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Editorial

Antifungal therapeutic drug monitoring: When, how, and why

Monitorización de niveles plasmáticos de los antifúngicos: cuándo, cómo y por qué

Santiago Grau[a,*], Sònia Luque[b]

[a] Servicio de Farmacia, Hospital del Mar, Universitat Autònoma de Barcelona, Barcelona, Spain
[b] Servicio de Farmacia, Hospital del Mar, Barcelona, Spain

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 hematopoietic 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 paediatric

* Corresponding author.
E-mail address: sgrau@hospitaldelmar.cat (S. Grau).

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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.[9]

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 cyclodextrine, 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 absortion and metabolism of itraconazole. This antifungal shows a non-linear pharmacokinetics that has it 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 this 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 Clínica* publishes a study conducted by Cabral-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.[13,26,27] 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.[13]

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 depurative 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

1. Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis. 2008;46:327–60.

2. Vazquez JA. Invasive fungal infections in the intensive care unit. Semin Respir Crit Care Med. 2010;31:79–86.
3. Salmon-Ceron D, Tubach F, Lortholary O, Chosidow O, Bretagne S, Nicolas N, et al. Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. Ann Rheum Dis. 2011;70:616–23.
4. Andes D, Lepak A. Antifungal therapeutic drug monitoring progress: getting it right the first time. Clin Infect Dis. 2012;55:391–3.
5. Andes D. Pharmnacokinetics and pharmacodynamics of antifungals. Infect Dis Clin N Am. 2006;20:679–97.
6. Grau S, Alvarez-Lerma F, Dominguez-Gil A. Pharmacokinetic/pharmacodynamics indices: are we ready to use them in daily practice. Expert Rev Anti Infect Ther. 2007;5:913–6.
7. Laverdiere M, Bow EJ, Rotstein C, Autmizguine J, Broady R, Garber G, et al. Therapeutic drug monitoring for triazoles: a needs assessment review and recommendations from a Canadian perspective. Can J Infect Dis Med Microbiol. 2014;25:327–43.
8. Sinnollareddy MG, Roberts MS, Lipman J, Robertson TA, Peake S, Roberts JA. Pharmacokinetics of fluconazole in critically ill patients with acute kidney injury receiving sustained low efficiency diafiltration. Int J Antimicrob Agents. 2015;45:192–5.
9. van der Elst KCM, Pereboom M, van den Heuvel ER, Kosterink JGW, Schölvinck EH, Alffenaar J-WC. Insufficient fluconazole exposure in pediatric cancer patients and the need for therapeutic drug monitoring in critically ill children. Clin Infect Dis. 2014;59:1527–33.
10. Smith J, Andes D. Therapeutic drug monitoring of antifungals: pharmacokinetic and pharmacodynamics considerations. Ther Drug Monit. 2008;30:167–72.
11. Hall SD, Thummel KE, Watkins PB, Lown KS, Benet LZ, Paine MF, et al. Molecular and physical mechanisms of first-pass extraction. Drug Metab Dispos. 1999;27:161–6.
12. Lass-Florl C. Triazole antifungal agents in invasive fungal infections: a comparative review. Drugs. 2011;71:2405–19.
13. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. J Antimicrob Chemother. 2014;69:1162–76.
14. Cabral-Galeano E, Ruiz-Camps I, Len-Abad O, Pou-Clavé L, Sordé-Masip R, Meije-Castillo Y, et al. Clinical usefulness of therapeutic drug monitoring of voriconazole in a university hospital. Enf Infecc Microbiol Clin. 2015;33:298–302.
15. Mitsani D, Nguyen MH, Shields RK, Toyoda Y, Kwak EJ, Silveira FP, et al. Prospective, observational study of Voriconazole therapeutic drug monitoring among lung transplant recipients prophylaxis: factors impacting levels of and associations between serum troughs, efficacy, and toxicity. Antimicrob Agents Chemother. 2012;56:2371–7.
