Posaconazole Plasma Concentrations in Patients with Hematologic Malignancies: A Cohort Study

Medical University of Graz

M. Hoenigl [1], R.B. Raggam [2] , T. Valentin [1], H.J. Salzer [1], A. Valentin [3], A. Woelfler [3], K. Seeber [1], A. Strohmeier [1], I. Zollner-Schwetz [1], A. Grisold [4], H. Sill [3], R. Krause [1]

1 Medical University of Graz, Section of Infectious Diseases, Division of Pulmonology, Graz/AT
2 Medical University of Graz, Clinical Institute for Laboratory Diagnostics, Graz/AT
3 Medical University of Graz, Division of Hematology, Graz/AT
4 Medical University of Graz, Institute of Hygiene, microbiology and Environmental Medicine, Graz/AT

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Objectives: Posaconazole is a new triazole antifungal agent that has broad activity against pathogenic fungi and is increasingly used for prophylaxis and treatment of invasive mould infections (IMI). Posaconazole is available only as oral formulation with varying absorption from the gastro-intestinal tract. Reports correlating posaconazole plasma concentrations (PPCs) with breakthrough IMI, however, are rare. The study objective was to analyze posaconazole serum levels in patients with hematologic malignancies and posaconazole prophylaxis.

Methods: We analyzed posaconazole plasma concentrations (PPCs) in patients with hematological malignancies and evaluated correlation of PPCs with breakthrough IMI by conducting a prospective observational single-centre study for seven months in 2010. We further evaluated risk factors associated with low PPCs. PPCs were analyzed by High Performance Liquid Chromatography and indicated as sufficient if above 0.50 mg/l.

Results: A total of 109 PPCs were measured in 34 patients receiving posaconazole prophylaxis (n=31) or treatment (n=3). Insufficient levels were detected in 24/34 (70%) of patients; in 15 of these 24 patients concentrations were found below 0.20 µg/ml. Insufficient PPCs yielded either way in a modification of intake procedures, discontinuation of PPIs or switch of antifungal therapy. In 12 of these 24 cases with insufficient PPC, modification of intake - i.e. with a high fat meal - led to sufficient PPCs. As discontinuation of PPIs led to an improvement of PPC levels in only 1/24 cases, antifungal therapy had to be switched due to insufficient PPCs in another five cases. In three patients with insufficient PPCs, antifungal therapy had to be changed from posaconazole prophylaxis to echinocandin empiric treatment due to development of febrile neutropenia. In these patients no fungal pathogen was detected.
Three patients on posaconazole prophylaxis met the criteria of breakthrough infection. Prior to development of invasive fungal infection (IFI), however, PPCs were insufficient in all three patients. Details are depicted in Table 1. Associated risk factors for insufficient PPCs varied from previous reports.

Fungal species	Posaconazole MIC (mg/L)	Patient`s age years/ sex	Specimen of fungal detection	Days of posaconazole prophylaxis before breakthrough infection	Last posaconazole plasma level before diagnosis of IMI (days before diagnosis)	Antifungal therapy after IMI diagnosis	Outcome
Aspergillus fumigatus	0.032	58/f	BAL	8	0.28 µg/ml (1)	Voriconazole	Died
Aspergillus spp.	n.a.	20/m	BAL / Serum	23	<0.20 µg/ml (4)	Voriconazole	Survived
Geosmithia argillacea	0.25	52/m	BAL / Blood culture	>60	0.31 µg/ml (7)	Voriconazole, LipAmph B	Died

Table 1. IMI under Posaconazole prophylaxis

Conclusion: Our data suggest that insufficient PPCs may lead to development of breakthrough IMI, as three patients developed insufficient PPC associated probable or proven IMI while on posaconazole prophylaxis. Previously four cases of possible IFI and one proven IFI under posaconazole prophylaxis all associated with insufficient PPCs have been reported. Considering that we found insufficient posaconazole plasma levels in 70% of patients therapeutic drug monitoring of posaconazole seems to be meaningful. Introduction of PPC measurement on a regular basis and, if necessary, consecutive modification of intake procedures or switch of antifungal therapy may lead to a decrease in rates of breakthrough invasive mould infection.

martin.hoenigl@medunigraz.at