Determination of Posaconazole in Human Serum: Enhancing Therapeutic Drug Monitoring in Hematopoietic Stem Cell Transplantation (HSCT) Recipients

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Background: Posaconazole, a broad-spectrum triazole antifungal agent, is extensively utilized for the prophylaxis and treatment of invasive fungal infections (IFIs) among patients undergoing hematopoietic stem cell transplantation (HSCT). Due to the considerable inter-individual variability in posaconazole's pharmacokinetics, monitoring its serum levels ls is crucial for optimizing prophylaxis or therapy in HSCT patients.

Methods: This method encompasses a straightforward protein precipitation step, followed by chromatographic separation on a Waters symmetry C18 column (250 × 4.6 mm, 5 μm). The mobile phase comprises a mixture of H_2O and acetonitrile in a 45.5:54.5 (v/v) ratio, with UV detection optimized at 261 nm. The method was validated according international guidelines for linearity, accuracy, precision, selectivity, lower limit of quantitation and stability under different conditions.

Results: This method exhibits robust linearity (correlation coefficients ≥0.999), high specificity with no interference from plasma components or concurrent medications, and remarkable sensitivity, with a lower limit of quantification of 0.1038 μg/mL. The assay is reproducible and accurate over the concentration range of 0.1038–10.3796 μg/mL. We further analyzed 311 serum samples from 91 patients with HSCT undergoing posaconazole prophylaxis, administered either in tablet or suspension form. Our analysis indicated that the tablet formulation significantly outperformed the oral suspension in achieving target posaconazole plasma concentrations greater than 0.7 mg/L, with a notable difference in the percentage of samples (80.4% for tablets vs. 67.9% for suspension; $p<0.05$). Additionally, we employed logistic regression analysis to identify determinants of posaconazole's therapeutic drug monitoring (TDM) utilization and constructed a receiver operating characteristic (ROC) curve to predict plasma concentration targets for posaconazole. The area under the curve (AUC) values for the tablet and suspension formulations were [OR (95% CI): 0.903 (0.829-0.977), $P < 0.001$] and [OR (95% CI): 0.866 (0.811–0.921), $P < 0.001$], respectively.

Conclusions: The analyses used in this study exhibits commendable linearity, precision, and accuracy, thereby validating its utility for monitoring plasma concentrations in patients undergoing posaconazole combination prophylaxis for IFIs. Also, patients receiving posaconazole tablets for prophylaxis may not necessitate routine TDM, given their higher likelihood of attaining therapeutic concentrations.

Key Words: Invasive fungal infections, Posaconazole, Therapeutic drug monitoring, Receiver operating characteristic curve, Hematopoietic stem cell transplantation, HPLC