D0870 is a triazole with a broad antifungal spectrum, and it has been shown to have both in vitro and in vivo activities against wild-type and fluconazole-resistant strains of *Candida albicans*. Twenty-two human immunodeficiency virus (HIV)-positive male subjects were enrolled in an open, nonrandomized trial investigating the pharmacokinetics of two different dosing regimens of D0870 and assessing the safety of multiple oral doses of D0870 in HIV-positive subjects and their ability to tolerate multiple oral doses. Nine subjects received an initial loading dose of 50 mg, followed by four once-daily maintenance doses of 10 mg. A further nine subjects received an initial 200-mg loading dose followed by four daily maintenance doses of 25 mg. All subjects were fasting. A single loading dose of 50 mg of D0870 resulted in a mean maximum concentration in serum ($C_{\text{max}}$) of 107 ± 32 ng/ml. Concentrations in plasma were maintained by the 10-mg once-daily dosing regimen as seen by the similar values of the area under the concentration-time curve from 0 to 24 h following dosing on days 1 and 5 and a mean accumulation ratio close to unity (0.90). The terminal plasma half-life of D0870 in plasma following dosing on day 5 ranged from 23 to 85 h (mean, 49 h). A single loading dose of 200 mg of D0870 resulted in a $C_{\text{max}}$ of 431 ± 186 ng/ml. Concentrations in plasma were again maintained by the 25-mg daily dosing regimen, with the mean accumulation ratio being close to unity (1.17). The terminal half-life of D0870 in plasma following dosing on day 5 of phase II of the study ranged from 34 to 137 h (mean, 71 h). In addition, the concentrations achieved in the plasma of these HIV-positive subjects were similar to the values predicted from simulations based on data derived from normal, healthy subjects. D0870 was well tolerated. No serious adverse events were experienced during the course of the study, and all volunteers completed the trial. A total of 15 adverse events were reported, but none were considered to be related to the administration of D0870 and all had resolved by the end of the trial. No changes in the hematology, clinical chemistry, or urinalysis parameters were considered to be related to dosing with D0870. No clinically significant changes in the electrocardiogram parameters were noted during the trial. The data generated in this trial support further investigation of these regimens with HIV-positive subjects with fluconazole-susceptible or -resistant oropharyngeal candidiasis.

The preclinical evaluation of D0870 has shown it to be extensively metabolized in rats and cynomolgus monkeys but to have a less complex metabolite profile in dogs. Prior to the start of the study none of the metabolites of D0870 had been tested for bioactivity. D0870 has also been demonstrated to be both an enzyme inducer and an inhibitor of P-450 and to be highly bound (98%) to human plasma proteins. The absolute bioavailability of D0870 was high and ranged from 56 to 60% in male cynomolgus monkeys and male dogs to 80 to 100% in female and male rats. In the safety evaluation, D0870 exhibited nonlinear kinetics with a decrease in clearance from plasma and a consequent increase in the terminal elimination half-life ($t_{1/2}$) for both increasing dose and duration of dosing. However, in an initial clinical study, ascending single oral doses in a cyclodextrin solution were given to healthy human volunteers on a milligram-per-kilogram basis, with the doses ranging from 0.042 to 2.86 mg/kg of body weight (2 to 190 mg). This trial showed that the mean elimination $t_{1/2}$ from plasma was 3.3 days (range, 1.1 to 8.0 days) and that the exposure to D0870 was in proportion to the increase in dose based on the maximum concentration of drug in serum ($C_{\text{max}}$) and the area under the concentration-time curve (AUC) from time zero to infinity (AUC$_{\text{0-\infty}}$). A further study demonstrated that the bioavailabilities of D0870 administered as tablets or in a cyclodextrin solution are comparable (mean ratio, 0.91; 95% confidence interval, 0.75 to 1.12) (22).

The aims of the trial described here were to investigate two...
potentially clinically relevant multiple-dose regimens of D0870 considered suitable for use in the treatment of oropharyngeal candidosis caused by fusocan-susceptible and -resistant strains to assess the tolerability, safety, and pharmacokinetics of these regimens. In studies with D0870 administered orally to cynomolgus monkeys, increases in the QT and the corrected QT (QTC) intervals were clearly related to the dose and the level in blood. These increases in the QT and QTC intervals are fully reversible following the withdrawal of D0870. These findings were also observed in studies with dogs. Hence, during this study electrocardiograms (ECGs) were monitored closely. The trial has been conducted with HIV-positive subjects because it was predicted that D0870 would have a major clinical use in this group of subjects, in whom D0870 might have pharmacokinetic characteristics (related to absorption and metabolism) which differ from those in normal, healthy subjects.

MATERIALS AND METHODS

Study design. The present study was a single-center, open, ascending-oral-dose, nonrandomized trial. Initially, HIV-positive volunteers received an initial loading dose of 10 mg of D0870 followed by four daily maintenance doses of 10 mg. A further group of HIV-positive subjects received an initial 200 mg loading dose of D0870, followed by four daily maintenance doses of 25 mg. The dosing of the second group could be initiated only if no safety issues had been identified during the previous dosing.

Approval for the trial was given by an independent ethics committee.

