The Clinical Pharmacokinetics of Itraconazole: An Overview

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Summary: Itraconazole (R 51211) is the prototype of a class of triazole antifungals characterized by a high lipophilicity. This property determines to a large extent the pharmacokinetics of itraconazole and differentiates it from the hydrophilic triazole antifungal fluconazole.

The pharmacokinetics of itraconazole in man are characterized by a good oral absorption, an extensive tissue distribution with tissue concentrations many times higher than in plasma, a relatively long elimination half-life of about one day and a biotransformation into a large number of metabolites. One of them, hydroxy-itraconazole, is antifungally active and explains why antifungal plasma levels, when measured by bioassay, are about three times the itraconazole levels measured by a specific HPLC-method.

Distribution studies have shown that therapeutically active levels of itraconazole are maintained much longer in some infected tissues than in plasma. For instance, active levels persist for four days in the vaginal epithelium after a one-day treatment and for 3 weeks in the stratum corneum of the skin after treatment has been stopped. Unlike fluconazole, itraconazole does not interfere with mammalian drug metabolizing enzymes, minimizing the risk of interaction with concomitantly administered drugs. These pharmacokinetic properties may contribute to the high efficacy and safety of itraconazole in patients with various mycotic infections. New pharmaceutical formulations are being explored in order to broaden the application field of itraconazole to intravenous and oral therapy of patients with malabsorption.

Introduction

Itraconazole (Figure 1) is the prototype of a class of triazole antifungals with high lipophilicity, good oral absorption and extensive tissue distribution. Its broad-spectrum antifungal activity in experimental animals and in patients with superficial and deep mycoses and its mode of action have been described extensively. The pharmacokinetics of itraconazole in experimental animals and man have been reviewed recently. The aim of the present overview is to update the clinical pharmacokinetics of itraconazole. Since 1987, new studies and insights with regard to the
Table 1: Mean (SD) model-independent pharmacokinetic parameters of itraconazole after intravenous and oral administration of 100 mg in 6 healthy male subjects.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>i.v.</th>
<th>p.o.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>1.0 (0.0)</td>
<td>5.0 (1.1)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>664 (234)</td>
<td>127 (37)</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>25 (5)</td>
<td>21 (6)</td>
</tr>
<tr>
<td>$V_d$ (l/kg)</td>
<td>10.7 (2.7)</td>
<td>—</td>
</tr>
<tr>
<td>$C_L$ (ml/min/kg)</td>
<td>5.1 (1.3)</td>
<td>—</td>
</tr>
<tr>
<td>AUC$_{0\text{-}t}$ (µg h/ml)</td>
<td>4.60 (1.39)</td>
<td>2.48 (0.74)</td>
</tr>
<tr>
<td>$f_{\text{abs}}$ (%)</td>
<td>100</td>
<td>55 (15)</td>
</tr>
</tbody>
</table>

*1 after a one-hour infusion

Figure 1: Structure of itraconazole (R 51211).

Figure 2: Mean plasma levels of itraconazole after intravenous (one-hour infusion) and oral administration (in solution) of 100 mg of itraconazole in 6 healthy male subjects.
pharmacokinetics of itraconazole became available. These new findings together with those already published will broaden our knowledge and understanding of the clinical pharmacokinetics of itraconazole.

Physico-chemical properties and drug formulations

Itraconazole is an extremely weak base (pKₐ = 3.7) and is only ionized at a low pH, such as in gastric juice. The log partition coefficient of itraconazole in a system of n-octanol and an aqueous buffer solution of pH 8.1 is 5.66, indicative of very high lipophilicity. This property may influence its plasma protein binding and tissue distribution. Itraconazole is almost insoluble in water and in diluted acidic solutions (less than 5 μg/ml). Concentrations exceeding 10 mg/ml can be obtained only in polar organic solvents or in acidified polyethylene glycols (PEG). The latter solvent system was successfully applied in the preparation of acceptable formulations containing itraconazole dissolved in a matrix of acidified high-molecular PEGs. Capsules with this formulation (PEG capsules) were used in earlier clinical studies and later replaced by capsules with itraconazole coated pellets (pellet capsules). The bioequivalence of both capsule formulations will be discussed further. Recently, another galenic breakthrough has been realized by the introduction of the cyclodextrins. Aqueous solutions of itraconazole at concentrations of 5 mg/ml can be prepared by the addition of 5% dimethyl-β-cyclodextrin and three equivalents of methanesulphonic acid. This cyclodextrin solution has been used as a reference in bioavailability studies (see further). The solubility of itraconazole could be further increased by using hydroxypropyl-β-cyclodextrin (HP-β-CD). Presently, concentrations of itraconazole as high as 25 mg/ml can be obtained in 60% HP-β-CD. Less concentrated HP-β-CD solutions can be used for intravenous infusion of itraconazole. As discussed below, this enabled to study the intravenous pharmacokinetics and absolute bioavailability of itraconazole in man. It is also hoped that these newly developed formulations will help to get around problems of malabsorption sometimes seen in neutropenic patients.

Single-dose pharmacokinetics of itraconazole

Intravenous pharmacokinetics and absolute bioavailability.

