Voriconazole Therapeutic Drug Monitoring Guidelines

About

Voriconazole is a triazole antifungal agent that is generally very well absorbed. However, there is also significant inter- and intra-patient variability in absorption. Additionally, its major metabolic pathway is through CYP2C19, which exhibits genetic polymorphisms resulting in reduced metabolism of voriconazole in up to 3-5% of Caucasians and Blacks, and up to 20% of non-Indian Asians. These "poor metabolizers" are therefore at greater risk of toxicity, as are patients with hepatic impairment. Alternatively, those patients who are rapid, or even ultra-rapid, metabolizers of voriconazole, risk sub-therapeutic levels of voriconazole to effectively treat their infections. Similar problems with predicting voriconazole concentrations arise as a result of the numerous drug interactions that impact voriconazole metabolism (e.g. anticonvulsants, anti-rejection medications, warfarin). A complete medication review looking for potential drug interactions should be completed for all patients when voriconazole therapy is initiated, and when other medications that interact with voriconazole are started or stopped while patient is on voriconazole.

Several recommendations have been published for voriconazole therapeutic drug monitoring[1,4,7,8,13], and several studies have looked at the association between voriconazole serum concentrations and treatment success, as well as toxicities. These TDM guidelines are based on this current level of evidence.

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Routine therapeutic drug monitoring (TDM) of voriconazole is not recommended unless patient meets inclusion criteria below.

Services Most Impacted by Voriconazole TDM:

1. Infectious Diseases
2. Transplant (especially lung)
3. Hematology
4. Critical care
5. Pharmacists
6. Laboratory Medicine and Pathology, and Microbiology

Treatment Dosing and Dose Adjustments:

Initiate therapy using weight-based dosing:

Pediatrics under 12 years old:

9 mg/kg IV or PO q12h (no loading dose)[19]

Adults and Pediatrics 12 years and older:

6 mg/kg IV or PO q12h on day one, then 4 mg/kg IV or PO BID.

For oral dosing, round dose up to nearest tablet strength available.

If TDM is required (see inclusion criteria below), dosing changes can be challenging due to the non-linear pharmacokinetics. Recommendation is to consult a pharmacist to discuss dosage adjustment recommendations.

Inclusion Criteria:

1. Patients on voriconazole treatment who are not responding adequately to therapy. This is defined as a lack of clinical response despite at least 5 days of therapy, failure of fever to resolve, or ongoing radiographic worsening.
2. Patients on voriconazole who are exhibiting signs/symptoms of voriconazole toxicity (e.g. liver dysfunction, persistent ocular or any CNS toxicity (confusion and visual hallucinations)).
3. Patients on voriconazole treatment where there is concern of drug interactions leading to increased or decreased serum concentrations of voriconazole that may impact toxicity or efficacy. Voriconazole is a CYP3A4, 2C19, and 2C9 inhibitor and has many clinically relevant drug interactions; check Lexicomp® or another drug information source[15].
4. Potential CNS involvement of invasive fungal infection.
5. Pediatrics patients undergoing treatment for invasive fungal disease.

Exclusion Criteria:

1. Patients on voriconazole prophylaxis. There is no evidence available regarding the dose or target levels required for prophylaxis so monitoring of serum levels is **not** recommended. One consideration for TDM in prophylaxis is for CF patients, post-lung transplant, based on lung transplantation guidelines[4].
2. Routine levels for patients who do not meet inclusion criteria are not recommended at this time due to lack of evidence.

Appropriate Sampling and Targets:

1. Levels, when ordered, should be drawn when therapy is at steady state (after 5-7 days on same dose regimen).
2. Only trough levels should be monitored (sample drawn within 0 to 60 minutes prior to next dose).
3. Target trough levels should be between 1.0-5.5 mg/L [1,7,8,13].
4. Subsequent levels should **only** be done if:
    a. dosage regimen has been changed (wait for steady state)
    b. there is a change in clinical status which has the potential to alter drug absorption, distribution and/or clearance.
    c. non-adherence with therapy is suspected.
    d. toxicity is suspected
    e. drug interaction(s) suspected

Sample Analysis:

1. Sample type: Serum, collected in plastic 6 mL No Gel (Red) Clot Activator (Ref #367815.
2. Assay: Tandem Mass Spectrometry, UAH Toxicology Laboratory (effective September 2016).
3. Laboratory Requisition:
    a. AHS Routine Requisition. Write in test under “Other Test Not Listed”.
    b. Include the following drug utilization information on the requisition:
        i. Date and time of last dose,
        ii. Date and time of next dose,
        iii. How long patient has been treated with current dosage regimen.
4. Availability: Analyses will be performed twice per week.

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