16. US Food and Drug Administration, Center for Drug Evaluation and Research. Clinical pharmacology and biopharmaceutics review: voriconazole (Vfend). FDA; 2002.
17. Dolton MJ, McLachlan AJ. Optimizing azole antifungal therapy in the prophylaxis and treatment of fungal infections. Curr Opin Infect Dis. 2014;27:493–500.
18. Dolton MJ, Ray JE, Chen SC, Ng K, Pont LG, McLachlan AJ. Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. Antimicrob Agents Chemother. 2012;56:4793–9.
19. Racil Z, Racil Z, Winterova J, Kouba M, Zak P, Malaskova L, Buresova L, et al. Monitoring trough voriconazole plasma concentrations in haematological patients: real life multicenter experience. Mycoses. 2012;55:483–92.
20. Denning DW, Ribaud P, Milpied N, Caillot D, Herbrecht R, Thiel E, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. Clin Infect Dis. 2002;34:563–71.
21. Murayama N, Imi N, Nakane T, Shimizu M, Yamazaki H. Roles of CYP3A4 and CYP2C19 in methyl-hydroxylated and noxidized metabolite formation from voriconazole, a new antifungal agent, in human liver microsomes. Biochem Pharmacol. 2007;73:2020–6.
22. Wang T, Zhu H, Sun J, Cheng X, Xie J, Dong H, et al. Efficacy and safety of voriconazole and CYP2C19 polymorphism for optimized dosage regimens in patients with invasive fungal infections. Int J Antimicrob Agents. 2014;44:436–42.
23. Mori M, Kobayashi R, Kato K, Maeda N, Fukushima K, Goto H, et al. Pharmacokinetics and safety of voriconazole intravenous-to-oral switch regimens in immunocompromised Japanese pediatric patients. Antimicrob Agents Chemother. 2014;59:1004–13.
24. Zonios D, Yamazaki H, Murayama N, Natarajan V, Palmore T, Childs R, et al. Voriconazole metabolism, toxicity, and the effect of cytochrome P450 2C19 genotype. J Infect Dis. 2014;209:1941–8.
25. Park WB, Him N-H, Kim K-H, Lee S-H, Nam W-S, Yoon SH, et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal Infections: a randomized controlled trial. Clin Infect Dis. 2012;55:1080–7.
26. Chau MM, Kong DCM, van Hal SJ, Urbancic K, Trubiano JA, Cassumbhoy M, et al. Consensus guidelines for optimizing antifungal drug delivery and monitoring to avoid toxicity and improve outcomes in patients with haematological malignancy. Intern Med J. 2014;44:1364–88.
27. Dolton MJ, McLachlan AJ. Voriconazole pharmacokinetics and exposure-response relationships: assessing the links between exposure, efficacy and toxicity. Int J Antimicrob Agents. 2014;44:183–93.
28. Dolton MJ, Ray JE, Marriott D, McLachlan AJ. Posaconazole exposure–response relationship: evaluating the utility of therapeutic drug monitoring. Antimicrob Agents Chemother. 2012;56:2806–13.
29. Krisna G, Ma L, Martinho M, Preston RA, O'Mara E. A new solid oral tablet formulation of posaconazole: a randomized clinical trial to investigate rising single- and multiple-dose pharmacokinetics and safety in healthy volunteers. J Antimicrob Chemother. 2012;67:2725–30.
30. Duarte RF, Lopez-Jiménez J, Cornely OA, Laverdiere ML, Helfgott D, Haider S, et al. Phase 1b study of new posaconazole tablet for prevention of invasive fungal infections in high-risk patients with neutropenia. Antimicrob Agents Chemother. 2014;58:5758–65.
31. Maseda E, Grau S, Villagran MJ, Hernández-Gancedo C, Lopez-Tofiño A, Roberts JA, et al. Micafungin pharmacokinetic/pharmacodynamics adequacy for the treatment of invasive candidiasis in critically ill patients on continuous venovenous haemofiltration. J Antimicrob Chemother. 2014;69:1624–32.
32. Aguilar G, Azanza JR, Carbonell JA, Ferrando C, Badenes R, Parra MA, et al. Anidulafungin dosing in critically ill patients with continuous venovenous haemodiafiltration. J Antimicrob Chemother. 2014;69:1620–3.
33. Weiler S, Seger C, Pfisterer H, Stienecke E, Stippler F, Welte R, et al. Pharmacokinetics of caspofungin in critically ill patients on continuous renal replacement therapy. Antimicrob Agents Chemother. 2013;57:4053–7.
34. Muilwijk EW, Schouten JA, van Leeuwen HJ, van Zanten ARH, de Lange DW, Colbers A, et al. Pharmacokinetics of caspofungin in ICU patients. J Antimicrob Chemother. 2014;69:3294–9.