In a randomized cross-over study with an interval of at least 2 weeks between the two phases, six healthy male subjects received 100-mg doses of itraconazole as a one-hour intravenous infusion of a 1-mg/ml solution in 8% HP-β-CD, and as a 10 mg/ml oral solution. Itraconazole doses were administered shortly after breakfast. At the end of the 1-hour infusion, itraconazole plasma levels averaged 664 ng/ml and they decayed triphasically with mean sequential half-lives of 2.5 min (α-phase), 2.35 hours (α-phase) and 25 hours (β-phase) (Figure 2, Table 1). The drug was widely distributed to the tissues with an apparent volume of distribution during the elimination phase (Vdₐrea) of 800 l (10.7 l/kg). Redistribution from the deep compartment was the rate-limiting step in the elimination of itraconazole from the body (k₃₁/k₁₀ = 0.075). Total plasma clearance averaged 381 ml/min (or 5.1 ml/min/kg), corresponding to a blood clearance of 660 ml/min (blood to plasma concentration ratio of 0.58). This represents 44% of the normal liver blood flow (1.5 l/min/70 kg). Considering the liver as the major elimination organ for itraconazole and assuming first-order kinetics of metabolism, the maximal oral bioavailability should be about 56%. After an oral 100 mg dose of itraconazole, the peak plasma levels of 127 ng/ml were about 5 times lower than those of the same dose given as an infusion (Figure 2, Table 1). The
Table 2: Influence of a meal and dose (50, 100 and 200 mg) on the pharmacokinetics of orally administered itraconazole. Mean (SD) pharmacokinetic parameters in six healthy male subjects (43).

<table>
<thead>
<tr>
<th>Dose</th>
<th>Capsules after a meal</th>
<th>Capsules fasting</th>
<th>Capsules after a meal</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>胶囊后饭</td>
<td>3.2 (1.3)</td>
<td>1.7 (0.3)</td>
</tr>
<tr>
<td>100 mg</td>
<td>胶囊后饭</td>
<td>44.5 (16.4)</td>
<td>223 (84)</td>
</tr>
<tr>
<td>200 mg</td>
<td>胶囊后饭</td>
<td>0.57 (0.26)</td>
<td>19 (4)</td>
</tr>
<tr>
<td>AUC ratio</td>
<td></td>
<td>0.32 (0.12)</td>
<td>100 (2)</td>
</tr>
</tbody>
</table>

1 relative bioavailability as compared with a solution in the fasting state
2 AUC ratios for doses of 50, 100 and 200 mg to dose of 100 mg

Table 3: Bioavailability/bioequivalence of 100-mg doses of itraconazole as two capsule formulations (PEG and pellet) versus an aqueous solution. Mean (SD) pharmacokinetic parameters in 24 healthy male subjects (44).

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Solution</td>
<td>PEG-capsule</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>4.2 (0.8)</td>
<td>3.6 (1.3)</td>
</tr>
<tr>
<td>C_{max} (ng/ml)</td>
<td>141 (90)</td>
<td>165 (123)</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>22 (6)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>AUC_{0-24} (μg h/ml)</td>
<td>2.46 (2.35)</td>
<td>2.49 (2.58)</td>
</tr>
<tr>
<td>F_{rel} (%)</td>
<td>100</td>
<td>107 (42)</td>
</tr>
<tr>
<td>F_{rel} (%)</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

1 relative bioavailability versus the solution as a reference
2 relative bioavailability versus the solution in study 1 as a reference
3 relative bioavailability versus the pellet-capsule in study 1

Terminal half-life after oral administration (21 hours) was similar to that after intravenous dosing. Comparing areas under the curve (AUC) for both routes of administration, an absolute bioavailability of 55% was calculated for oral itraconazole, close to the predicted value (Table 1). As will be discussed further, itraconazole exhibits dose-dependent kinetics after oral administration, leading to a more than dose-proportional increase in the plasma levels, especially after multiple dosing (see Table 4). It may be expected, therefore, that the absolute bioavailability of oral itraconazole in conditions of saturated first-pass metabolism is much higher.

Influence of food and dose

The influence of food and dose (50, 100 and 200 mg) on the oral bioavailability of itraconazole was studied in six healthy male volunteers (43). The main results are summarized in Table 2. The relative systemic availability of itraconazole (PEG capsules) compared with solution averaged 40% in the fasting state but 102% in the post-prandial state. Food did not significantly affect the rate of absorption of the capsules. Areas under the curve at single doses of 50, 100 and 200 mg had a ratio of 0.3:1:3, suggesting non-linear itraconazole pharmacokinetics in the range of therapeutically used
doses. It was also concluded from the study that, to ensure optimal oral absorption, itraconazole may be administered either in capsules shortly after a meal or in solution, the absorption of which is not influenced by the presence of food in the stomach.

Bioequivalence of oral formulations

The oral bioavailability and bioequivalence of two capsule formulations and of a reference solution were determined in two separate cross-over studies of two periods each. The same 24 healthy male subjects volunteered in the two studies, which were separated from each other by an interval of 6 months. In each study, the volunteers were randomly assigned to a single oral dose of 100 mg of itraconazole.

Study 1: two 50-mg PEG-capsules and 20 ml of a 5 mg/ml aqueous solution of itraconazole in dimethyl-β-cyclodextrin.

Study 2: one 100-mg pellet-capsule and 20 ml of a 5 mg/ml aqueous solution of itraconazole in dimethyl-β-cyclodextrin.

All itraconazole formulations, including the solution, were taken immediately after a standard breakfast. The mean kinetic parameters are listed in Table 3. The absorption of itraconazole from the solution was somewhat slower than from both capsule formulations, in contrast with the intake of the solution under fasting conditions (Table 2). The studies also demonstrated the bioequivalence of the 50 mg PEG-capsule and the 100 mg pellet-capsule each with respect to a reference cyclodextrin solution. In addition, it was shown that the bioavailability of the solution was the same in the two studies and that the PEG-capsule and the pellet-capsule can be regarded as bioequivalent formulations, although the inter-subject variability was lower for the pellet-capsule (Table 3).

Steady-state pharmacokinetics of itraconazole

Hardin et al (13) evaluated the steady-state pharmacokinetics of itraconazole in five healthy male volunteers. Each subject was studied on days 1 and 15 at the following dosages: 100 mg once daily, 200 mg once daily, and 200 mg twice daily. Itraconazole capsules were administered with a standard meal. Steady-state was obtained within 2 weeks of treatment. AUCs for single and repeated dosing increased more than proportionally (Table 4). The half-life of 15-25 h after single dosing was prolonged to 34-42 hours after the last dose. These data support the dose-dependent pharmacokinetics of itraconazole in man (13, 43).

