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# The pharmacokinetics of oral itraconazole in AIDS patients

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**Abstract**—To test the hypothesis that absorption of orally administered itraconazole may be reduced in patients with the Acquired Immunodeficiency Syndrome (AIDS), 8 patients with AIDS were given two 100 mg capsules of itraconazole for 15 days. Plasma levels were measured by HPLC hourly for the first 8 h following ingestion, then at 24, 48, 72 and 96 h on days 1, 8 and 15. Peak plasma levels occurred after approximately 4 h. Mean peak plasma concentrations were $446 \pm 196$ and $530 \pm 214$ ng $mL^{-1}$ at days 8 and 15. The area under the curve over 24 h ($AUC_{0-24}$) was $2105 \pm 1241$, $7679 \pm 3838$ and $8748 \pm 4385$ ng $mL^{-1}$ h for days 1, 8 and 15, respectively. Steady-state was achieved after one week of dosing. There was no evidence of hepatotoxicity and one patient stopped itraconazole due to a rash. It may be concluded that the absorption of oral itraconazole capsules is reduced in AIDS patients, by a factor of approximately 50%, when compared with normal volunteers. AIDS patients may require higher doses of itraconazole than used in non-AIDS patients to achieve comparable plasma levels.

Itraconazole is an orally active triazole agent which has been used in patients with AIDS for the treatment of oral or oesophageal candida infections (Smith et al 1991), a number of systemic mycoses including cryptococcosis (Denning et al 1989a), histoplasmosis (Saag et al 1988; Kell et al 1991), aspergillosis (Denning et al 1989b) and coccidioidomycosis (Tucker et al 1990).

As other azoles, such as ketoconazole, have impaired absorption in AIDS patients (Lake-Bakaar et al 1988), probably related to a degree of hypochlorhydria (Lake-Bakaar et al 1987), it was hypothesized that the absorption of itraconazole, which is dependent on gastric acidity, may also be reduced. The pharmacokinetics of orally administered itraconazole was therefore evaluated in 8 AIDS patients over a 15 day period.

## Patients and methods

All patients had AIDS as defined by the Centers for Disease Control (Centers for Disease Control 1987) and gave written informed consent for the study, which was approved by the local ethics committee. Patients less than 18 years of age, female patients and patients with either profuse diarrhoea (more than three liquid stools per day), severe hepatic impairment or currently receiving rifampicin, antacids, anticholinergic agents or $H_2$ antagonists were excluded.

Eight male homosexual AIDS patients entered the study. Individual patient ages, weights, AIDS defining illnesses, duration of AIDS and reason for current hospital admission at entry to the study are given in Table 1. Patients received two 100 mg pelleted itraconazole capsules once daily with or immediately following breakfast for 15 days. Ten mL of blood was taken at 0, 1, 2, 3, 4, 5, 6, 8 and 24 h after the first, eighth and fifteenth doses. Further blood was taken at 32, 48, 72 and 96 h following the final dose. Samples were analysed by HPLC (Woestenborghs et al 1987) by the Pharmacokinetics Department, Janssen Pharmaceutica, Beerse, Belgium. The assay detection limit was 5 ng $mL^{-1}$.

Peak ($C_{max}$), trough ($C_{min}$), and time to peak plasma concentrations ($T_{max}$) were determined from the individual plasma concentrations. Areas under the curve of a 24 h dosing interval ($AUC_{0-24}$) were calculated by trapezoidal summation. The differences between day 1 and day 8, day 1 and 15, and day 8 and day 15 were analysed using a paired *t*-test for $C_{max}$, $C_{min}$ and $AUC_{0-24}$. $T_{max}$ was analysed using the Wilcoxon Signed Rank Sum test.

Blood samples were taken at entry, days 8 and 15 for haematology and biochemistry.

## Results

There was a significant difference between $C_{max}$ and $AUC_{0-24}$ values at days 1 and 8 ($P = 0.0035$ and $P = 0.0002$, respectively) and days 1 and 15 ($P = 0.0053$ and $P = 0.0028$, respectively) (Fig. 1) in the AIDS patients studied. There was no significant differences between $C_{max}$, $C_{min}$, $AUC_{0-24}$ and $t_{max}$ between days 8 and 15 (Table 2). There was a wide variation in individual itraconazole peak concentrations at steady state: from 200 to 725 ng $mL^{-1}$ at week one and from 212 to 736 ng $mL^{-1}$ after 2 weeks of dosing.

One patient, who had a widespread maculopapular rash at day 13, withdrew from the study because of toxicity. The rash cleared five days after discontinuing itraconazole.

There was no change in the haematological parameters measured. Three patients had elevated aspartate transaminase levels (127, 95 and 55 int. units $L^{-1}$) which fell while receiving itraconazole (to 106, 59 and 36 int. units $L^{-1}$, respectively).

