Safety of triazole antifungal drugs in patients with cancer

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Triazole drugs are widely used in cancer patients for prophylaxis and treatment of life-threatening invasive fungal infections. Fluconazole, available for over two decades, is safe and effective in patients with cancer; however, the excellent safety profile of fluconazole may not be applicable to the newer triazoles. Itraconazole, voriconazole and posaconazole are associated with adverse events, and drug interactions frequently occur, particularly in cancer patients, since the triazoles and many drugs used in cancer chemotherapy are metabolized via a common metabolic pathway, the hepatic cytochrome P450 system. Close monitoring for drug interactions is needed when triazoles are used with anti-neoplastic drugs and dosage modification of the triazole or its discontinuation may be required. Monitoring of triazole serum concentrations is becoming an important aspect of management to minimize toxicity and ensure efficacy.

Keywords: drug interactions, azoles, chemotherapy, adverse events, serum levels

Introduction

Cancer patients receiving chemotherapy that can compromise their immune system are at high risk of developing invasive fungal infections. This has resulted in increased clinical demand for newer and safer antifungal drugs.1 New triazoles showed promise but it has become apparent that they are not free from adverse effects.2,3 Also importantly, the different medications taken by patients with cancer may place them at an increased risk of drug interactions. This review examines the safety profile and drug interactions of the currently available triazole antifungal drugs in cancer patients.

Fluconazole was first introduced in the 1980s and rapidly found its way into clinical practice in cancer patients.5 It is indicated for prophylaxis and treatment of candidiasis in patients receiving chemotherapy or radiation and for cryptococcal meningitis. Itraconazole was heralded as an advance over fluconazole because of its broader spectrum of antifungal activity; however, use of the former drug has decreased over time due to the availability of newer agents with improved activity against aspergillus, better absorption and less gastrointestinal intolerance.5,6 Also an intravenous formulation of itraconazole is no longer available in the USA.

Since its introduction in 2002, voriconazole use has rapidly escalated. It has activity against Candida spp. (including Candida krusei) and moulds such as Aspergillus, Fusarium and Scedosporium.5 Voriconazole, however, has no activity against zygomycetes. Posaconazole released recently has the broadest spectrum of activity against yeasts and moulds including zygomycetes, resembling the spectrum of activity of amphotericin B.

Triazoles exhibit their antifungal effect by inhibiting sterol 14-α-demethylase, which impairs the production of ergosterol in the fungal cell membrane.7 Triazoles and several drugs used in cancer chemotherapy are metabolized via the same hepatic cytochrome enzyme system (CYP P450), hence drug combinations that include triazoles may lead to a wide range of drug interactions.8

Pharmacokinetic considerations

Fluconazole is eliminated renally and displays linear kinetics over doses ranging from 50 to 800 mg per day.9 However, it has a dose-dependent effect on the CYP P450 enzyme system as evidenced by reports of interactions with other drugs that utilize this enzyme pathway.10 Itraconazole displays non-linear pharmacokinetics, and the oral bioavailability can be markedly decreased by concurrent use of antacids. The capsule is poorly absorbed, while the solution (dissolved in cyclodextrin) has improved absorption irrespective of gastric pH. The drug has a long half-life and may take up to 14 days or more to achieve steady-state levels.11 Oral administration of itraconazole may therefore be inappropriate in the seriously ill patient. The drug is both an inhibitor and a substrate for the CYP P450 3A4 enzyme and P-glycoprotein.12 The oral bioavailability of voriconazole in healthy volunteers approaches 96%, but in critically ill patients or those with gastrointestinal abnormalities, such as stem-cell recipients with severe graft versus host disease (GVHD) of the gastrointestinal tract, the bioavailability may be decreased. The intravenous formulation is solubilized with a
cyclohextrin derivative that is renally eliminated, hence dose adjustment may need to be made in patients with renal impairment. Voriconazole exhibits non-linear pharmacokinetics and serves as an inhibitor and substrate for hepatic CYP 2C19, CYP 2C9 and CYP 3A4 isoenzymes. Patients who express genetically determined increased or decreased CYP 2C19 activity can experience high or low voriconazole serum concentrations, resulting in either toxicity or poor clinical response. 

Unlike voriconazole, posaconazole is an inhibitor of CYP 3A4 enzyme but does not serve as a substrate, and may thus have a reduced propensity for drug–drug interactions. Nevertheless, it is prudent to monitor for potential interactions if medication metabolized by the CYP 3A4 pathway is used concurrently. Linear pharmacokinetics are observed with oral doses of 50–800 mg of posaconazole with absorption saturation occurring at ≥800 mg per dose. Fractioned dosing (two to four times daily) of posaconazole with a high-fat meal is recommended to enhance its absorption.

