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Triazoles therapeutic drug monitoring: from recommendation to applicability

Gómez-López Alicia

CNM, ISCIII, Spain

Background: The new antifungal triazoles (fluconazole FCZ, voriconazole VCZ, itraconazole ICZ, posaconazole PCZ and isavuconazole ISvZ) are widely used for the management of invasive fungal infections (IFI). These drugs exhibit significant pharmacokinetic (PK) variability and are associated to multiple drug interactions. Measuring blood concentrations of them and their metabolites could be used for characterization of this PK variability.

Objective: The aim of the study was to describe systemic azoles PK in a collection of clinical samples using a validated high-pressure liquid chromatography assay (HPLC-PDA).

Method: The method consists in a stepwise gradient elution profile. It enables the simultaneous quantification of azoles in serum samples and its specific UV profile characterization. We tested this method by monitoring azole concentrations in a collection of serum clinical samples and by using external quality controls (QC). To assess the relevance of metabolites on routine azole TDM an additional description of the metabolic rate (mr=metabolite/parent drug) is also determined.

Results: The chromatographic assay took 15 minutes per sample and was linear in the analytical range between 0.25 and 16 mg/L for all components. Regarding the QC, we found a good correlation between target and calculated concentration. A high percentage of clinical samples were received to assess VCZ and Noxide-VCZ (46% and 44% respectively). We also found a high percentage of subtherapeutic samples (sbTh, samples in which azole did not reach the established concentration for efficacy). The mean VCZ mr for each sample was estimated in 1.7-2, ranging between 0.09 and 25. In the case of ICZ, the mean mr was 1.3-2.No metabolites have been described for PCZ, so no mr was calculated. Significant differences were observed between mr values. Higher values were found in sbTh samples compared to those for which upTh concentrations were detected.

Conclusions: This method resulted simple, fast, cheap and useful for azoles TDM application. According to the results described here, we suggest a role of the mr value on azole TDM.

Biography

Gómez-López Alicia (representative investigator of this research team) has been part of the CNM Mycology Reference Laboratory since 2000. Since her incorporation as a PhD student, has participated in several research projects related to research in human fungal infection. In 2007 she was in charge of creating a new research line into the Laboratory. This is a line of cutting-edge research in Medical Mycology, which seeks to define relationships between dose and therapeutic response, and also better explain the clinical significance of resistance, by evaluating parameters PK/PD of antifungals and their relationship with efficacy. New strategies using alternative models of infection are now on going in this field with interesting perspectives and applications. This research is also evaluating the effect of the patient genetic background in treatment efficacy (pharmacogenetic). This new line is nowadays working actively in the lab. Each year new staff is incorporating to advance in this research by means of competitive applications. Thanks to these resources new methods have been developed and validated, contributing positivity to assist the national health system in fungal infection management.

aliciagl@isciii.es

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