



## 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 [5]. 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  $< 1$   $\mu\text{g}/\text{mL}$  [6]. In another study, breakthrough *Candida* infection correlated with trough levels below 2  $\mu\text{g}/\text{mL}$  [7]. 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  $\geq 5.5$   $\mu\text{g}/\text{mL}$  versus none in patients with lower levels [6]. Others reported no correlation between blood level and hepatic enzyme elevation [8].

**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). Levels observed in dogs receiving 10 mg/kg/day of brand name itraconazole (Sporonox) ranged from 1.8 to 28 µg/mL, averaging 13.5 µg/mL, while those receiving 5 mg/kg/day had levels ranging from 0.7 to 10.8 µg/mL, averaging 3.6 µg/mL [12]. In one report toxicity correlated directly with trough blood concentration [13], 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 <sup>1</sup> µg/mL		Vori <sup>2</sup> µg/mL	Itra µg/mL	Human <sup>3</sup>	Animal <sup>4</sup>
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%	<sup>1</sup> N=1125, <sup>2</sup> N=1110, <sup>3</sup> N=320, <sup>4</sup> N=107		

Guidelines for Treatment of Serious Mycoses <sup>1</sup>			
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 <sup>1</sup>

<sup>1</sup>Based on data reviewed by Andes et. al. [1], except for evidence correlating toxicity with itraconazole concentration [13]

#### 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. Smith J, Safdar N, Knasinski V et al. Voriconazole therapeutic drug monitoring. *Antimicrob Agents Chemother* 2006; 50:1570-2.

6. 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.
7. 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.
8. Neely M, Rushing T, Kovacs A, Jelliffe R, and Hoffman J. Voriconazole pharmacokinetics and pharmacodynamics in children. Clin Infect Dis 2010; 50:27-36.
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. Legendre AM, Rohrbach BW, Toal RL, Rinaldi MG, Grace LL, and Jones JB. Treatment of blastomycosis with itraconazole in 112 dogs. J Vet Intern Med 1996; 10:365-71.
13. 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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