**Clinical Pharmacokinetics of Antifungal Drugs**

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The pharmacokinetic parameters and pharmacodynamics for systemic antifungal drugs are reviewed in this article, together with advice on how to optimise dosing in severely ill patients and practical information for pharmacists.

**Introduction**

The current therapeutic management of disseminated fungal infections mostly includes triazoles (fluconazole, itraconazole, voriconazole, posaconazole), echinocandins (caspofungin), flucytosine and the various formulations of amphotericin B. Echinocandins and amphotericin B are given intravenously while triazoles (except posaconazole) and flucytosine can also be administered orally.

**A description of the pharmacokinetics of antifungal drugs**

The pharmacokinetic parameters for systemic antifungal agents in adults are presented in Table 1 [1-7].

As shown in the table, the absolute bioavailability of oral fluconazole and voriconazole is high (>90%), reflecting a near complete absorption and a lack of first pass effect [3, 5]. Lipophilic triazoles display variable exposure after oral absorption partly due to their low aqueous solubility in the gastrointestinal tract. The absolute bioavailability of itraconazole (oral solution) is around 55% [4], but is unknown for both itraconazole capsules and posaconazole solution due to the lack of coupled intravenous kinetic data. The relative bioavailability of itraconazole solution is 35% greater than that of the capsule. There is no evident increase in posaconazole exposure at oral doses greater than 800 mg because of its poor solubility [6].

Itraconazole, voriconazole and caspofungin are almost exclusively cleared by biotransformation [4, 5, 7]. By contrast, flucytosine and fluconazole are mainly eliminated by the renal route [2, 3]. Posaconazole and probably amphotericin B undergo predominantly biliary elimination [6].

The clearance of caspofungin is low (<15 mL/minute) and is associated with a small volume of distribution [7]. Most antifungal agents display relatively long half-lives, partly supporting once or twice daily dosing. However, given its low solubility, posaconazole is administered in oral doses twice to four times daily, in order to enhance exposure, regardless of its long

<table>
<thead>
<tr>
<th>Drug administration</th>
<th>Route of bioavailability</th>
<th>Absolute oral elimination</th>
<th>Metabolic elimination</th>
<th>Renal</th>
<th>Vd (L)</th>
<th>Cl (mL/min)</th>
<th>t1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B (deoxycholate)</td>
<td>intravenous</td>
<td>NA</td>
<td>NR</td>
<td>20.6%</td>
<td>280</td>
<td>30</td>
<td>366</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>oral</td>
<td>45-90%</td>
<td>minor</td>
<td>major</td>
<td>99</td>
<td>50</td>
<td>3-4</td>
</tr>
<tr>
<td></td>
<td>intravenous</td>
<td>NA</td>
<td>minor</td>
<td>major</td>
<td>63</td>
<td>63</td>
<td>3-4</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>oral</td>
<td>90%</td>
<td>minor (11%)</td>
<td>major (80%)</td>
<td>53</td>
<td>19</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>intravenous</td>
<td>NA</td>
<td>minor (11%)</td>
<td>major (80%)</td>
<td>53</td>
<td>17</td>
<td>40</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>oral</td>
<td>55% (solution)</td>
<td>major</td>
<td>negligible</td>
<td>NR</td>
<td>NR</td>
<td>21-37</td>
</tr>
<tr>
<td></td>
<td>intravenous</td>
<td>NA</td>
<td>major</td>
<td>negligible</td>
<td>770</td>
<td>381</td>
<td>25</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>oral</td>
<td>90%</td>
<td>major (98%)</td>
<td>negligible</td>
<td>107-160</td>
<td>139-333</td>
<td>4.7-8.2</td>
</tr>
<tr>
<td></td>
<td>intravenous</td>
<td>NA</td>
<td>major (98%)</td>
<td>negligible</td>
<td>63-131</td>
<td>100-233</td>
<td>5.3-8.1</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>oral</td>
<td>NR</td>
<td>minor (15%)</td>
<td>negligible</td>
<td>486-781</td>
<td>192-363</td>
<td>24-31</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>intravenous</td>
<td>NA</td>
<td>major</td>
<td>negligible (2%)</td>
<td>10</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

Vd: volume of distribution; Cl: Clearance or apparent clearance; t1/2: terminal half-life; NA: not applicable; NR: not reported.
Drug-drug kinetic interactions are a major problem with triazole antifungal agents.