Adverse effects

There is a 5%–24% incidence of nausea, vomiting, diarrhea and hepatotoxicity in patients receiving triazoles (Table 1). With similar gastrointestinal side effects from cancer chemotherapeutic drugs, simultaneous intake of azoles may be a challenge. In a prophylactic study of itraconazole versus fluconazole in hematopoietic stem cell (HSC) recipients, more patients reported side effects with the former. 

Hepatotoxicity (detected by abnormal liver function tests) is commonly seen with triazoles but is usually asymptomatic and reversible once therapy with the triazole is discontinued, although potentially fatal fulminant hepatitis may occur on rare occasions. Liver injury may manifest as acute hepatocellular, cholestatic or mixed hepatocellular–cholestatic reactions. Fluconazole, unlike other triazoles, is primarily excreted unchanged in the urine. The drug may cause abnormalities in liver function tests; significant liver injury is rare. Itraconazole occasionally causes prolonged cholangiopathy. With voriconazole, although asymptomatic elevation of hepatic enzyme levels is the most frequent presentation, several patients have suffered life-threatening hepatitis. Increased serum voriconazole concentrations correlate well with the development of hepatitis, and discontinuation usually results in normalization of hepatic enzyme levels. Elevation of serum transaminase concentrations related to posaconazole is infrequent (2%–3%).

Adverse events associated with voriconazole include those affecting the liver, eyes, skin and CNS. In some reports, the most common adverse effect was visual, occurring in up to 30% of patients. A report from the French Pharmacovigilance post-marketing database examined adverse events associated with voriconazole in 178 adults. Liver function abnormalities (23%) were the most common, followed by visual (18%), skin rash (17%), neurological (14%), cardiovascular (10%), haematological (8%) and renal (4%) abnormalities. In this database, neurological events (in 33 patients) suspected as related to voriconazole were described as agitation, dizziness, confusion, anxiety and tremor. Of the 22 cardiovascular reports, five had QT interval prolongation/torsade de pointes; there were five fatalities. Results from a global trial involving 107 patients treated for scedosporiosis found a low incidence of visual disturbance due to voriconazole. Visual disturbances have not been reported with posaconazole. Although adverse events with posaconazole are reported in up to 43% of patients, the majority are associated with the gastrointestinal tract (18%). Other side effects include headache (5%–17%) and fever (12%). 

Other triazole-related adverse events are uncommon. Fluconazole has been associated with a long QTc interval and torsade de pointes. Other triazoles may also be proarrhythmogenic, and may need to be withheld when drugs with similar propensity (e.g. anthracycline class) are used. Itraconazole has been associated with negative inotropic effect and cardiac failure. Bullous skin eruptions were related to voriconazole administration in two allogeneic HSC transplant patients and a case of voriconazole-induced pseudoporphyria with bullae formation occurred in another after mild sun exposure. Although not reported in cancer patients, voriconazole has been linked to a painful neuromuscular disorder in nine lung transplant patients. A possible association between voriconazole and neuropathy has also been suggested. Cancer patients receiving voriconazole had visual and auditory hallucinations with elevated serum voriconazole concentrations. Although such reactions are uncommon, they may be serious and should result in prompt discontinuation of the offending triazole. However, the clinical situation is often confounded by concurrent use of multiple drug classes and therefore pinpointing the drug responsible is often difficult.

Triazole-associated interactions (Tables 2 and 3)

Combination of a triazole with chemotherapeutic agents may result in substrate competition, with enhanced toxicity of either or both drugs. Tamoxifen, widely employed in the breast cancer population, is deactivated by CYP 3A4/5 to N-desmethyl tamoxifen. Vinca alkaloids (vincristine, vinblastine and vinorelbine) and their analogues are metabolized through this enzyme system. Bohme et al. documented an association between itraconazole-enhanced neurotoxicity with vincristine exposure, and since then more cases have been cited. Two cases of neurotoxicity (abdominal neuropathy) were reported in adults receiving vindesine and itraconazole. Voriconazole may be safer than itraconazole when used in combination with vincristine.