Similar findings were made by other investigators (17, 43). Steady-state plasma levels fluctuated between 193 and 621 ng/ml for 100 mg once daily and the half-life of itraconazole measured during the elimination phase (after cessation of treatment) was in the order of 30 hours (Table 4, Figure 5).

Metabolism of itraconazole and kinetics of hydroxy-itraconazole

Excretion and metabolism

The routes of excretion and metabolism of itraconazole have been studied in three healthy male volunteers after a single oral dose of 3H-itraconazole in an aqueous dimethyl-β-cyclodextrin solution (17, 30). One week after dosing, urinary excretion of radioactivity amounted to 35% of the dose and faecal excretion represented 54% of the dose. Unchanged itraconazole could not be detected in urine and amounts of 3 to 18% of the dose were found in the faeces. These facts point to an almost complete absorption of itraconazole after oral administration and to an extensive metabolism of the fraction absorbed. Main metabolic pathways were oxidative scission of the dioxolane ring, oxidative degradation of the piperazine ring and aliphatic oxidation and N-dealkylation at the 1-methylpropyl substituent (17, 30). As a result of the various metabolic pathways, a very large number of metabolites was formed, each representing less than 1-5% of the dose.
Table 4: Single-dose and steady-state pharmacokinetics of itraconazole in healthy subjects. Mean (SD) pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Dose</th>
<th>Duration</th>
<th>Tmax (h)</th>
<th>Cmax (ng/ml)</th>
<th>Cmax Td (ng/ml)</th>
<th>t1/2 (h)</th>
<th>AUC² (μg.h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardin et al. (13)</td>
<td>5 M</td>
<td>100 mg</td>
<td>single</td>
<td>2.8 (1.1)</td>
<td>110 (58)</td>
<td>15 (9)</td>
<td>15 (6)</td>
<td>1.32 (0.65)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 mg</td>
<td>single</td>
<td>3.0 (0.7)</td>
<td>272 (81)</td>
<td>50 (31)</td>
<td>21 (9)</td>
<td>4.16 (1.95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 mg</td>
<td>2 doses, 12 h apart</td>
<td>3.4 (0.5)</td>
<td>553 (179)¹</td>
<td>130 (60)</td>
<td>25 (10)</td>
<td>12.6 (4.60)</td>
</tr>
<tr>
<td>Hardin et al. (13)</td>
<td>5 M</td>
<td>100 mg</td>
<td>o. d. for 14 d.</td>
<td>3.0 (1.2)</td>
<td>412 (80)</td>
<td>124 (48)</td>
<td>34 (9)</td>
<td>5.33 (1.47)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 mg</td>
<td>o. d. for 14 d.</td>
<td>4.4 (2.1)</td>
<td>1070 (499)</td>
<td>419 (180)</td>
<td>37 (4)</td>
<td>15.4 (6.88)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 mg</td>
<td>b. i. d. for 14 d.</td>
<td>6.0 (2.0)</td>
<td>1980 (308)</td>
<td>1420 (338)</td>
<td>42 (10)</td>
<td>39.3 (9.97)</td>
</tr>
<tr>
<td>Van Peer et al. (43)</td>
<td>6 M</td>
<td>100 mg</td>
<td>o. d. for 15 d.</td>
<td>3.4 (1.1)</td>
<td>483 (60)</td>
<td>205 (57)</td>
<td>30 (8)</td>
<td>7.88 (0.97)</td>
</tr>
<tr>
<td>Heykants et al. (17)</td>
<td>10 M</td>
<td>100 mg</td>
<td>o. d. for 29 d.</td>
<td>3.5 (0.7)</td>
<td>621 (337)</td>
<td>196 (170)</td>
<td>28 (8)</td>
<td>8.17 (5.23)</td>
</tr>
</tbody>
</table>

¹ For single-dose studies, Cmax represents plasma levels at 24 hours after intake.
² For single-dose studies: AUC₀₋₅ h; for multiple-dose studies: AUC₀₋₂₄ h.
³ 12 hours following the second dose.

Figure 3: Structure of hydroxy-itraconazole (R 63373), formed by (ω-1) oxidation of the 1-methylpropyl substituent.
One metabolic pathway deserves special attention, since the plasma levels of this particular metabolite exceed those of the parent drug. The metabolite was identified by mass spectrometry and HPLC co-chromatography as hydroxy-itraconazole (R 63373) formed by (ω-1) oxidation of the 1-methylpropyl substituent (Figure 3).

**Kinetics of hydroxy-itraconazole**

Plasma levels of hydroxy-itraconazole could be measured by an HPLC-method, published by R. Woestenborghs et al. (48), provided that a more polar extraction solvent was used in the extraction procedure, i.e. heptane/isoamyl alcohol 95/5 (v/v) instead of 98.5/1.5 (v/v). Under the same chromatographic conditions, capacity factors were 2.5 and 7.1 for hydroxy-itraconazole and itraconazole, respectively. The lower limit of detection for the hydroxylated metabolite was 2-5 ng/ml.

The plasma levels of hydroxy-itraconazole were measured simultaneously with those of parent drug in various pharmacokinetic studies. Figure 4 shows the mean plasma levels of both itraconazole and its hydroxylated metabolite after a single oral dose of 100 mg itraconazole in 24 healthy male subjects. In comparison with itraconazole, peak plasma levels of hydroxy-itraconazole were on average 70% and AUCs 130% higher. After peak time, which was similar for both compounds, plasma levels of the metabolite decayed monophasically with a half-life of 14 hours, which was shorter than the elimination half-life of itraconazole (25 hours).

