was attained for each subject within 6 days of dosing (day 22), with an average steady-state trough fluconazole concentration ranging between 14.2 and 15.1 µg/ml. Fluconazole pharmacokinetic parameters on days 16 and 30 are provided in Table 3. The fluconazole CLp.o. was significantly lower (22%), AUC was significantly greater (32%), and $C_{max}$ was significantly higher (threefold) on day 30 (after 2 weeks of fluconazole) than on day 16 (first dose of fluconazole).

**Cortisol ratios.** There were no significant differences in the median cortisol ratios (6-β-hydroxycortisol to free cortisol) between groups on day 15, 16, or 30 ($P > 0.07$). Also, within-group comparisons of cortisol ratios for subjects receiving fluconazole and delavirdine mesylate showed no significant difference ($P > 0.15$) between median ratios on day 15 (before fluconazole administration, 3.7 [range, 0.8 to 10]) and day 16 (after the first dose of fluconazole, 2.2 [range, 1.0 to 4.0]) or day 30 (after 2 weeks of fluconazole treatment, 1.8 [range, 0.8 to 6.4]). In both subject groups the cortisol ratio was highly variable.

The median ratio of 6-β-hydroxycortisol to free cortisol pooled across subject groups was significantly reduced from the baseline value (5.0 [range, 1.3 to 13]) after treatment with delavirdine mesylate for 24 h (2.0 [range, 1.1 to 5.5]; $P = 0.0058$). By day 15, the cortisol ratio (3.7 [range, 0.8 to 10]) was not significantly different from the baseline value ($P = 0.10$).

**DISCUSSION**

Findings from studies with both rat and human liver microsomes have suggested that the oxidative metabolism of delavirdine is mediated, at least in part, by CYP3A and that delavirdine inhibits its own metabolism both acutely and chronically (37). Results of several multiple-dose clinical studies have furthermore suggested that delavirdine has an acute inhibitory effect on CYP3A, as shown by reductions in the urinary ratio of 6-β-hydroxycortisol to free cortisol (2, 5, 9). This acute effect was also observed in the present study, with day 2 cortisol ratios being significantly reduced relative to baseline values. By day 15 (steady state) the ratios had returned to baseline values.

Fluconazole, an inhibitor of hepatic microsomal enzymes in humans, did not affect the pharmacokinetics of delavirdine when the two compounds were coadministered in this multiple-dose study. Steady-state plasma delavirdine concentrations and pharmacokinetic parameters in both the control group

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**TABLE 1. Delavirdine and desalkyl delavirdine pharmacokinetic parameters after oral administration of delavirdine mesylate to the control group**

<table>
<thead>
<tr>
<th>Drug and day</th>
<th>CLp.o. (liters/h)</th>
<th>$C_{min}$ (µM)</th>
<th>$C_{max}$ (µM)</th>
<th>$T_{max}$ (h)</th>
<th>Fluct</th>
<th>$t_{1/2}$ (h)</th>
<th>$\text{CL}_{F/\text{CLM}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delavirdine</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>3.5 (2.0–4.8)</td>
<td>19 (14–34)</td>
<td>10 (7.6–24)</td>
<td>31 (22–44)</td>
<td>1.0</td>
<td>2.8 (1.8–3.4)</td>
<td>4.9 (4.3–8.5)</td>
</tr>
<tr>
<td>16</td>
<td>3.4 (2.3–5.5)</td>
<td>20 (12–29)</td>
<td>14 (6.6–23)</td>
<td>26 (20–36)</td>
<td>2.0</td>
<td>1.9 (1.5–2.5)</td>
<td>6.1 (4.2–13)</td>
</tr>
<tr>
<td>30</td>
<td>3.6 (2.3–5.4)</td>
<td>19 (13–29)</td>
<td>12 (7.8–19)</td>
<td>28 (18–40)</td>
<td>0.75</td>
<td>2.4 (2.0–2.8)</td>
<td>5.6 (4.6–5.7)</td>
</tr>
</tbody>
</table>

| **Desalkyl delavirdine** | | | | | | | |
| 15          | 2.8 (2.4–3.8)    | 2.1 (2.0–3.4)  | 3.2 (2.0–4.2)  | 2.5 (1.5–6.0)| 1.5   | 1.2 (1.2–1.6)| 13 (7.0–15)$^b$  |
| 16          | 2.4 (2.1–3.6)    | 2.0 (1.8–3.4)  | 2.8 (2.3–4.0)  | 2.5 (0.75–6.0)| 1.3   | 1.2 (1.2–1.6)| 7.3 (7.3–16)$^c$  |
| 30          | 2.5 (2.2–4.0)    | 2.0 (1.9–3.2)  | 2.8 (2.5–4.5)  | 2.5 (1.0–5.0)| 1.4   | 1.3 (1.3–1.4)| 11 (6.4–15)       |

$^a$ Delavirdine mesylate was administered to the control group ($n = 5$) at a dosage of 300 mg every 8 h for 30 days. Values are medians (ranges).