Caspofungin, since these drugs are predominantly cleared by liver metabolism. No real dosage adjustment is required for itraconazole unless indicated from the measurement of plasma concentrations.

Factors influencing pharmacokinetics

Food is a major factor influencing itraconazole and posaconazole oral absorption. Itraconazole capsules are given immediately after a meal to ensure maximal absorption [4].

While posaconazole should be administered with food whenever possible, since this increases exposure 2.6-4 fold [6].

Disease states such as HIV infection may reduce fluconazole bioavailability but without pharmacodynamic impact [8]. A 50% reduction in the absorption of itraconazole capsules has been observed in patients with HIV infection when compared to healthy volunteers [4] and therefore the dosage may be adjusted based on the measurement of plasma concentrations. Patients with allogeneic bone marrow or stem cell transplants exhibit lower exposure after oral administration of itraconazole or posaconazole. In this case, itraconazole is now replaced by posaconazole, which is approved for use as a prophylactic treatment for high-risk patients (i.e. with graft-versus-host disease), or voriconazole. According to the official labelling, the dosing of posaconazole is 200 mg, three times a day, in this specific population.

Pharmacodynamic and pharmacokinetic (PK/PD) relationships

PK/PD data (i.e. relating kinetic variability to clinical effects) are relatively scarce in this field. Bone marrow toxicity has been associated with high concentrations of fluconazole [2] and there are some case reports which indicate that voriconazole toxic effects could be linked to high trough levels [5]. The highly variable absorption of posaconazole leads to variable plasma concentrations and exposure; the higher plasma concentrations of posaconazole have been associated with greater response rates in patients with invasive aspergillosis and lower exposure to more frequent treatment failures [9]. Limited evidence suggests increased antifungal activity with total plasma concentrations of itraconazole and its active metabolite hydroxyitraconazole above 1 mg/L. In addition, successful antifungal prophylaxis with itraconazole in terms of reduced mortality appears to be associated with adequate exposure [10]. As a consequence, pharmacokinetic monitoring has been recommended for optimising dosing of fluconazole and itraconazole in certain patients and may also be warranted in posaconazole treated patients. It has to be kept in mind that, as yet, no formal randomised study has established the clinical benefit of dose adjustment based on pharmacokinetic monitoring, as is the case for many drugs where it seems reasonable to perform therapeutic drug monitoring to optimise dosing.

Drug-drug interactions

Drug-drug kinetic interactions are a major problem with triazole antifungal agents. Pharmacokinetic interactions commonly occur via metabolising enzymes (i.e. the cytochrome (CYP) P450 isoenzymes superfamily) or drug transporters (i.e. P-glycoprotein or P-gp). Itraconazole (as well as its metabolites), voriconazole, posaconazole and fluconazole, to a lesser extent, are inhibitors of the isoenzyme CYP3A4 [11-13]. Thus, they can delay the elimination of numerous drugs, since CYP3A4 is thought to be involved in the metabolism of 50% of all marketed drugs. Nevertheless, besides some hypolipidemic agents (statins), most significant clinical interactions (those leading to contraindications or dosage reductions) will occur with drugs with a narrow therapeutic index and whose elimination predominantly involves biotransformation catalysed by CYP3A4. Given the clinical profile of inpatients receiving triazoles (mainly those in oncology or intensive care units), major drugs of current concern are immunosuppressants (cyclosporine, tacrolimus, sirolimus), some anticancer agents (vincristine), some analgesics (alfentanil) and hypnotics (midazolam). It should be remembered that ketoconazole is considered as one of the most potent CYP3A4 inhibitors. However, at the present time, it is most exclusively used as a test drug in the exploration of drug-drug interactions rather than in the treatment of invasive fungal diseases. Fluconazole and voriconazole are inhibitors of CYP2C9. As such, they can increase the anticoagulant effect of warfarin-type anticoagulants, including acenocoumarol.

Itraconazole is an inhibitor of the drug transporter P-gp [14] and breast cancer resistance protein (BCRP) [15] indicating that it can increase concentrations of digoxin or the minimally metabolised statin, rosuvastatin. From the substrate point of view, antifungal activity is...
markedly decreased when triazoles (fluconazole to a lower extent) are co-administered with enzymes or drug transporter expression inducers (i.e. rifampicin).

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**References**