Under steady-state conditions (100 mg itraconazole once daily for 4 weeks), the mean plasma levels of hydroxy-itraconazole fluctuated between 396 ng/ml (trough) and 785 ng/ml (peak) (Figure 5). Average steady-state plasma levels of the metabolite were almost double those of itraconazole, which fluctuated between 193 and 621 ng/ml (Figure 5, Table 4). The half-life of hydroxy-itraconazole at steady-state was shorter than that of the parent drug (18 hours versus 28 hours). After intravenous
Parameter | itraconazole | metabolite
--- | --- | ---
Cmin | 193±170 | 396±306
Cmax | 621±337 | 785±327
Css | 340±218 | 592±320

Figure 5: Mean plasma levels and pharmacokinetic parameters of itraconazole and hydroxy-itraconazole after 100 mg itraconazole once daily for 4 weeks in 10 healthy male subjects (steady-state pharmacokinetics).

Figure 6: Evaluation of bioassay versus HPLC in 29 plasma samples of treated subjects, taking into account the HPLC-measured plasma levels of itraconazole (R 51221) alone (A) or those of itraconazole and hydroxy-itraconazole (R 63373) (B).
infusion of 100 mg itraconazole, peak plasma levels of hydroxy-itraconazole, obtained within 2-3 hours after the end of the infusion, were three times less than those of itraconazole (212 ng/ml versus 664 ng/ml). After a 100 mg oral dose in the same subjects, peak levels of the hydroxylated metabolite were almost twice those of the parent drug (247 ng/ml versus 127 ng/ml).

After intravenous administration of itraconazole, the metabolite showed a monoexponential decline with a mean half-life of 14 hours. The AUC ratios of hydroxy-itraconazole over itraconazole were 1.1 after intravenous and 1.9 after oral administration. This may indicate that hydroxy-itraconazole is formed predominantly by first-pass metabolism of the parent drug. Assuming an equal potency of both substances (see further), the absolute bioavailability of the antifungally active substances, represented by the sum of the AUCs of itraconazole and its hydroxylated metabolite, may be estimated at 80% in man.

**Antifungal activity of hydroxy-itraconazole**

As the structure of hydroxy-itraconazole closely resembles that of the parent drug, the antifungal activity of the metabolite was investigated in some animal models. In comparison with itraconazole, the hydroxylated metabolite was less active in rats (treatment of vaginal candidosis) and 2-4 times less potent in guinea-pigs (treatment of Microsporum canis infection and of systemic candidosis). These differences in the in vivo antifungal activity between itraconazole and its hydroxylated metabolite are most likely related to pharmacokinetic differences, e.g. in absorption and first-pass metabolism. The in vitro antifungal activity of both substances was similar.

**Bioassay versus HPLC**

Antifungal plasma levels of itraconazole measured by bioassay employing different Candida strains were reported to be higher than those assessed by HPLC (10, 46). Therefore, both assays were compared by assaying plasma samples (n = 29) from treated patients and volunteers for total antifungal activity by bioassay (with Candida albicans strain ATCC 28516 as a test organism) and for itraconazole and hydroxy-itraconazole (R 63373) by HPLC. When only the levels of unchanged itraconazole (determined by HPLC) were taken into account, antifungal levels (measured by bioassay) were at least three times higher (Figure 6A). A similar relationship was reported by Warnock et al. (46). When accounting for both itraconazole and its hydroxylated metabolite (Figure 6B), a regression slope much closer to unity was found (1.4 instead of 3.3). Moreover, a comparative study with spiked serum samples showed a similar response for the hydroxylated metabolite in the bioassay method (y = 0.14 + 1.3 x, r = 0.995, n = 16), whereas for itraconazole both assay methods gave essentially identical results (y = 0.07 + 0.96 x, r = 0.997, n = 16). It may be concluded that, most likely, only hydroxy-itraconazole accounts for the substantially higher levels measured by the bioassay method. The latter method gives a good estimate of the antifungally active levels of itraconazole in the clinical situation.

**Distribution characteristics of itraconazole**

**Protein binding and tissue distribution**

Itraconazole is highly protein-bound. Its binding to plasma proteins, primarily albumin, is 99.8% in healthy subjects (17, 31) as well as in the elderly and patients with severe renal insufficiency (3). The low free fraction of itraconazole in plasma, i.e. 0.2% of the total plasma concentration, is freely available for distribution over the total body water. As a consequence, itraconazole concentrations in body fluids equivalent to body water such as CSF, eye fluid and saliva are negligible (about 1-2 ng/ml). In fluids which contain organic material, such as spu-
Figure 7: Uptake and elimination kinetics of itraconazole in vaginal tissue after single-day therapy (400 mg itraconazole total dose, divided over two intakes 12 hours apart). Vaginal tissue/blood concentration ratios (A) and schematic representations of blood and vaginal tissue levels (B) as a function of time.

Figure 8: Distribution and elimination kinetics of itraconazole in skin. Mean plasma and stratum corneum levels of different skin types during and after oral administration of itraconazole 100 mg once daily for 4 weeks.
tum and bronchial exudate, concentrations of itraconazole were up to 400 ng/ml and in pus even 1-3 μg/ml. Because of the negligible renal excretion of itraconazole, urine concentrations were below 5 ng/ml (17).

In spite of the high plasma protein binding, tissue concentrations of itraconazole are higher than those in plasma, indicating that the drug is extensively distributed to the tissues. This is also expressed by the volume of distribution of more than 10 l/kg (Table 1). In most tissues, itraconazole concentrations are at least 2-3 times the corresponding plasma levels, in adipose tissue even 20 times. In rats and dogs, brain concentrations of itraconazole were higher than concentrations in plasma (17). This may explain that in spite of negligible concentrations of itraconazole in the CSF (34), the drug is highly active in the treatment of cryptococcal meningitis (45). This fact disproves the general belief that the free drug concentration alone accounts for the activity of antimicrobials.