Subjects. HIV-positive subjects volunteering to take part in the trial could be included if they were males, were between 18 and 62 years of age, and had a history of alcohol or drug abuse.

The volunteers were clinically assessed for disease status and were assigned to the following CDC categories: A (n = 4), B (n = 13), and C (n = 1). The mean CD4 cell count was 276 cells/mm³ (range, 49 to 659 cells/mm³). Nine subjects were entered into part I of the study and nine subjects were entered into part II of the study.

The following concomitant medications were prohibited: other investigational drugs, anti-AIDS agents known to affect carbohydrate or alcohol metabolism or those known to affect calcium or magnesium metabolism or, if so, drug therapy baseline level.

The following pharmacokinetic parameters were assessed: Cmax, on days 1 and 5, AUC0–24 on days 1 and 5, t1/2 after administration of the last dose, and the accumulation ratio based on the AUC0–24 on days 1 and 5, AUC0–24 on days 1 and 5, t1/2 after administration of the last dose, and the accumulation ratio based on the AUC0–24 on days 1 and 5

The concentrations of D0870 in plasma were estimated with blood samples taken on days 1 and 5 before dosing and 1, 2, 3, 4, 6, 8, 10, 12, and 18 h after dosing; on days 2, 3, 4, and 5 before dosing; and on days 6, 7, 9, 12, and 19 after dosing. Similarly, 24 to 336 h after administration of the first dose; 4, 8, 12, and 24 h after administration of the second dose (i.e., 24 h after the administration of the first dose), plasma D0870 levels remained above the limit of detection (2.01 ng/ml) 14 days after administration of the last dose (day 19), further samples were taken at fortnightly intervals until the level of D0870 in plasma was predicted to have fallen below the limit of detection. Samples for pharmacokinetic analysis were centrifuged at 1,000 × g for 10 min (4°C), and the plasma was deep frozen and stored at –20°C until it was analyzed. At –20°C D0870 was found to be stable for up to 1 month in human plasma.

The samples were analyzed for D0870 by high-performance liquid chromatography with UV detection by the following procedure. To an aliquot (1 ml) of each unknown was added an internal standard (ZM196144), borate buffer (1 ml; pH 10), and methyl-tertiary butyl ether (5 ml). After shaking on a reciprocating shaker for 10 min and centrifuging at 1,000 × g for 5 min at 5°C to separate the phases, the organic layer was removed, placed in a clean tube, and evaporated to dryness under oxygen-free nitrogen at 25°C. The extracted dry residue was reconstituted in a suitable amount of mobile phase and was injected onto the following high-performance liquid chromatography system: a Hichrom RP-18 column (5 µm, 4.6 mm inner diameter) with a linear mobile phase with a base and a mobile phase of degassed acetonitrile-water (55:45) plus 1 µl of trifluoroacetic acid per liter. The flow rate was 1 ml/min. The detector was a variable-wavelength UV spectrophotometer set at 292 nm.

A calibration series covering the expected concentration range was constructed in control human plasma by adding known amounts of D0870 and an amount of internal standard equivalent to the amount added to the unknowns and extracted together with each batch of unknowns. The data were captured and processed by using the VG Multichrom (version 2) laboratory data capture system incorporating a 1/2 weighting factor to the calibration regression, where x is the known concentration of each calibration. Unknown concentrations of D0870 were determined by comparison of the peak height ratios to the calibration series. The chromatography was free of any endogenous or exogenous components at the relevant retention times and had a total assay variation of less than 10% for concentrations in excess of the limit of detection of 2.01 ng/ml, for which it was 15%.

The following pharmacokinetic parameters were assessed: Cmax, on days 1 and 5, AUC0–24 on days 1 and 5, t1/2 after administration of the last dose, and the accumulation ratio based on the AUC0–24 on days 1 and 5, AUC0–24 on days 1 and 5

The samples were analyzed for D0870 by high-performance liquid chromatography with UV detection by the following procedure.
TABLE 1. Mean values of pharmacokinetic parameters for D0870 for trial days 1 and 5 and accumulation ratio

<table>
<thead>
<tr>
<th>Study part and day</th>
<th>AUC(_{0-24}) (ng \cdot h/ml)(^a)</th>
<th>(C_{\text{max}}) (ng/ml)(^a)</th>
<th>(T_{\text{max}}) (h)(^b)</th>
<th>(t_{1/2}) (h)(^c)</th>
<th>Accumulation ratio (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1 ((n = 9))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1,733.49 (494.95)</td>
<td>106.47 (32.87)</td>
<td>3.00 (3–10)</td>
<td>8.00 (3–12)</td>
<td>48.85 (22.56)</td>
</tr>
<tr>
<td>5</td>
<td>1,657.65 (1,014.92)</td>
<td>87.08 (49.47)</td>
<td>8.00 (3–12)</td>
<td>48.85 (22.56)</td>
<td>0.96 (0.45–1.86)</td>
</tr>
<tr>
<td>Part 2 ((n = 9))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7,785.36 (2,963.86)</td>
<td>431.34 (186.27)</td>
<td>8.00 (3–24)</td>
<td>70.51 (34.28)</td>
<td>1.17 (0.29–2.57)</td>
</tr>
<tr>
<td>5</td>
<td>7,748.11 (3,728.80)</td>
<td>429.96 (193.90)</td>
<td>6.00 (3–10)</td>
<td>70.51 (34.28)</td>
<td>1.17 (0.29–2.57)</td>
</tr>
</tbody>
</table>