The pro-drug cyclophosphamide is activated by several cytochrome enzymes to 4-hydroxy-cyclophosphamide and phosphoramid mustard (the alkylating component) plus acrolein (the metabolite responsible for causing haemorrhagic cystitis). CYP 3A4 is an important enzyme system in this process, so any agent that is a substrate, an inhibitor or an inducer could enhance or attenuate cyclophosphamide toxicity. Cyclophosphamide causes cardiotoxicity, haemorrhagic cystitis and neurotoxicity. Less neurotoxicity is seen with cyclophosphamide than with ifosfamide, which shares a similar metabolic pathway. Marr et al. studied 209 patients receiving cyclophosphamide and concurrent fluconazole or itraconazole solution as prophylaxis during HSC transplantation. Findings suggested greater hepatotoxicity in the itraconazole arm presumably due to its effect on CYP 3A4 and consequent enhanced effect of cyclophosphamide. Another explanation offered was a protective effect of...
Table 2. Triazole drug effect on other drugs

<table>
<thead>
<tr>
<th>Triazole</th>
<th>Other drug(s)</th>
<th>Serum concentration</th>
<th>Comment [reference(s)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>All triazoles</td>
<td>tamoxifen</td>
<td>potential increase</td>
<td>suspect increased tamoxifen toxicity</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>vinca alkaloids</td>
<td>increase</td>
<td>increased neurotoxicity; avoid combination, voriconazole may be safer, but needs to be proved</td>
</tr>
<tr>
<td>Itraconazole and fluconazole</td>
<td>cyclophosphamide</td>
<td>altered</td>
<td>more hepatotoxicity with itraconazole combination, safety of other triazoles not evaluated</td>
</tr>
<tr>
<td>All triazoles</td>
<td>cyclophosphamide</td>
<td>altered cyclophosphamide metabolite levels</td>
<td>these combinations have not been clinically evaluated, avoid if possible or monitor clinical outcome closely</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>imatinib</td>
<td>potential increase</td>
<td>severe pustular skin eruption; advise close monitoring of imatinib concentrations if available or monitor for signs of imatinib toxicity; caution: may be a class effect</td>
</tr>
<tr>
<td>Voriconazole and posaconazole</td>
<td>cyclosporine and tacrolimus</td>
<td>voriconazole: increased AUC of cyclosporine x2, tacrolimus x3</td>
<td>decrease dose of CSA and tacrolimus at least 50% following triazole addition</td>
</tr>
<tr>
<td>Voriconazole and posaconazole</td>
<td>sirolimus</td>
<td>increase (posaconazole: increased mean AUC of sirolimus x8)</td>
<td>most clinicians avoid combination, one study found reduced sirolimus dose 90% with voriconazole; involves competition for P-glycoprotein; other triazoles not evaluated</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>paroxetine</td>
<td>increase (increased AUC of paroxetine x1.5, with itraconazole)</td>
<td>potential increase in side effects of statins</td>
</tr>
<tr>
<td>Voriconazole and posaconazole</td>
<td>benzodiazepines</td>
<td>increase (voriconazole and posaconazole: increased AUC of midazolam x8–10)</td>
<td>possible prolonged sedation, monitor closely</td>
</tr>
<tr>
<td>Voriconazole and posaconazole</td>
<td>HMG-CoA reductase inhibitors (statins)</td>
<td>potential increase</td>
<td>potential increase in side effects of statins</td>
</tr>
<tr>
<td>Voriconazole and posaconazole</td>
<td>dihydropyridine calcium channel blockers</td>
<td>increase (demonstrated in vitro)</td>
<td>possible increase in side effects</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>omeprazole</td>
<td>reduce dose of omeprazole by 50% if 40 mg/dose is employed</td>
<td>monitor for hypoglycemia</td>
</tr>
</tbody>
</table>

Table 1. Adverse events associated with triazoles

<table>
<thead>
<tr>
<th>Adverse event(s)</th>
<th>Fluconazole (%)</th>
<th>Itraconazole (%)</th>
<th>Voriconazole (%)</th>
<th>Posaconazole (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, vomiting, diarrhoea</td>
<td>5</td>
<td>24 (oral solution)</td>
<td>—</td>
<td>8 – 18</td>
<td>15, 16</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>5 – 20</td>
<td>8.5</td>
<td>10 – 23</td>
<td>2 – 3</td>
<td>1, 6, 8, 15, 16, 21</td>
</tr>
<tr>
<td>Skin rash</td>
<td>6</td>
<td>5 – 19</td>
<td>5</td>
<td>—</td>
<td>15, 16</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>—</td>
<td>—</td>
<td>1 – 30</td>
<td>—</td>
<td>6, 17</td>
</tr>
<tr>
<td>Headache</td>
<td>&lt;3</td>
<td>&lt;3</td>
<td>—</td>
<td>5 – 17</td>
<td>15, 16</td>
</tr>
</tbody>
</table>
fluconazole via inhibition of CYP 2C9 resulting in decreased formation of hydroxy-cyclophosphamide and its associated toxic metabolites.\textsuperscript{35,36}