$^b$ $n = 4$.

$^c$ $n = 3$. 

FIG. 2. Mean ± standard deviation steady-state plasma desalkyl delavirdine concentrations in control group ($n = 5$) on delavirdine mesylate at 300 mg every 8 h for 30 days (A) and fluconazole group ($n = 8$) on delavirdine mesylate at 300 mg every 8 h (days 1 to 30) and fluconazole in both lines as indicated 400 mg once daily (days 16 to 30) (B).
Significant increases in phenytoin when the two compounds were coadministered (3).

Fluconazole at 400 mg once daily was administered with delavirdine mesylate at 300 mg every 8 h.

Delavirdine at 300 mg every 8 h (days 1 to 30) and fluconazole at 400 mg once daily (days 16 to 30) were administered to the fluconazole group (n = 8).

M. Metabolite parameters did not differ significantly among study days for the control group. Although statistically significant differences in several metabolite pharmacokinetic parameters were observed after 1 day of coadministration of fluconazole and delavirdine mesylate (day 16) relative to those after the administration of delavirdine mesylate alone (day 15), these differences were small (<30%) and were not present after 2 weeks of treatment with fluconazole and delavirdine mesylate (day 30). The cortisol ratio also remained unchanged after fluconazole was added to the delavirdine mesylate dosing regimen. These findings indicate that fluconazole does not appear to inhibit the metabolism of delavirdine. Although this study was conducted with a 900-mg total daily dose of delavirdine mesylate and the currently recommended dose is 1,200 mg (400 mg three times daily), results of several pharmacokinetic studies have demonstrated that due to the high intersubject variability in the pharmacokinetics of delavirdine, there is considerable overlap in drug concentrations between these dosing regimens. Overall, the mean steady-state trough delavirdine level for a dosage of 900 mg/day in the present study (about 12 μM) is similar to the value reported for patients receiving a dosage of 1,200 mg/day (about 14 μM) (5, 6). Thus, the findings from this study should be applicable to the recommended delavirdine mesylate dosage regimen.

There are many reports of clinically significant drug interactions when fluconazole is coadministered with other compounds which are metabolized by cytochrome P-450. Fluconazole administered at a dosage of 200 mg/day resulted in a 75% increase in the AUC and a 128% increase in the AUC (liters/h) (5, 6). The area under the prothrombin activity curve for warfarin was just 7% higher when this compound was taken with fluconazole (23). Fluconazole had different effects on the multiple-dose pharmacokinetics of two compounds whose metabolic pathways are unknown, didanosine and rifabutin. Pharmacokinetic parameters for didanosine were unchanged, whereas the AUC and Cmax of rifabutin were increased by about 80% when each of these compounds was taken with fluconazole (7, 30). These findings suggest that the inhibitory action of fluconazole is selective for certain cytochrome P-450 isozymes and that substrates for CYP2C are the most greatly affected by fluconazole. This is consistent with the lack of a pharmacokinetic interaction between fluconazole and delavirdine, a compound that does not appear to be metabolized by CYP2C. The results of in vitro studies have indicated that the metabolism of delavirdine is not affected by sulphasphenazole, a known CYP2C9 inhibitor (35, 36). Fluconazole did, however, appear to inhibit the metabolism of atevirdine, a structural analog of delavirdine. Atevirdine CLp.o. was 38% lower, resulting in about 30% higher steady-state plasma drug concentra-

### Table 2. Delavirdine and desalkyl delavirdine pharmacokinetic parameters after oral administration of delavirdine mesylate and fluconazole to the fluconazole group