For lipophilic antifungals such as ketoconazole and itraconazole, the protein- or tissue-bound concentration better reflects the availability and high affinity of these lipophilic substances to the bio-phase. The bio-phase must not be restricted to the mammalian tissue cells, but it includes also the micro-organisms, yeasts and fungi, which may invade the tissues of the host. In other words, the availability of a drug to the infection site in the body is not necessarily related to the (free) concentration of drug in plasma and body water, but rather to its concentration in the tissues. In this respect it may be explained that itraconazole with relatively low plasma concentrations is as effective as fluconazole, a drug with high levels in plasma and body water but with a weak affinity for tissues and, presumably, also a weak affinity for the micro-organisms. Therefore, the distribution kinetics of itraconazole into tissues which are prone to fungal invasion, such as the female genital tract and the skin, have been studied in more detail.

Pharmacokinetics in the female genital tract

In patients undergoing hysterectomy, itraconazole concentrations were measured in various parts of the genital tract after a single 200-mg dose of itraconazole (23). The drug was detectable in vaginal tissue as early as 1 hour after oral intake.

The maximum itraconazole concentration in the vaginal wall was found 6-8 h after intake, with a tissue to blood concentration ratio of 2.9. This ratio further increased to 4 at 10-13 h after dosing.

Concentrations of itraconazole in other parts of the genital tract were 3 to 10 times higher than the plasma concentrations (17).

Two other studies in non-pregnant patients with chronic vaginal candidosis, who were treated with itraconazole 200 mg once daily for 3 d or 400 mg divided in two intakes 12 h apart, showed that itraconazole levels in the vaginal mucosa remained elevated much longer than corresponding blood levels (Larosa E. et al., unpublished data).

For instance, two and three days after itraconazole therapy, vaginal levels were on average 5-6 times the corresponding blood levels (Figure 7). These data point to a relatively slow but extensive uptake of itraconazole in the vaginal tissue.

Once equilibrium between blood and tissue is established, elimination of the drug from the vaginal tissue occurs with a half-life similar to that from blood.

This suggests that redistribution of itraconazole from the tissues dictates also its elimination rate from the vaginal mucosa. Consequently, the tissue to blood concentration ratio of 5-6 is maintained during the entire elimination phase and explains why therapeutically active concentrations are maintained for about 4 d in the vaginal mucosa but only for one day in blood.

This is graphically represented in Figure 7 for the common dosage schedule of itraconazole in vaginal candidosis.
Figure 9: Itraconazole concentrations in plasma, sebum, sweat and stratum corneum (of the handpalm) during and after oral administration of 200 mg once daily for 1 week.

Figure 10: Uptake and elimination kinetics of itraconazole in finger- and toenails of onychomycosis patients treated with itraconazole 100 mg once daily for 3 months.
The skin uptake and elimination kinetics of itraconazole were studied in volunteers who took 100 mg o.d. for 4 weeks (7). Skin samples were taken from three sites of the body, each representing a different skin type. Steady-state plasma levels were reached within 7 d after the start of therapy (Figure 8). The uptake of itraconazole in the stratum corneum was slower and peak concentrations were observed at the end of the 4-week treatment period. Concentrations in the (thick) palmar stratum corneum were three times lower than in plasma, whereas in the stratum corneum of the back (with sweat glands) and of the beard region (with hair and sebum) concentrations of itraconazole were two to five times higher than in plasma. After cessation of treatment, plasma levels of itraconazole decreased to almost undetectable levels with 7 d. Palmar stratum corneum, however, contained drug levels which persisted for at least three weeks after the end of treatment. The beard region showed a gradual decrease of itraconazole levels but the drug was still measureable 4 weeks after the end of therapy. Finally, the stratum corneum of the back still had therapeutic levels 1 week after stopping therapy (Figure 8).

The mechanism of uptake and removal of itraconazole was further studied in a volunteer who took 200 mg once daily for one week (7). Concentrations of itraconazole were measured in sebum (from the nasolabial folds), sweat (collected after exercise from face, neck and back) and palmar stratum corneum, during and up to two weeks after stopping treatment. Figure 9 shows that the concentrations in sebum were almost six times those in plasma, whereas concentrations in sweat were nearly 5 times lower than corresponding plasma levels. Concentrations in the palmar stratum corneum persisted at least for 2 weeks after stopping treatment, while levels in sebum and sweat gradually decreased at a rate similar to that in plasma. These findings indicate that the major routes of itraconazole delivery into the skin likely are passive diffusion from the blood in the keratinocytes (with strong adherence to keratin) and excretion by sebaceous glands. Excretion in sweat, the major route of delivery for ketoconazole (14) and griseofulvin to the skin (11, 36), seems to be a minor one for itraconazole.

The distribution of sebum and sweat glands within the skin and the difference in thickness of the stratum corneum may explain the different uptake of itraconazole in various skin areas of the body (Figure 9).

Redistribution of itraconazole from these tissues into plasma appears negligible and renewal of the stratum corneum or growth of the hair are the rate-limiting steps in the disappearance of itraconazole from these tissues (7, 17).

Based on the kinetics of itraconazole in the skin, its uptake and removal kinetics were also studied in finger- and toenails of patients treated for onychomycosis at 100 mg o.d. for 3 months (Willemsen R. et al., unpublished data). Itraconazole levels in the distal nailplate were measured by HPLC from the end of therapy up to 6 months posttherapy (Figure 10).

For toenails, itraconazole persisted up to 6 months after the end of treatment at average concentrations of approximately 100 ng/g. For fingernails, itraconazole was still detectable several months after the end of treatment but after 6 months the drug could not be detected anymore.

