



Azole Blood Level Monitoring

Therapeutic drug level monitoring should be considered when using posaconazole, voriconazole, or itraconazole for treatment of serious mycoses. Guidelines have been reviewed [1] and will be briefly summarized here. For blood level monitoring to be useful clinically, the turnaround time must be short [2]. Blood should be obtained 7-14 days of after starting therapy at the trough time just before next dose. Repeat testing may be indicated following a change in dosage, formulation, initiation or discontinuation of an interfering medication, suspected treatment failure or non-adherence with treatment.

Posaconazole. Posaconazole blood levels vary widely, and may be insufficient in some patients receiving therapy. Based on experience at MiraVista Diagnostics, showing very low levels in 41% of determinations (Table), blood level monitoring should be routine for posaconazole. In treatment of refractory aspergillosis, patients in the lowest concentration quartile (mean concentration 0.13 $\mu\text{g}/\text{mL}$) had the lowest response (24%) and those in the highest quartile (mean 1.25 $\mu\text{g}/\text{mL}$) had the highest response (75%) [3]. In a prophylaxis study, concentration was lower in those who developed an invasive mycosis and in those who did not [4]. Trough levels above >0.5 - 1.5 $\mu\text{g}/\text{mL}$ are recommended for treatment (Table) and above >0.5 $\mu\text{g}/\text{mL}$ for antifungal prophylaxis [1] (Table). There are no data showing a correlation of posaconazole concentration and toxicity, but high levels (>5 $\mu\text{g}/\text{mL}$) are rare with posaconazole: levels were above 5 $\mu\text{g}/\text{mL}$ in only 1 of 1125 determinations (Table).

Voriconazole. Emerging data also support blood level monitoring when using voriconazole for serious mycoses. In testing at MiraVista Diagnostics levels were below 1 $\mu\text{g}/\text{mL}$, potentially sub-therapeutic, in 32.8% of measurements and above 5 $\mu\text{g}/\text{mL}$, potentially toxic, in 17.3% of measurements (Table). In immunocompromised children receiving voriconazole for treatment of invasive mycoses, 75% of those who died had at least 1 low voriconazole trough versus only 20% of those who survived. Of adults with invasive mycoses, mostly aspergillosis, 44% of those with concentrations below 2.05 $\mu\text{g}/\text{mL}$ died versus none with higher concentrations [6]. In a prospective study response correlated with trough concentration > 1 $\mu\text{g}/\text{mL}$: 88% response with trough > 1 $\mu\text{g}/\text{mL}$ responded vs. 54% with trough < 1 $\mu\text{g}/\text{mL}$ [7]. In another study, breakthrough *Candida* infection correlated with trough levels below 2 $\mu\text{g}/\text{mL}$ [8]. Trough levels above 1 to 2 $\mu\text{g}/\text{mL}$ are recommended for treatment (Table) and above >0.5 $\mu\text{g}/\text{mL}$ for prophylaxis [1] (Table). Some data suggest a relationship between concentration and toxicity. Neurologic abnormalities were seen in about 30% of patients with trough levels of ≥ 5.5 $\mu\text{g}/\text{mL}$ versus none in patients with lower levels [7]. Others reported no correlation between blood level and hepatic enzyme elevation [5].

Itraconazole. Several reports indicate the effectiveness of prophylaxis correlates with itraconazole blood concentration [9], but limited data are available on blood level monitoring for treatment of serious mycoses [10]. Of AIDS patients with cryptococcal meningitis whose trough concentrations were above 1 $\mu\text{g}/\text{mL}$, 100% responded compared to 66% with lower concentrations [11]. At

MiraVista, itraconazole levels were below 1 µg/mL in 13% specimens from humans and 52% from animals (table). In one report toxicity correlated directly with trough blood concentration [12], and appeared higher in patients with concentrations above 10 µg/mL: itraconazole levels at MiraVista have exceeded 10 µg/mL in 18% of specimens from humans and 24% from animals. Trough levels above >1 to 2 µg/mL are recommended for treatment (Table) and above >0.5 µg/mL for prophylaxis [1](Table).

Results at MiraVista Diagnostics					
Posa ¹ µg/mL		Vori ² µg/mL	Itra µg/mL	Human ³	Animal ⁴
None	3.2%	5.0%	None	1.9%	15.0%
< 0.05	1.2%	5.0%	<0.3	3.4%	22.4%
0.05-0.4	36.2%	11.0%	0.3-0.9	7.5%	14.9%
0.5-0.9	32.9%	11.8%	1.0-9.9	79.1%	23.4%
1.0-4.9	26.5%	49.9%	10-19.9	11.2%	15.0%
5.0-9.9	.09%	13.0%	>20	6.9%	9.3%
≥10	0%	4.3%	¹ N=1125, ² N=1110, ³ N=320, ⁴ N=107		

Guidelines for Treatment of Serious Mycoses¹			
Parameter	Posaconazole	Voriconazole	Itraconazole
Therapeutic	>0.5 to >1.5 µg/mL	>1 to >2 µg/mL	>1 to >2 µg/mL
Toxic	No data	> 6 µg/mL	> 10 µg/mL ¹

¹Based on data reviewed by Andes et. al. [1], except for evidence correlating toxicity with itraconazole concentration [12]

Reference List

1. Andes D, Pascual A, and Marchetti O. Antifungal therapeutic drug monitoring: established and emerging indications. *Antimicrob Agents Chemother* 2009; 53:24-34.
2. Drusano GL. How many steps along the path is too far? *Clin Infect Dis* 2010; 50:37-9.
3. Walsh TJ, Raad I, Patterson TF et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. *Clin Infect Dis* 2007; 44:2-12.
4. Ullmann AJ, Lipton JH, Vesole DH et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med* 2007; 356:335-47.
5. Neely M, Rushing T, Kovacs A, Jelliffe R, and Hoffman J. Voriconazole pharmacokinetics and pharmacodynamics in children. *Clin Infect Dis* 2010; 50:27-36.
6. Smith J, Safdar N, Knasinski V et al. Voriconazole therapeutic drug monitoring. *Antimicrob Agents Chemother* 2006; 50:1570-2.

7. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, and Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. *Clin Infect Dis* 2008; 46:201-11.
8. Trifilio SM, Bennett CL, Yarnold PR et al. Breakthrough zygomycosis after voriconazole administration among patients with hematologic malignancies who receive hematopoietic stem-cell transplants or intensive chemotherapy. *Bone Marrow Transplant* 2007; 39:425-9.
9. Buchkowsky SS, Partovi N, and Ensom MH. Clinical pharmacokinetic monitoring of itraconazole is warranted in only a subset of patients. *Ther Drug Monit* 2005; 27:322-33.
10. Smith J and Andes D. Therapeutic drug monitoring of antifungals: pharmacokinetic and pharmacodynamic considerations. *Ther Drug Monit* 2008; 30:167-72.
11. Denning DW, Tucker RM, Hanson LH, Hamilton JR, and Stevens DA. Itraconazole therapy for cryptococcal meningitis and cryptococcosis. *Arch Intern Med* 1989; 149:2301-8.
12. Lestner JM, Roberts SA, Moore CB, Howard SJ, Denning DW, and Hope WW. Toxicodynamics of itraconazole: implications for therapeutic drug monitoring. *Clin Infect Dis* 2009; 49:928-30.

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