UKHealthCare

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| **Guideline/Protocol Title** | Therapeutic Drug Monitoring of Antifungal Agents Guideline |
| **Authors** | Antimicrobial Stewardship Team Core Members |
| **Committee Review** | Antimicrobial Stewardship Subcommittee<br>Pharmacy and Therapeutics Committee |
| **Target Population** | Patients requiring therapy with antifungal therapy – azoles and flucytosine. Primarily hematology/oncology and transplant patients. |
| **Overview** | This guideline provides evidence-based recommendations for dosing, administration, and monitoring of the antifungal agents voriconazole, itraconazole, and posaconazole, fluctyosine, and isavuconazole which require therapeutic drug monitoring. |
| Effective Date | 1/1/2016 |
| Revised Date | 2/20/2018; 4/30/2020, 4/30/2022 |
| Expiration Date | 4/30/2024 |
| **Schedule for Periodic Review** | Every 2 years |
| **Implementation Strategy** | Pharmacists are aware of the guideline |
| **Education Strategy** | Guideline will be posted on CareWeb and the Stewardship app |
| **Primary Outcome (s)** | Percent adherence to guideline |
| **Outcome Assessment Plan** | Review outcomes based on AST annual priorities |
| **Information Technology Needs** | Access to CareWeb and Stewardship app |

# Therapeutic Drug Monitoring (TDM) of Antifungal Agents

Agents that are ideal candidates for routine TDM demonstrate 3 characteristics – a high degree of inter-patient variability in dose-exposure relationship; an established relationship between drug exposure and either efficacy, safety, or both; and an assay that is able to accurately measure drug concentrations. Increased understanding of antifungal pharmacokinetics and pharmacodynamics has led to a growing role for TDM of certain antifungals in routine clinical practice. Currently, there is evidence to support the use of TDM for itraconazole, voriconazole, posaconazole, flucytosine, and isavuconazole. TDM of fluconazole is not routinely required. Clinical input and judgment still remains central to the process of TDM.

**Table 1.** Clinical circumstances that may favor the use of TDM

| Context | Example | Comment |
|---|---|---|
| **Pharmacokinetic variability** | Children, neonates, elderly, obese, organ dysfunction, critical illness, hemodialysis, hemofiltration, extracorporeal membrane oxygenation, cardiopulmonary bypass | Pharmacokinetics of many antifungal agents very poorly defined in special populations |
| **Changing pharmacokinetics** | Physiological instability, critical illness, diarrhea, IV-PO switch | |
| **Interacting drugs** | Antacids, histamine antagonists, proton pump inhibitors and itraconazole capsules, agents known to decrease concentrations of triazoles | Drug-drug interactions well defined and documented for many antifungal compounds |
| **Compliance** | | Compliance may be significant issue for longer-term consolidation therapy or secondary prophylaxis |
| **Poor prognostic disease** | Extensive or bulky infection, lesions contiguous with critical structures (mediastinum), CNS disease; multifocal or disseminated infection | |
| **Persistent and/or significant underlying immunological defects** | Prophylaxis versus established disease | |

The optimal frequency of TDM for patients on long-term antifungal therapy is unknown, but will largely depend on clinical judgement. Once target concentrations have been achieved, consideration of the circumstances described in above table should guide the frequency with which repeat TDM levels are made, as well as the context in which the drug is being used.

**Table 2.** Dosing and monitoring of antifungals

| | Itraconazole | Voriconazole | Posaconazole | Flucytosine | Isavuconazonium sulfate (prodrug to isavuconazole) |
|---|---|---|---|---|---|
| Formulations | Solution: 10mg/ml<br>Capsule: 100mg | Tablet: 50mg, 200mg<br>Suspension: 40mg/ml<br>IV: 200mg vial | Suspension: 40mg/ml<br>Delayed Release Tablet: 100 mg<br>IV: 18mg/ml (300mg vial) | Capsule: 500mg | Capsule: 186mg (100mg isavuconazole)<br>IV: 372 mg (200mg isavuconazole) |
| Loading Dose | 200mg PO Q8H for 3 days | Treatment<br>6 mg/kg IV/PO Q12H for 2 doses<br>*Use ideal body weight for obese patients* | Treatment<br>300mg tablet or IV Q12H for 2 doses | N/A | 372mg IV or PO Q8H for 6 doses |
| Maintenance Dose | Treatment<br>Oral: 200mg Q12H<br>*Solution is preferred due to 30% higher bioavailability than capsule* | Prophylaxis<br>200mg PO Q12H<br><br>Treatment<br>4 mg/kg IV/PO Q12H until clinically stable (~1 week) then 200mg PO Q12H | Prophylaxis<br>Tablet or IV: 300mg Q24H<br>Suspension: 200mg Q8H<br><br>Treatment<br>Tablet or IV: 300mg Q24H<br>Suspension: 200mg Q6H | Treatment<br>25 mg/kg PO Q6H in combination with Amphotericin B products<br><br>*Use ideal body weight in obese patients*<br><br>*Dosage reduction is required if CrCl ≤ 40 ml/min. Monitor carefully* | Treatment<br>372mg IV/PO Q24H<br>*to begin 12-24 hours after the last dosing dose* |
| Administration | Solution: Take on an empty stomach<br>Capsule: Take after a full meal, absorption improved with acidic environment | Take oral tablets one hour before or after a meal | Tablet: Can be taken without food (do not crush)<br>Suspension: Take with fatty meal or acidic carbonated drink | N/A | Capsule: Can be taken with or without food<br>IV: infuse for a minimum of 1 hour via an infusion set with an in-line filter (pore size 0.2 to 1.2 micron) |
| Feeding Tube Administration | Use solution. Stop tube feeds 2 hurs before and 1 hour after the dose | Use suspension. Stop tube feeds 1 hour before and 2 hours after the dose | Use suspension. Do not need to hold tube feeds. | Do not need to hold tube feeds. | Do not need to hold tube feeds.<br><br>Per package insert, it is recommended to swallow capsules whole and to not chew, crush, dissolve or open. However, recent case reports have shown that administration of isavuconazole through feeding tubes can result in levels comparable to oral intake |
| Minimum trough concentration (efficacy) | Prophylaxis: 0.5 mg/L<br>Treatment: 1 mg/L<br><br>*Liquid chromatography-mass spectrometry (LC-MS) assay used at UKHC so must sum itraconazole + hydroxyitraconazole levels*<br><br>*Send-out to Viracor* | Prophylaxis/Treatment: 1- 1.5 mg/L (2 mg/L in CNS infections, multifocal infection, etc)<br><br>*Send-out to Viracor* | Prophylaxis: 0.7 mg/L<br>Treatment: 1 mg/L<br><br>*Send-out to Viracor* | **PEAK CONCENTRATIONS**: 30-80 mcg/ml (defined as 2 hours after an oral dose)<br>$C_{max}$ >100 mcg/ml should be avoided<br><br>*Send-out to Viracor* | No clear efficacy or toxicity concentration thresholds have been identified.<br><br>Prophylaxis/Treatment: > 1 mg/L<br><br>*Send-out to Viracor* |