This difference correlates with the different speed in nail growth between finger- and toenails. The study demonstrates that long-term treatment with itraconazole results in therapeutically active levels of the antifungal in nails. The delayed removal of itraconazole after the end of therapy should be of benefit in the treatment of onychomycosis.
Table 5: Single-dose (100 mg) and steady-state (100 mg once daily for 14 days) pharmacokinetics of itraconazole in 12 (6M/6F) elderly subjects (age 65-74 years). Mean (SD) pharmacokinetic parameters (5).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single dose</th>
<th>Steady-state</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_{\text{max}} ) (h)</td>
<td>4.5 (1.4)</td>
<td>4.5 (1.1)</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>118 (61)</td>
<td>507 (171)</td>
</tr>
<tr>
<td>( t_{1/2p} ) (h)</td>
<td>—</td>
<td>176 (64)</td>
</tr>
<tr>
<td>AUC( _{0-24} ) (µg h/ml)</td>
<td>23 (4)</td>
<td>46 (20)</td>
</tr>
<tr>
<td>AUC( _{0,\infty} ) (µg h/ml)</td>
<td>1.52 (0.75)</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 6: Single-dose pharmacokinetics of itraconazole in patients with hepatic (27) or renal insufficiency (3). Mean (SD) pharmacokinetics parameters.

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients</th>
<th>Dose</th>
<th>( T_{\text{max}} ) (h)</th>
<th>( C_{\text{max}} ) (ng/ml)</th>
<th>( t_{1/2p} ) (h)</th>
<th>AUC( _{0-24} ) (µg h/ml)</th>
<th>AUC( _{0,\infty} ) (µg h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic insufficiency</td>
<td>10M/2F</td>
<td>100 mg</td>
<td>2.3 (0.9)</td>
<td>87 (62)</td>
<td>37 (18)</td>
<td>—</td>
<td>1.45 (0.72)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uraemic</td>
<td>4M/3F</td>
<td>200 mg</td>
<td>4.0 (1.2)</td>
<td>213 (178)</td>
<td>—</td>
<td>1.03 (0.82)</td>
<td>3.45 (3.13)</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>6M/1F</td>
<td>200 mg</td>
<td>4.7 (1.4)</td>
<td>140 (119)</td>
<td>—</td>
<td>0.63 (0.51)</td>
<td>—</td>
</tr>
<tr>
<td>CAPD</td>
<td>2M/3F</td>
<td>200 mg</td>
<td>4.4 (2.2)</td>
<td>77 (29)</td>
<td>—</td>
<td>0.33 (0.11)</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 7: Mean (SD) peak plasma levels (ng/ml) of itraconazole after repeated oral dosing in neutropenic (17) and AIDS patients (16).

<table>
<thead>
<tr>
<th>Patients</th>
<th>Treatment</th>
<th>Duration of treatment in weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Neutropenic children</td>
<td>50 mg once daily</td>
<td>75 (29)</td>
</tr>
<tr>
<td>(age 3-15 years)</td>
<td>(n=7)</td>
<td>(n=7)</td>
</tr>
<tr>
<td>Neutropenic patients</td>
<td>200 mg twice daily</td>
<td>335 (43)</td>
</tr>
<tr>
<td>(n=34)</td>
<td></td>
<td>(n=31)</td>
</tr>
<tr>
<td>AIDS patients</td>
<td>100 mg twice daily</td>
<td>—</td>
</tr>
<tr>
<td>(n=4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS patients</td>
<td>200 mg once daily</td>
<td>472 (201)</td>
</tr>
<tr>
<td>(n=6)</td>
<td></td>
<td>(n=5)</td>
</tr>
</tbody>
</table>

Pharmacokinetics in special patients groups

Elderly

Six male and six female healthy elderly subjects (mean age: 69 years, range 65-74 years) received a single 100-mg dose of itraconazole and two weeks later a 14-day treatment of itraconazole 100 mg once daily (5). After single as well as after repeated intake, pharmacokinetic variables in the elderly (Table 5) were in good agreement with those determined in young and middle-aged adults (Table 4). Although the terminal half-life after repeated dosing tended to be...
somewhat longer compared to young volunteers, the AUC at steady-state in the elderly was similar to that reported for the same dose in younger subjects. Hence, dose-adjustment is not required in the elderly. As also observed in studies with young subjects, the steadystate AUC in the elderly was 4 times larger than the single-dose AUC (Table 5). Furthermore, pharmacokinetics of itraconazole in male and female subjects were not different.

Hepatic and renal insufficiency

The oral absorption and pharmacokinetics of itraconazole were studied after a single oral dose of 100 mg in 12 patients with liver cirrhosis, related to chronic alcohol abuse (27). Two of them had also viral hepatitis B. Peak plasma levels were slightly lower than those in the elderly, whereas the half-life in cirrhotic patients was prolonged to 37 h (Table 6). The reduced absorption may be explained by the fact that the subjects were almost in the fasting state at the time of drug intake (27). The longer half-life is consistent with a reduced first-pass metabolism in this group of patients.

The disposition of itraconazole in patients with end-stage renal disease was studied by Boelaert et al. (3). A single-dose study was conducted in 7 elderly uraemic patients (mean creatinine clearance 13 ml/min/1.73 m²; mean age 66 years) not yet on maintenance dialysis and in 7 patients (mean age 62 years) with end-stage renal disease undergoing thrice weekly haemodialysis. The pharmacokinetic variables in non-dialysis and haemodialysis patients (Table 6) were in general comparable with those in young, healthy volunteers (Table 2). In haemodialysis patients, plasma concentrations of itraconazole on a dialysis day were similar to those on an off-dialysis day. During haemodialysis, a slight (2 to 14%) haemoconcentration was noticed. No drug could be detected in the haemodialysate fluid. This is in keeping with the high plasma protein binding of 99.8% in uraemic patients, which was the same as in normal individuals. In 5 patients (mean age 66 years) with chronic uraemia treated with chronic ambulatory peritoneal dialysis (CAPD), the peak level of itraconazole was half the value obtained in the two other groups (Table 6). The cause of this reduced oral bioavailability could most likely be related to the co-administration of antacids. In conclusion, itraconazole dosage in uraemic patients, whether dialyzed or not, should not be lower than in patients with normal renal function.

