Posaconazole Therapeutic Drug Monitoring Guidelines

About

Posaconazole is a triazole antifungal agent that is available in multiple formulations- intravenous, oral suspension, and oral delayed-release tablets. Historically, posaconazole was only available as an oral suspension and exhibited significant variability in inter- and intra-patient pharmacokinetics, which were largely attributable to differences in absorption.[1,2] Absorption of posaconazole suspension is significantly increased by the presence of high fat food and gastric acidity, and is significantly reduced with concomitant acid suppressant use and in the presence of mucositis or diarrhea. Posaconazole also exhibits saturable absorption, which requires the oral suspension to be given in multiple daily doses despite its long half-life. The availability of delayed-release oral tablets has significantly reduced the variation in posaconazole absorption, with no significant effects observed with the concomitant administration of food or acid suppressants, and also allowing for once-daily administration.[1] Despite the clear advantages of the delayed-release tablets, there are still patients who will require administration of the oral suspension as the tablets must be swallowed whole and can not be crushed or chewed.

Posaconazole's major metabolic pathway is through glucuronidation. Although this makes it less prone to drug interactions than other triazole antifungals, it is still subject to several significant drug interactions affecting its metabolism (e.g. anticonvulsants).[1,2] A complete medication review looking for potential drug interactions should be completed for all patients when posaconazole therapy is initiated, and when other medications that interact with posaconazole are started or stopped while the patient is on posaconazole.

Few recommendations have been published for posaconazole therapeutic drug monitoring, and the existing literature has looked at the association between posaconazole serum concentrations and treatment success, as dose-related toxicities appear to be minimal.[2] These TDM guidelines are based on this current level of evidence.

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Created by: Antimicrobial Stewardship Program
ahs.antimicrobialstewardship@ahs.ca

Alberta Health Services

Routine therapeutic drug monitoring of posaconazole is not recommended unless patient meets eligibility criteria below.

Services most impacted by Posaconazole TDM:

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

Posaconazole Dosing and Dose Adjustments:

Pediatrics under 13 years old (off label):			
	IV Formulation (300 mg/vial)	Delayed Release Tablet (100 mg tab)	Oral Suspension (40 mg/mL)
Prophylaxis	Not studied	Not studied	4mg/kg/dose TID
Treatment	Not studied	Not studied	**≥ 2 years**: 5mg/kg/dose QID **< 2 years**: insufficient evidence contact ID[6]
Adults and Pediatrics 13 years and older[4]:			
Prophylaxis	300 mg BID x 1 day then 300 mg QDaily	300 mg BID x 1 day then 300 mg QDaily	200 mg TID
Treatment	300 mg BID x 1 day then 300 mg QDaily	300 mg BID x 1 day then 300 mg QDaily	400 mg BID or 200 mg QID with high fat meal/supplement

Inclusion Criteria:

1. Patients on posaconazole 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. When posaconazole is used for salvage therapy, or when used for non-Aspergillus invasive moulds (e.g. Mucorales).

3. Patients receiving posaconazole **treatment** with oral suspension, in whom there is concern of poor absorption from the enteral route (e.g. concomitant acid suppression medication, mucositis, graft vs host disease (GVHD), administration by NG tube, inability to tolerate high fat food).
4. Patients in whom there is concern of significant drug interactions leading to increased or decreased serum concentrations of posaconazole.
5. Patients in whom there are significant changes in normal physiology that have the potential to alter drug absorption, distribution and/or clearance (e.g. persistent organ dysfunction).
6. Non-adherence with therapy is suspected.
7. Pediatric patients undergoing treatment for invasive fungal disease, Patients who appear to be failing when posaconazole is used for prophylaxis.

Exclusion Criteria:

1. Asymptomatic patients on posaconazole prophylaxis. There is no evidence available regarding the dose or target levels required for prophylaxis so monitoring of serum levels is **not** recommended.
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. Routine therapeutic drug monitoring of posaconazole is not recommended unless patient meets eligibility criteria.
2. Levels, when ordered, should be drawn when therapy is at steady state (after 6-7 days on same dose regimen)[3].
3. Only trough levels should be monitored (sample drawn within 0 to 60 minutes prior to next dose.
4. Target trough levels should be greater than 700 ng/mL (µg/L)[3].
5. If a patient has an initial posaconazole level measured, 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. there has been initiation or discontinuation of interacting medications (e.g. phenytoin, proton-pump inhibitor), or if
    d. non-adherence with therapy is suspected.

Monitoring for adherence may be done at any point; repeat levels as a result of a change in dose, interacting medication or patient status should be performed after steady state has been reached (ie. 7-10 days AFTER the change).

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.

References:

1. Guarascio AJ,Slain D. Review of the new delayed-release oral tablet and intravenous dosage forms of posaconazole. *Pharmacotherapy*. 2015;35(2):208–19.
2. Laverdiere M, Bow EJ, Rotstein C, et al. Therapeutic drug monitoring for triazoles: a needs assessment review and recommendations from a Canadian perspective. *Can J Infect Dis Med Microbiol*. 2014;25:327-43.
3. Dolton MJ, Ray JE, Marriott D, et al. Posaconazole exposure-response relationship: evaluating the utility of therapeutic drug monitoring. *Antimicrob Agents Chemother*. 2012;56(6):2806-13.
4. Posanol® Canadian Product Monograph, Revision date 20 October 2014.
5. Thompson GR, Rinaldi MG, Pennick G, et al. Posaconazole therapeutic drug monitoring: a reference laboratory experience. *Antimicrob Agents Chemother*. 2009;53(5):2223–4.
6. Gwee A, Cranswick N, Curtis N. Posconazole: Promising but problematic in practice in pediatric patients. Ped Infec Dis J 2015; 34: 604-606.