Antifungal therapeutic drug monitoring: When, how, and why
Monitorización de niveles plasmáticos de los antifúngicos: cuándo, cómo y por qué

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In recent years, the incidence of invasive fungal infections (IFI) has risen in parallel with a growing population of patients immunosuppressed as a consequence of different conditions, such as HIV infection, increasingly aggressive surgical techniques, solid organ and hematoepoietic transplantations, illness severity of critically ill patients and, in a lower rate, anti-TNF therapies.1–3 In spite of the increased number of antifungal drugs that are currently available, particularly after the echinocandins introduction, treatment outcome has not sufficiently improved and remains a real challenge for those medical specialties dealing with IFI affected patients. Beyond antifungal therapy, multiple factors conditioning clinical response have been described, such as the patient’s immunologic status, pathogen-dependent variables, infection focus, time to diagnosis and time to antifungal therapy initiation, as well as the use of the most appropriate and safe antifungal drugs according to the patient’s clinical status.4 At the present time, three different groups of antifungals can be used to treat IFI: polyenes, triazoles, and echinocandins. While there is extensive knowledge about the antifungal activity of these drug classes, information on the pharmacokinetic behaviour of each molecule is more limited. In general, pharmacokinetic data from studies conducted in animal models or in healthy volunteers are usually available when a new antimicrobial drug is launched, but information on specific patient populations appears later on and, frequently, evidence different drug behaviours as compared with those observed in patients included in pivotal studies. Pharmacokinetic analysis include the understanding of the interactions between a drug and the type of patient who receives that drug, specifically by studying the drug’s absorption, for oral pharmaceutical formulations, distribution, metabolism, and elimination phases. Pharmacodynamics examines the relationship between pharmacokinetics and therapeutic results of a given drug. When the relationship between the drug exposure and the potency of this drug against a microorganism (determined by minimum inhibitory concentrations [MIC]) is examined, the known pharmacokinetic–pharmacodynamic (pK–pD) parameters are obtained.5 Regarding the antifungals, some considerations for therapeutic drug monitoring has been proposed.6 First, the analytical conditions, such as the need for precise and accurate techniques providing data within acceptable timeframes and with reasonable costs should be considered. Second, those related to pharmacologic conditions, such as the need for defining plasma levels ranges determining the efficacy and toxicity of antifungal drugs. Third, those considerations related to the patient’s clinical status, including the type and location of infection, concomitant therapies, comorbidities, and potential ability of response to infection. Fourth, the availability of a pharmacokinetic simulator software, which is difficult in the specific case of antifungals, to be used for dose adjustment recommendations. And last, considerations related to the economic constraints of pharmacokinetic departments, which are currently limiting the development of methods and their spread to a greater number of molecules and patients.

It has been proposed that the selected drug should have shown an unpredictable dose–plasma exposure relationship and/or to be a drug with a narrow therapeutic range, i.e., with very close therapeutic and toxic levels. Traditionally, these characteristics had been considered practically exclusive for itraconazole, voriconazole, itraconazole, and posaconazole.

The need for fluconazole monitoring was dismissed due to its favourable pharmacokinetic characteristics, with rapid absorption and high bioavailability, extended body distribution, and relatively high plasma levels.7 Additionally, a direct correlation was observed between the fluconazole dose and the attained plasma levels: this confers the drug a predictable pharmacokinetics and, for this reason, monitoring of plasma levels is widely considered unnecessary. However, fluconazole plasma levels monitoring might be necessary for specific patient groups. In particular, a study conducted in critically ill patients undergoing extended dialysis demonstrated that fluconazole doses of 200 mg were associated with area under the concentration curve during 24 hours AUC0–24 values below those observed with continuous renal depuration techniques.8 The variability present in the methodology used for implementing these techniques, frequently in terms of the type of membrane, would warrant monitoring of fluconazole plasma levels in these populations. A study conducted in critically ill pediatric patients...
patients raised the same need, as 40% of patients showed subtherapeutic fluconazole levels and the inverse correlation between the observed plasma values and the patient’s age and the fact of having underlying cancer. 

Pharmacokinetic studies with itraconazole demonstrated a large variability in plasma levels among the studied patients. This variability was related to the different galenic formulations used for oral administration, and it was higher with those preparations including cycloedrine, which are more rapidly absorbed and attain AUC0–24 values 30% above than those observed with other oral formulations.10 Biomolecular barriers in the intestinal lumen limit the proper absorption of this triazole.11 The cytochrome P450 CYP3A4 isoenzyme and the glycoprotein P are involved in the intra- and intervariability observed in the absorption and metabolism of itraconazole. This antifungal shows a non-linear pharmacokinetics that has been considered a key condition than can influence on the patient clinical outcomes. Pharmacokinetic studies conducted in healthy volunteers with itraconazole showed differences in plasma levels with a 47% variation coefficient while a range in the exposure of 11–83% was observed in subsequent pharmacokinetic population studies. Itraconazole metabolism results in over 30 metabolites, which are excreted through urine or faecal routes. The antifungal activity of hydroxy-itraconazole, one of these metabolites, is similar to that of the parental drug.12 In this case, the analytical technique used for measurement of itraconazole levels is a key issue to assess if a dose adjustment needs to be done. Bioassay-based techniques can detect both, itraconazole and hydroxy-itraconazole, whereas high performance liquid chromatography (HPLC)-based or spectrometry-based techniques only can detect itraconazole. For this reason, the obtained values when using this later technique are approximately 5-fold lower than those observed with the bioassay technique and, thus, this information should be known before performing any dose modification. Plasma levels monitoring is considered a valuable strategy for the maintenance of itraconazole levels within the therapeutic range. When HPLC or spectrometry methods are used, the achievement of trough and peak concentrations between >0.5 and 1 mg/L or slightly exceeding 3 mg/L, respectively, is considered essential.13 As it takes two weeks to attain steady state, it is advisable to weekly monitor the levels of this antifungal drug until the end of treatment.