Neutropenic patients

Steady-state plasma concentrations of itraconazole have been measured in neutropenic children (age 3-15 years) and adults for dosages of 50 mg once daily to 200 mg once or twice daily (Table 7). Plasma concentrations were generally lower than in healthy volunteers (Table 4). The incidence of fatal fungal infections was dramatically reduced among patients maintaining adequate plasma levels (> 250 ng/ml) (4, 39). In these studies inadequate plasma concentrations were frequently found in patients whose anti-neoplastic therapy predisposed them to very poor oral intake and frequent vomiting (17, 28). In this case, antiemetics can be coadministered, and itraconazole capsules should be given with meals. The ultimate solution of the malabsorption problem in these patients is hopefully close by when the HP-β-CD solutions of itraconazole for oral and intravenous use come available.

AIDS patients

The absorption of itraconazole in AIDS patients was evaluated by studying the plasma levels after the first dose and at steady-state (Smith D. et al., unpublished data). The patients were treated with itraconazole 200 mg o.d. for 14 d. The drug was taken together with or shortly after breakfast. After the first dose, peak plasma levels
in five patients were 37% and AUCs 52% lower than in healthy subjects, receiving a single 200-mg dose. Also at steady-state, trough (331 ng/ml) and peak plasma levels (594 ng/ml) in five patients (Table 7) were lower than in healthy subjects (Table 4). In another group of 8 AIDS patients treated with AZT (zidovudine) 8 mg/kg/d and itraconazole 100 mg twice daily (16), trough and peak levels of itraconazole were 210 and 504 ng/ml (Table 7). The AUC over a dosing interval (3.97 µg.h/ml) was lower than expected from volunteer data (Table 4). The findings in both studies point to a reduced absorption of itraconazole capsules in AIDS patients, especially in those with achlorhydria (22).

Interaction potential of itraconazole

The induction and inhibition potential of itraconazole has been investigated in several in-vitro and in-vivo studies in experimental animals as well as in man. In some studies the findings obtained for itraconazole were compared with those of other antifungals of the azole type, i.e. micnazole, ketoconazole and fluconazole. Whereas the former drugs are imidazole antifungals, fluconazole is, as itraconazole, a triazole derivative. In contrast with itraconazole, however, fluconazole is a hydrophilic compound with a weak plasma protein binding and an even distribution over the body water including intracellular water (18).

Inhibition potential

After addition of itraconazole to hepatic microsomes of untreated, phenobarbital- or 3-methylcholanthrene-treated rats, the drug reversibly interacted through an azole nitrogen with the haem group of cytochrome P-450, as evidenced by the formation of type II difference spectra (25). The drug showed only weak inhibitory properties towards rat microsomal enzyme activities, catalyzed by distinct forms of cytochrome P-450. These weak inhibitory properties were confirmed by in-vivo experiments in the rat which showed that concomitant administration of itraconazole at 20 mg/kg did not interact with the disposition of cyclosporin (47) and that a single dose of 100 mg/kg did not influence the antiagulant effect of acenocoumarol (29). No inhibitory effect of a single dose of itraconazole at 10 mg/kg was noted on the metabolism of zoxazolamine, tolbutamide and dicoumarol in the rat, and on the metabolism of phenytoin in the mouse (9). Itraconazole did not prolong the methohexitol induced hypnosis in rats after a single dose of 40 mg/kg (2).

Itraconazole 100 mg once daily for 4 weeks (17) and itraconazole 200 mg once daily for 5 weeks (42) in volunteers did not inhibit the pharmacokinetics of antipyrine, a test drug which is recognized as a sensitive index of hepatic microsomal oxidation. A rise of cyclosporin plasma levels associated with concomitant therapy with itraconazole (100 mg twice daily) was reported in two patients (20, 38), but not in thirteen other patients treated at the same dose (33).

Fluconazole was reported not to interact with antipyrine metabolism at low doses of 50 mg daily in man (35). However, interactions with fluconazole at higher doses have been reported. At 200 mg/d for 5 days fluconazole interacted with warfarin (19). Inhibition of the metabolism of cyclosporin by fluconazole 200 mg every second day was suggested as the cause of the development of renal impairment in a patient receiving both drugs (8). At doses of 400 mg/d fluconazole inhibited phenytoin metabolism resulting in raised serum phenytoin levels and clinical signs of phenytoin toxicity (32). A recent study by La Delfa et al. (21) provided evidence that fluconazole is a potent, partially selective, and reversible inhibitor of the cytochrome P-450-dependent enzyme system in mice. Fluconazole doses as low as 1 and 10 mg/kg strongly
inhibited the metabolism of $^{14}$C-antipyrine in mice, whereas ketoconazole at 100 mg/kg had no effect. The inhibitory properties of ketoconazole with regard to various cytochrome P-450 catalyzed activities on endogenous (e.g. steroid hormones) and exogenous substrates (i.e. drugs) have been documented over the last few years by several publications.

In conclusion, unlike ketoconazole, itraconazole exhibits only weak inhibitory properties in experimental animals at higher dose levels. At therapeutic doses of itraconazole in patients, its inhibition potential is thought to be clinically irrelevant. However, rare events of inhibition of co-administered drugs by high doses of itraconazole can never be excluded.

**Induction potential**

After subacute administration of itraconazole to male rats for 7 d at 160 mg/kg/d, itraconazole was completely devoid of inducing properties towards hepatic drug metabolizing enzyme activities (24). Also hepatic cytochrome P-450 content remained unchanged. Consequently, the drug did not induce the enzymatic activity towards any of the substrates measured, the hydroxylation of aniline, the $N$-demethylation of $N$- and $O$-dimethylaniline and the $O$-demethylation of $P$-nitroanisole. In mice, itraconazole at 160 mg/kg/d for 1 month did not induce the $N$-demethylation of $N$, $N$-dimethylaniline, the $O$-deethylation of 7-ethoxyresorufin, the $O$-dealkylation of 7-pentoxyresorufin or the hydroxylation of lauric acid (Figure 11). These metabolic pathways cover the substrate specificity of different forms of cytochrome P-450 dependent enzyme activities. Besides cytochrome P-450 dependent activities, also other components of the hepatic microsomal drug metabolizing enzyme system, i.e. NADPH-cyt c-reductase, and the phase-II activity UDP-glucuronosyltransferase towards 4-nitrophenol, were not affected by the antifungal. The results of the **in-vitro** studies were further confirmed by **in-vivo** studies which showed that itraconazole did not interact with the metabolism of a number of drugs which are known to be metabolized by distinct forms of cytochrome P-450 (2, 9, 29).