\(\text{Values are means (standard deviations).}\)
\(\text{Values are medians (ranges).}\)

RESULTS

Pharmacokinetics. The mean values of the pharmacokinetic parameters obtained following dosing with D0870 on days 1 and 5 are presented in Table 1. A single loading dose of 50 mg of D0870 resulted in a mean \(C_{\text{max}}\) of 107 ng/ml. \(T_{\text{max}}\) ranged from 3 to 12 h. The concentrations of D0870 in plasma were relatively well maintained by the 10-mg once-daily dosing regimen, as seen by the similar AUC\(_{0-24}\) values obtained following dosing on days 1 and 5 and a mean accumulation ratio calculated to be related to dosing with D0870. A review of the ECG and laboratory results at the end of the trial. No changes in any of the hematology, clinical chemistry, or urinalysis parameters were considered to be related to dosing with D0870. A review of the ECG and Holter monitoring parameters by an independent cardiologist did not identify any significant abnormalities during the trial. There were no deaths during the trial.

DISCUSSION

D0870 is a triazole antifungal agent which belongs to the same structural class as fluconazole and itraconazole. D0870, in common with the related triazoles, exerts its antifungal activity through selective inhibition of the fungal P-450-dependent 14-alpha-demethylase step in ergosterol biosynthesis, resulting in a fungistatic mechanism. In vitro D0870 is highly active against a wide range of fungi, including various Candida species, Aspergillus species, Cryptococcus neoformans, Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis, Sporothrix schenckii, Trichophyton species, and Pseudallescheria boydii (14–16, 21).

D0870 is also active in vitro against fluconazole-resistant Candida species (20). D0870 has been shown to be active in various animal models including infections with C. albicans, Candida parapsilosis, Candida krusei, and Candida lusitaniae (1, 10, 11, 17, 21). Other infections such as cryptococcosis, histoplasmosis, coccidioidomycosis, and blastomycosis in immunocompromised mice have been treated effectively by D0870 (6, 13, 17).

The long \(t_{1/2}\) of D0870 in humans (1 to 8 days), determined after the administration of single oral doses to normal, healthy subjects, suggested that therapeutic levels of D0870 will be most rapidly achieved and maintained by means of a loading-dose-maintenance dose regimen. The doses and duration of dosing used in this trial were designed to be potentially clinically effective against fluconazole-susceptible and fluconazole-resistant strains causing oropharyngeal candidosis. On the basis of the \(t_{1/2}\) observed in the study, loading dose-maintenance dose ratios of 5 to 1 and 8 to 1 were chosen such that patients in whom the \(t_{1/2}\) of D0870 was at each end of the \(t_{1/2}\) range would not have significant over- or underexposure over the 5-day dosing period. An additional aim of this study was to assess if the pharmacokinetics of D0870 in HIV-positive subjects was significantly different from the pharmacokinetics in normal, healthy subjects. Plasma concentration-time data after oral dosing of D0870 to normal, healthy subjects (22) was modeled with a one-compartment oral model with a lag time. Parameters from this model were then used to predict the concentrations in plasma resulting from the dosing regimens chosen for this trial, and these were compared to the concentrations that were actually determined.

A mean \(C_{\text{max}}\) of 107 and 431 ng/ml after the administration of single doses of 50 and 200 mg, respectively, compared well to the predicted range of D0870 (52 to 135 ng/ml). The range of \(C_{\text{max}}\)s observed (34 to 174 ng/ml) after the administration of 50 mg of D0870 followed by the administration of 10 mg/day for 4 days compared well to the predicted range of D0870 (52 to 135 ng/ml). The range of terminal \(t_{1/2}\)s seen in HIV-positive subjects after the administration of multiple doses (1 to 6 days) was also similar to the range seen in normal, healthy subjects after the administration of single doses. Terminal \(t_{1/2}\)s were longer after the higher-dose regimen. It is probable that this reflects the trial design and subject randomization rather than evidence of dose-dependent kinetics. In addition, the accumulation in individual subjects seen over the dosing period, which was within acceptable limits, correlated well with the final terminal \(t_{1/2}\).

Within each regimen similar exposures, as assessed by the AUC over the doing interval, were achieved between days 1 and 5.

In summary, there was no evidence of nonlinear kinetics following the administration of multiple doses of D0870 and no
evidence of a difference in the pharmacokinetics of D0870 in HIV-positive subjects compared to that in normal, healthy subjects. In addition, the exposures were comparable on days 1 and 5, and D0870 was well tolerated, with no safety issues. This study supported the further investigation of these regimens in HIV-positive patients with oropharyngeal candidosis caused by fluconazole-susceptible and fluconazole-resistant strains. Data from these later studies indicated that no safe and effective dosing regimen could be established, and the development of D0870 was discontinued outside Japan.

REFERENCES