The current issue of the journal Enfermedades Infecciosas y Microbiología Clinica publishes a study conducted by Cabrall-Galeano et al. about the clinical usefulness of voriconazole plasma levels monitoring in 52 patients, mainly lung transplanted, who received oral voriconazole.14 In 40 (85.1%) of these patients, voriconazole was used for the treatment of different clinical presentations of aspergillosis, with a median treatment duration of 8 weeks (IQR: 3–14). On average, 2.7 (IQR: 2–3.75) measurements of plasma levels were conducted per patient, and the first sample was mainly collected on day 6 of treatment (IQR: 5–15). Voriconazole plasma levels were subtherapeutic in 8 (17%) patients, as indicated by minimum or trough concentrations below 1 mg/L, while 5 (10.6%) patients showed levels exceeding 5.5 mg/L, which are considered predictors of toxicity. After a dose increase, plasma levels were within the therapeutic range in 8 (80%) of 10 patients with subtherapeutic levels. Due to observed neurologic toxicity, voriconazole was replaced by other therapeutic options in half of those patients who showed voriconazole levels above the acceptable values. In the univariate analysis, age and cystic fibrosis were significantly associated to a greater likelihood of having plasma levels below 1 mg/L. These results are consistent with those observed in a previous study, in which patients with cystic fibrosis had a greater risk of achieving minimum voriconazole concentrations < 1 mg/L.15 Finally, 11 (21.2%) patients had adverse events of muscle weakness; these were patients submitted to muscular transplant and treated with steroids. Limited information is available about a possible pharmacokinetic interaction between voriconazole and prednisolone resulting in a 1.3-fold increase in steroid AUC.16 Due to the lack of more specific information on this type of interaction, the authors raised the need of conducting prospective studies to elucidate this finding. A consistent relationship between plasma voriconazole levels and therapeutic clinical response has been described in medical literature, therefore, as occurs with itraconazole, this antifungal requires plasma concentration monitoring for a therapeutic follow-up.17 A high pharmacokinetic variability was observed when similar doses were administered to different patients,18,19 with an over 100-fold variation in minimum concentrations among them.20 Voriconazole is metabolized by cytochrome P450 isoenzymes, particularly CYP2C19, CYP3A4 and, in a lower rate, CYP2C9.21 This metabolic route is closely related to the trough and peak concentrations observed with voriconazole treatment, both in adults and children, as plasma levels depend on CYP2C19 polymorphisms, and dose adjustments based on different genetic variables have been proposed.22,23 However, other authors have questioned the effect of the different genotypes of these isoenzymes on voriconazole metabolism.24 Routine monitoring of voriconazole plasma levels has been related to a lower probability of adverse events occurrence, and to better therapeutic response.25 Voriconazole plasma levels monitoring for the first 5 days of therapy, with subsequent regular monitoring, and maintenance of trough concentrations >1–2 mg/L are recommended in order to optimize clinical efficacy and avoid plasma levels exceeding 5–6 mg/L, as these levels have been associated with increased toxicities, primarily neurologic toxicity.26,27 In spite of the lack of enough evidence, modifying the current voriconazole dosing regimen to 300–400 mg orally administered or 300 mg intravenously, both administered twice daily, might increase the percentage of patients with plasma levels within the therapeutic range for this antifungal.4

To date, no evidences are available on a possible relationship between posaconazole levels and the occurrence of adverse effects.28 The primary limitation of the use of this azole is its administration in the form of suspension, a pharmaceutical form requiring a close pharmacokinetic monitoring to ensure an optimal therapy.13 The drug shows important similarities with itraconazole because its bioavailability is highly variable depending on the gastric pH.17 Fortunately, a new tablet formulation with an improved relationship between the administered dose and the expected levels is currently available.29 These results were confirmed in patients at high risk of neutropenia, in whom the administration of posaconazole 300 mg was related to a 97% chance of attaining the therapeutic pharmacokinetic goal on day 8 of therapy.30 Trough concentrations above 0.7 mg/L and 1 mg/L have been recommended for fungal infection prophylaxis and treatment, respectively, with a first monitoring within the first treatment week and subsequent regular monitoring throughout the therapy.11 Finally, currently available evidences indicate that the benefit of antifungal drugs monitoring seems to be reserved to azoles. No enough evidence is available to routinely recommend this practice for patients treated with echinocandins or lipid-containing amphotericin B formulations. Published studies conducted with the three available echinocandins have demonstrated that in patients undergoing continuous extra-renal deputative techniques or even in critically ill patients, no dose modifications are needed,31–34 and therefore, monitoring of plasma levels of these drugs should be reserved to not yet defined patient groups.

References