In man, itraconazole did not alter the metabolic clearance of antipyrine at daily doses of up to 200 mg/d for 5 weeks (17, 42). Up to now, enzyme induction of concomitantly administered drugs has never been reported during clinical trials, even not when itraconazole was given chronically at doses of 200 mg twice daily.

In comparison with otherazole antifungals, itraconazole is the only drug devoid of inducing properties in experimental animals, even at subacute administration of doses as high as 160 mg/kg/d. Miconazole when compared to ketoconazole is a more potent inducer. So, miconazole at 40 mg/kg/d significantly induced several phase-I and phase-II activities in rats whereas a similar induction was seen for ketoconazole at 160 mg/kg/d but only for a few enzymatic activities (24). Fluconazole on the other hand behaved as a high magnitude inducer of cytochrome P-450 and of cytochrome P-450 dependent enzyme activities, in a dose-dependent way in mice (Figure 11) as well as in rats (Figure 12). Even at 10 mg/kg/d a significant induction of several enzymatic activities was seen in both animal species (26). The ED$^{50}$ of fluconazole to shorten the methohexital hypnosis time in rats by more than 50% was 22.6 mg/kg (2). These effects occurred already at plasma and liver concentrations of fluconazole comparable to those obtained in man at therapeutic dose levels. Therefore, these findings might have therapeutic implications, especially since fluconazole seems to have an effect on the balance between phase-I and phase-II enzymes (26).

In conclusion, itraconazole is completely devoid of inducing properties in experimental animals, even at high dose levels. This feature is unique for itraconazole since
Figure 11: Differential induction potential of hepatic cytochrome P-450 and drug metabolizing enzymes in male mice by itraconazole and fluconazole (1 month gavage at the dose levels stated). Legend: 1 = cytochrome P-450; 2 = 7-ethoxyresorufin O-deethylase; 3 = 7-pentoxyresorufin O-dealkylase; 4 = lauric acid hydroxylase. Doses of 10 and 40 mg/kg/day are not shown for itraconazole.

Figure 12: Differential induction potential in male rats by itraconazole and fluconazole (7 days gavage at the dose levels stated). Legend: 1 = cytochrome P-450; 2 = N,N-dimethylaniline N-demethylase; 3 = p-nitroanisole O-demethylase; 4 = UDP-glucuronosyltransferase. Doses of 10 and 40 mg/kg/day are not shown for itraconazole.
other azole antifungals do have inducing potential at high dose levels (e.g. miconazole and ketoconazole) or at low doses (e.g. fluconazole).

Other interaction studies

The plasma protein binding of itraconazole was not influenced by high therapeutic concentrations of several drugs strongly bound to albumin or to other plasma proteins (17). Tested drugs included imipramine, propranolol, diazepam, cimetidine, indomethacin, tolbutamide, sulphamethazine, warfarin and phenytoin. High itraconazole concentrations of 2 μg/ml did not displace other drugs from their binding sites.

Preliminary results of an ongoing study in women suggest that itraconazole 200 mg once daily for 2 weeks did not change the oral bioavailability of oral contraceptives, as plasma levels of ethinylestradiol and norethisterone were comparable with those in the control state.

The interaction with the antituberculous agent rifampicin, a powerful inducing agent of hepatic drug metabolizing enzymes (1), was studied in volunteers and in one patient (17). The study in volunteers showed that simultaneous oral administration of itraconazole 100 mg and rifampicin 600 mg increased the AUC of itraconazole by 80%, but three days later, the AUC was strongly reduced to 20% of the value in the control state. Hence, a single dose of rifampicin apparently inhibited itraconazole metabolism when given together but strongly increased the clearance of itraconazole for at least three days after rifampicin administration. In one aspergilloma patient, an almost complete disappearance of itraconazole from plasma was noted when rifampicin was given concomitantly for several weeks. When rifampicin was discontinued, itraconazole levels returned to normal after about one week (17). Decreased itraconazole plasma concentrations (< 50 ng/ml) were reported in two patients receiving itraconazole 100 to 200 mg daily for onychomycosis while maintained on phenobarbital and phenytoin for control of epilepsy (15).

The effects of the H2-receptor antagonists cimetidine and ranitidine on the pharmacokinetics of itraconazole were studied in a randomized cross-over study in 12 healthy male volunteers (37). On one occasion itraconazole 200 mg was taken orally. On the other occasions cimetidine 400 mg or ranitidine 150 mg twice daily were taken for 3 d before and 4 d after the itraconazole dose. Peak plasma levels and AUCs of itraconazole were slightly lower after coadministration with H2-receptor antagonists, but not significantly different from baseline. It was concluded that concurrent H2-receptor antagonist treatment does not alter single-dose kinetics of itraconazole.

In 8 patients with full-blown AIDS treated with AZT 8 mg/kg/d for 11 months, the pharmacokinetics of AZT were determined at two occasions: the first study was carried out during treatment with AZT and the second following itraconazole treatment 100 mg twice daily for 11 to 118 d (16). AZT peak serum levels and AUCs were comparable for both tests, indicating that itraconazole did not influence the pharmacokinetics of AZT. Plasma levels of itraconazole were generally lower than expected from volunteer data.

In conclusion, itraconazole administered at therapeutic doses has a low potential to interact, in a clinically relevant way, on the absorption, distribution or metabolism of concomitantly administered drugs. This makes of itraconazole a safe antifungal. These unique properties of itraconazole have been confirmed in many clinical studies and in thousands of patients, treated for superficial and systemic mycoses.

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