Other chemotherapeutic agents known to be metabolized via the CYP 3A4 enzyme pathway include docetaxel, etoposide, paclitaxel, irinotecan, teniposide and ixabepilone, recently introduced for the management of metastatic breast cancer.\textsuperscript{29,37} Imatinib, an example of an expanding class of tyrosine kinase inhibitors employed to treat chronic myeloid leukaemia, is metabolized via the CYP 3A4 enzyme pathway. Others from this drug class include dasatinib, erlotinib, gefitinib, lapatinib, sorafenib and sunitinib.\textsuperscript{29,38–42} Severe pustular eruption was noted in a patient with elevated imatinib levels following the addition of voriconazole.\textsuperscript{43}

The calcineurin antagonists cyclosporine A (CSA) and tacrolimus, employed for the prevention and management of GVHD in HSC recipients, are metabolized via the CYP 3A4 enzyme pathway, and so drug interactions occur with triazole antifungal drugs. It is generally recommended that the dose of either CSA or tacrolimus be reduced by up to 50% following the addition of posaconazole or voriconazole and that blood levels of the calcineurin antagonist be followed closely.\textsuperscript{44,45} As the enzyme system may take several days to a few weeks to recover, blood levels of the calcineurin antagonists need continued monitoring after antifungal therapy has ceased. Fluconazole at a dose of \(<400\) mg undergoes minimal CYP-mediated metabolism and is a poorer inhibitor of CYP 3A4 in vitro than other triazoles.

Sirolimus is used to prevent and/or treat graft rejection or GVHD. Co-administration of voriconazole has been shown to cause an 11-fold increase in sirolimus peak plasma concentrations and clinicians have avoided using sirolimus if voriconazole or posaconazole was needed. Marty et al.\textsuperscript{46} recommended that voriconazole may be safely co-administered with sirolimus if the dose of the latter is empirically decreased by 90%.

Antidepressants are commonly employed in the cancer population and any drug interaction resulting in increased levels of a serotonin substrate receptor inhibitor (SSRI) could result in serotonin syndrome. Elevated paroxetine levels have been reported with fluconazole and itraconazole, as the latter drugs competitively inhibit P-glycoprotein.\textsuperscript{47} Voriconazole and fluconazole decrease fentanyl (a widely used narcotic analgesic) clearance by 23\% and 16\%, respectively.\textsuperscript{48} This drug interaction could lead to greater fentanyl levels increasing the potential for respiratory depression. The anti-arrhythmic agent amiodarone is heptatically metabolized through many CYP enzyme pathways, including CYP 3A4.\textsuperscript{49} It has a long half-life (40–55 days) and, as a result, any drug interaction is likely to have prolonged consequences; for this reason concurrent use of triazoles is not recommended. Loperamide, often used to control chemotherapy-induced diarrhoea, is metabolized via P450 CYP 2C8 and 3A4 and is also a substrate for P-glycoprotein, thus a likely candidate for triazole interaction.\textsuperscript{50} On occasion, levels of both interacting drugs may be affected. Such is the case with the interaction between voriconazole and phenytoin: voriconazole levels can be reduced by 49\% and phenytoin levels increased by 67\%.\textsuperscript{51} The enzymes involved are CYP 3A4 and CYP 2C19. Careful monitoring of both drug levels is recommended when these two drugs are given together.

Warfarin is a CYP 2C9 substrate. A placebo-controlled study in healthy volunteers determined that combining voriconazole with warfarin increased prothrombin time.\textsuperscript{52} Stringent monitoring of the international normalized ratio (INR) is strongly recommended when voriconazole or fluconazole is added to a warfarin-containing regimen. Posaconazole is not a CYP 2C9 inhibitor, so little interaction with warfarin is expected.

