Therapeutic drug monitoring of Voriconazole, Posaconazole and Itraconazole

Key concepts

- Certain azoles, notably Voriconazole, Posaconazole and Itraconazole, require therapeutic drug monitoring (TDM) since serum levels are indicators of both efficacy and safety. TDM is not required for Fluconazole, and the value of TDM for Isavuconazole has not yet been established
- Check for drug-drug interactions before prescribing azoles – consult pharmacy for additional guidance.
- Azoles levels should be drawn at steady state ie. **5 to 7 days after starting the therapy, then q7 d after while admitted and/or if clinically relevant; blood should be collected 30 minutes before the first dose of the test day**. There is no need for TDM if treatment duration is less than 7 days (typically serum levels are reported within 48 to 96 h – send out test).
- For recommendations on indications and dosages of azole antifungals, refer to treatment of invasive fungal infections guidelines
- In addition to TDM, patients on azoles should have
    - Baseline ECG and repeat ECG after day 5 of treatment, to monitor for QTc prolongation
    - Baseline bloods including electrolytes (K, Mg) and LFTs, to be repeated weekly while hospitalized and periodically after
- Patient should be monitored for the development of:
    - GI intolerance
    - Skin reactions
    - Electrolyte imbalance (K, Mg)
    - QTc interval prolongation
    - Liver toxicity
    - Neurotoxicity (hallucinations, delirium, delusions)
    - Ophthalmic toxicity (abnormal vision, photophobia (with voriconazole only)

Agent	Indication for TDM	Targets
Voriconazole	• Beginning of treatment or prophylaxis • After dose adjustment • Special populations (ex: extreme weight, asian, elderly, hepatic dysfunction, critically ill and altered GI function) and fluctuating pharmacokinetics parameters (ex: hepatic function) • Suspected clinical failure and/or toxicity • Suspected drug interactions • Transition from IV formulation to PO • Suspected malabsorption and/or non-compliance	**Efficacy**: Treatment: > 1.5 mg/L For HSCT patients or poor prognosis (Ex: CNS or multifocal infection), aim for >2 mg/L Prophylaxis: > 0.5 mg/L Safety: < 5.5 mg/L
Posaconazole Absorption of oral tablet is	• Beginning of treatment • After dose adjustment • Special populations (ex: extreme weight, elderly, hepatic dysfunction, critically ill and altered GI function) and fluctuating pharmacokinetics parameters (ex: hepatic function)	**Efficacy**: Treatment: > 1 mg/L Prophylaxis: > 0.7 mg/L

better than solution. **Favor tablet formulation if possible**.	• Profuse diarrhea • Suspected clinical of clinical failure and/or toxicity • Oral solution (poor absorption) • Suspected drug interaction • Treatment of pathogens with reduced susceptibilty (ex: *C.glabrata* and *C.tropicalis)* • Suspected malabsoprtion and/or non-compliance	**Safety**: No clear association between level and toxicity
Itraconazole Absorption of itraconazole is greater with oral solution than with capsule. **Favor solution formulation if possible**.	• Beginning of treatment and prophylaxis • After dose adjustment • Special populations (ex: extreme weight, elderly, hepatic dysfunction, critically ill and altered GI function) and fluctuating pharmacokinetics parameters (ex: hepatic function) • Suspected clinical of clinical failure and/or toxicity • Suspected drug interaction • Treatment of pathogens with reduced susceptibilty (ex: *C.glabrata* and *C.tropicalis)* • Suspected malabsoprtion and/or non-compliance	**Efficacy:** Treatment: >1 mg/L Prophylaxis: > 0.5 mg/L **Safety**: < 4 mg/L

Conversion: 1 mcg/mL = 1 mg/L; Azoles significantly increase concentration of calcineurin inhibitors and MTOR inhibitors. Dose adjustment +/- TDM of those drugs is recommended when starting and stopping azoles. Consult clinical pharmacist for guidance.

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