**Table 2.** continued

| | Itraconazole | Voriconazole | Posaconazole | Flucytosine | Isavuconazole |
|---|---|---|---|---|---|
| Maximum trough concentration (safety) | < 5mg/L<br>*to minimize toxicity but threshold not well established | < 5-6mg/L to minimize toxicity | None | | None |
| Dose adjustment | Subtherapeutic:<br>Increase to 300mg Q12H if on 200mg Q12H<br>- Change capsules to solution<br>- If using caps, stop or reduce H2 antagonists or proton pump inhibitors<br>- If using solution, check it is being given in the fasting state<br>- Check compliance<br>Stop interacting drugs (CYP3A4 substrate)<br><br>Supratherapeutic:<br>Dose reduction should typically be reserved for patients who actually experience adverse events and for when alternate agents would be inappropriate | Subtherapeutic:<br>Increase IV therapy by 50% to a maximum of 6mg/kg twice daily (adults); increase oral therapy from 200mg twice daily to 300mg twice daily (if close to target, may only need to increase by 50mg/dose)<br>- Check compliance<br>- Stop interacting drugs (CYP2C19 substrate)<br>- Significant inter- and intra-patient variability due to Michaelis-Menten pharmacokinetics and polymorphisms in CYP2C19<br><br>Supratherapeutic:<br>Consider repeating level and if still elevated, decrease dose. If toxicity, discontinue and reassess need for additional therapy | Subtherapeutic:<br>Increase by 100mg/day with the tablet.<br>Suspension – increase from 600mg/day to 800mg/day and administer Q6H<br>If suspension:<br>- Administer with food<br>- Administer with high-fat food<br>- Remove acid suppression if possible<br>- Check compliance<br>- Stop interacting drugs<br><br>Supratherapeutic:<br>Unknown if dose adjustments needed as no consistent association between elevated troughs and side effects | Subtherapeutic:<br>Increase dose by 50%. Use caution due to risks with supratherapeutic concentrations and limited data supporting minimum concentrations.<br><br>Supratherapeutic:<br>Not much data on adjustments but may change from Q6H dosing to Q8H dosing | Unknown if dose adjustments needed as no data is available. Troughs < 1 mg/L may warrant a dose increase, depending on the patient's clinical response. Doses should be increased or decreased by 186mg, the dose in which isavuconazole capsules are manufactured. |
| Time of Sampling | Trough (pre-dose) at the end of the first week of therapy and then at regular intervals, especially if interacting medications are started or stopped, there is suspicion of toxicity, or concerns with oral absorption. Due to the long half-life, levels obtained in the middle of the dosing interval shouldn't substantially differ from troughs. | Trough should be measured after at least 5 days of therapy. Consider ordering a level before transitioning to the maintenance dose in critically ill patients or those with a high burden of disease. A second sample should be routinely collected to ensure voriconazole concentrations are stable and in a desired therapeutic range. The same sampling strategy is required if there is a change in dosage, change in clinical condition, or an IV-PO switch | Trough at the end of the first week of therapy and after 7 days if dosing changes are made. Repeat testing is required if the clinical condition changes or following a dosage adjustment. Due to the long half-life, levels obtained in the middle of the dosing interval shouldn't substantially differ from troughs | Concentrations should be measured in patients who are on prolonged course of therapy or displaying signs of toxicity. It isn't necessary to continue to check peaks as long as renal function is monitored closely and flucytosine is renally adjusted. | Trough level should be measured after at least 5 days of therapy.<br><br>Consider checking more frequently in the setting of: suspected non-compliance, therapeutic failure, unexplained hepatotoxicity, obesity, or concomitant therapy predicted to reduce isavuconazole concentration. |
| Adverse Advents | Gastrointestinal disturbances, neurological problems, hepatitis, QTc prolongation | Visual disturbances, liver dysfunction, skin reactions, neurotoxicity (confusion and visual hallucinations), QTc prolongation | Nausea, vomiting, hepatotoxicity, QTc prolongation | Bone marrow suppression (neutropenia), gastrointestinal intolerance, hepatitis, rash | QTc shortening, gastrointestinal disturbances, LFT elevations, hypersensitivity reactions |

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