<table>
<thead>
<tr>
<th>Drug and day</th>
<th>CLp.o. (liters/h)</th>
<th>Cmax (μM)</th>
<th>Cmin (μM)</th>
<th>Cmax (μM)</th>
<th>Tmax (h)</th>
<th>Fluc</th>
<th>t1/2 (h)</th>
<th>CLp/CLM</th>
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<tr>
<td>Delavirdine</td>
<td></td>
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</tr>
<tr>
<td>15</td>
<td>4.6 (1.6–16)</td>
<td>7.2 (1.1–28)</td>
<td>24 (8.5–54)</td>
<td>1.0 (1.0–2.0)</td>
<td>3.1 (1.9–7.7)</td>
<td>4.5 (2.1–6.2)</td>
<td>0.17 (0.08–0.64)</td>
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<tr>
<td>16</td>
<td>4.8 (1.7–15)</td>
<td>7.8 (1.3–27)</td>
<td>21 (7.0–51)</td>
<td>1.5 (1.0–2.5)</td>
<td>2.6 (1.7–5.4)</td>
<td>4.7 (3.5–7.2)</td>
<td>0.14 (0.08–0.47)</td>
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<tr>
<td>30</td>
<td>4.6 (1.4–12)</td>
<td>7.1 (2.6–35)</td>
<td>23 (9.2–64)</td>
<td>1.0 (0.75–1.5)</td>
<td>3.1 (1.6–4.0)</td>
<td>4.8 (3.6–12)</td>
<td>0.15 (0.09–0.42)</td>
<td></td>
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<tr>
<td>Desalkyl delavirdine</td>
<td>2.7 (2.4–3.4)</td>
<td>2.0 (1.7–2.9)</td>
<td>3.3 (2.7–3.7)</td>
<td>2.2 (1.0–4.0)</td>
<td>1.5 (1.3–2.1)</td>
<td>10 (4.8–18)</td>
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<tr>
<td>16</td>
<td>2.2 (1.8–3.0)</td>
<td>1.9 (1.5–2.7)</td>
<td>2.6 (2.1–3.4)</td>
<td>2.0 (0.0–3.0)</td>
<td>1.4 (1.2–1.7)</td>
<td>13 (10–19)</td>
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<td>30</td>
<td>2.5 (2.0–4.5)</td>
<td>1.9 (1.6–4.1)</td>
<td>2.8 (2.4–5.0)</td>
<td>1.5 (0.75–4.0)</td>
<td>1.5 (1.2–1.6)</td>
<td>13 (5.2–27)</td>
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</table>

* Delavirdine mesylate at 300 mg every 8 h (days 1 to 30) and fluconazole at 400 mg once daily (days 16 to 30) were administered to the fluconazole group (n = 8).

### Table 3. Fluconazole pharmacokinetic parameters after oral administration of fluconazole on study days 16 to 30

<table>
<thead>
<tr>
<th>Day</th>
<th>CLp.o. (liters/h)</th>
<th>AUC (μg · h/ml)</th>
<th>Cmax (μg/ml)</th>
<th>Cmin (μg/ml)</th>
<th>Cmax (μg/ml)</th>
<th>Tmax (h)</th>
<th>t1/2 (h)</th>
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</thead>
<tbody>
<tr>
<td>16</td>
<td>1.2 (0.77–1.8)</td>
<td>323 (220–520)</td>
<td>18 (14–26)</td>
<td>8.5 (6.8–12)</td>
<td>1.5 (1.0–6.0)</td>
<td>30 (22–48)</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>0.94 (0.64–1.2)</td>
<td>426 (347–626)</td>
<td>13 (11–21)</td>
<td>24 (20–36)</td>
<td>1.8 (1.0–3.0)</td>
<td>34 (24–68)</td>
<td></td>
</tr>
</tbody>
</table>

* Fluconazole at 400 mg once daily was administered with delavirdine mesylate at 300 mg every 8 h.

* P = 0.014.

* AUCp.0. on day 16; AUCp.2. on day 30.
tions when atevirdine mesylate was taken with fluconazole (4). Detailed in vitro metabolism studies with atevirdine have not been conducted. However, on the basis of what is known about the effects of fluconazole on cytochrome P-450, it can be inferred that the relative proportion of isof orm systems responsible for the metabolism of atevirdine and delavirdine differ, with the possible involvement of CYP2C isozymes in the bio-transformation of atevirdine.

Although this study was not designed to look at the potential effect of delavirdine mesylate on fluconazole pharmacokinetics, it is possible to make some general observations in relation to published pharmacokinetic data for fluconazole. Fluconazole pharmacokinetic parameters in this study were similar to those previously reported for healthy volunteers, HIV-positive patients, and patients with AIDS who show no clinical signs of safety, tolerance, and pharmacokinetics of oral U-90152S (delavirdine DLV) in HIV-1 infected males and females with CD4 counts of 200–500 cells/mm³, which are maintained on a stable dose of AZT, abstr. 564, p. 158. In Program and abstracts of the First National Conference on Human Retroviruses and Related Infections. American Society for Microbiology, Washington, D.C.