Some interactions occur because of alterations in gastrointestinal absorption of drugs leading to changes in bioavailability. Nagappan and Deresinski\textsuperscript{53} commented that although gastric pH does not affect the absorption of posaconazole, concomitant metronidazole administration reduced posaconazole exposure. A manufacturer-sponsored study concluded that the absorption of posaconazole is affected by gastric pH and the co-administration of proton pump inhibitors is likely to decrease drug absorption.\textsuperscript{54}

Certain foods affect the activity of CYP 3A4 and consequently cause minor alterations in serum concentrations of triazoles and other similarly metabolized drugs. A classic example is the inhibitory effect of grapefruit juice on the activity of intestinal CYP 3A4.\textsuperscript{55}

### Serum drug concentration monitoring

In the case of antibacterial antibiotics, therapeutic outcome can be related to three parameters: the time the antibiotic serum concentration exceeds the MIC of the drug; the maximum serum concentration of the antibiotic achieved; and the area under the serum concentration–time curve in relation to MIC (AUC/MIC ratio). Unlike antibacterial antibiotics, few published studies have addressed these issues with antifungal drugs.\textsuperscript{56}
Pai et al.\textsuperscript{57} looked at the relationship between clinical outcome and fluconazole levels in 77 patients with Candida bloodstream infections. The results showed a trend towards improved survival in those patients with high AUC/MIC ($P=0.03$).\textsuperscript{57} Other retrospective studies found similar results.\textsuperscript{58,59} However, data regarding serum fluconazole concentrations and toxicity are scant. One study found that 2000 mg/day fluconazole caused neurological toxicity in 3 of 39 patients. The average serum steady-state peak concentration was 91.8 mg/L.\textsuperscript{60}

Serum drug concentration monitoring may be considered under the following circumstances: (i) intra- or inter-patient pharmacokinetic variability that cannot be predicted or reasonably overcome within the therapeutic window of drug dosing; (ii) ceiling effect of dosing escalation because of drug toxicity or suboptimal absorption; (iii) lack of a more immediate alternative endpoint useful for assessing drug response, as is true for all invasive fungal infections; (iv) availability of a rapid, sensitive and specific assay with a quick turnaround time; and (v) clinically validated therapeutic/toxic ranges for the antifungals. Among these, both (i) and (ii) are true for itraconazole, voriconazole and posaconazole but not for fluconazole.\textsuperscript{61}

Serum concentrations of >0.5 mg/L of itraconazole have been associated with good clinical outcome.\textsuperscript{62,63} Although serum itraconazole concentrations are not generally determined, it has been suggested that for the treatment of histoplasmosis and aspergillosis, serum concentrations be monitored and targeted for trough concentrations between 0.5 and 1 mg/L.\textsuperscript{64}

More information has amassed on voriconazole serum concentration monitoring than with any other triazole. Administration of voriconazole with food decreases its oral bioavailability by >20%, resulting in low serum levels.\textsuperscript{65} Because of genetic polymorphism shown by CYP 2C19, up to 20% of Asians and 5% of Caucasians and African Americans show poor drug metabolism and will have higher voriconazole concentrations.\textsuperscript{66} Retrospective studies in cancer/HSC transplant patients have shown therapeutic failure associated with voriconazole trough concentrations of <2 mg/L and toxicity occurring with concentrations of >6 mg/L.\textsuperscript{67-69} Although such studies have limitations, it is suggested that 1–5.5 mg/L be used as a therapeutic range for voriconazole drug concentrations obtained during therapy.\textsuperscript{69}

Posaconazole demonstrates a wide inter-patient variability in pharmacokinetic parameters.\textsuperscript{70,71} In a murine model, treatment efficacy was shown to be related to the AUC/MIC ratio.\textsuperscript{72} An open label multicentre study found that when posaconazole mean maximum and average serum concentrations were 0.14 and 0.13 mg/L, respectively, only 24% of the cohort responded, but >75% responded when these levels were 1.48 and 1.25 mg/L, respectively.\textsuperscript{73} No correlation was demonstrated between any reported adverse event and serum posaconazole concentrations.

Another clinical investigation in allogeneic stem cell recipients with GvHD showed that posaconazole concentrations were nearly 2-fold lower in five patients who developed a breakthrough fungal infection than in the cohort (241 patients) that did not develop infection.\textsuperscript{74} Such data are strongly suggestive of a relationship between drug exposure and efficacy, justifying further evaluation of the utility of therapeutic drug monitoring.

The use of newer triazoles among cancer/transplant patients is on the rise. Accumulating data strongly suggest significant drug interactions between triazoles and cancer chemotherapeutic drugs. Currently, there are no clear dosing guidelines for drugs commonly employed in the cancer/transplant population when the newer triazoles are concurrently administered.

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