Table 1. Patient features.

| Patient number | Weight (kg) | Age (years) | AIDS defining illness | Duration of AIDS (months) | Current illness |
|---|---|---|---|---|---|
| 1 | 59 | 30 | PCP | 8 | CMV retinitis |
| 2 | 61 | 32 | Wasting syndrome | 2 | Staphylococcal septicaemia |
| 3 | 43 | 36 | PCP | 2 | Cryptococcal meningitis |
| 4 | 63 | 34 | PCP | 12 | Suspected PCP |
| 5 | 76 | 52 | CMV retinitis | 17 | Chest infection |
| 6 | 64 | 40 | Oesophageal candidosis | 2 | Chest infection |
| 7 | 62 | 26 | PCP | 5 | Chest infection |
| 8 | 53 | 40 | PCP | 21 | PCP |
| Mean | 60·1 | 36·25 | | 8·6 | |

PCP = *Pneumocystis carinii* pneumonia. CMV = Cytomegalovirus.

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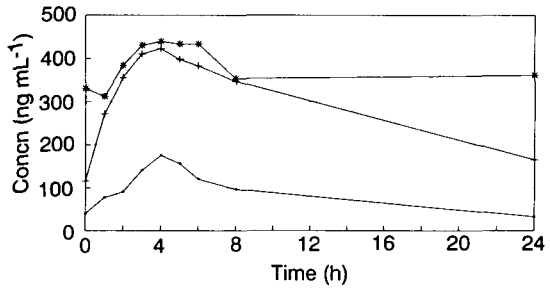


FIG. 1. Mean peak itraconazole plasma concentrations (ng $mL^{-1}$) on days 1 (■), 8 (+) and 15 (*), in 8 AIDS patients.

Table 2. Pharmacokinetic parameters of orally administered itraconazole (200 mg $day^{-1}$) after doses 1, 8 and 15.

| | Dose 1 | Dose 8 | Dose 15 |
|---|---|---|---|
| $C_{max}$ (ng $mL^{-1}$) | 196 (82) | 446* (196) | 530* (214) |
| $C_{min}$ ng ($mL^{-1}$) | — | 266 (167) | 280 (118) |
| $T_{max}$ (h) | 4·3 (1·0) | 4·9 (1·6) | 3·5 (1·8) |
| $AUC_{0-24}$ (ng h $mL^{-1}$) | 2105 (1241) | 7679* (3838) | 8748* (4385) |

* $P < 0.01$ for difference between doses 1 and 8 and between doses 1 and 15. s.d. values are shown in parenthesis.

## Discussion

The pharmacokinetic profile for these AIDS patients is similar to that seen in healthy volunteers given 100 mg once daily, where the steady-state $C_{max}$ and $AUC_{0-24}$ values of 412 ng $mL^{-1}$ and 5330 ng h $mL^{-1}$, respectively, reported by Hardin et al (1988) at day 15 are similar to that obtained after a 200 mg daily dosage in this study. This represents a reduction of almost 50% in absorption in AIDS patients. Similarly, if the $C_{max}$, $t_{max}$ and AUC values obtained for normal volunteers given a 200 mg dose are compared with AIDS patients given a 200 mg dose, then there is a significant difference between $T_{max}$ and AUC values at day 1 ($P = 0.028$ and $P = 0.039$, unpaired $t$-test) and between $C_{max}$ values at day 15 ($P = 0.019$). There is also a trend for AUC values to differ between groups at day 15 ($P = 0.055$). There was up to a threefold variation in absorption between individual AIDS patients at day 15, which is similar to that noted in normal volunteers (Hardin et al 1988).

Peak levels were reached after approximately 4 h and steady state was attained after 1 weeks treatment.

Itraconazole was well tolerated by these patients with only one adverse event (a rash), attributable to itraconazole and reversible on stopping the drug. The incidence of adverse drug reactions, predominantly rashes, appears to be increased in AIDS patients in response to many therapies (Gordin et al 1984; Centers for Disease Control 1988). The mechanism for this remains unknown. No hepatotoxicity, reported with other azoles such as ketoconazole (Hayes 1982), was seen. The three patients with abnormal liver function tests at entry to the study showed an improvement during the study.

Itraconazole has been shown to be an effective agent in-vitro (Van Cutsem 1990) against most fungi which cause disease in AIDS patients (Klein et al 1984; Graybill 1988; Clark et al 1990; Denning et al 1991), as well as other organisms such as *Leishmania* spp. (Borelli 1987). Lack of success clinically in some of these patients with orally administered itraconazole may be related to poor drug absorption and it may be necessary to use higher doses of itraconazole in those patients.

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