Antifungal therapeutic drug monitoring: focus on drugs without a clear recommendation

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Antifungal therapeutic drug monitoring: focus on drugs without a clear recommendation

Running title: Antifungal exposure

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Código de campo cambiado

Keywords

Antifungal exposure; azoles, polyenes, echinocandins, therapeutic drug monitoring, pharmacodynamics target

Abstract

Background. The goal of therapeutic drug monitoring is to determine the appropriate exposure of difficult-to-manage medications to optimize the clinical outcomes in patients under various clinical situations. Concerning antifungal treatment, and knowing that this procedure is expensive and time consuming, it is particularly recommended for certain systemic antifungals, i.e., agents with a well-defined exposure-response relationship and unpredictable pharmacokinetic profile or narrow therapeutic index. Little evidence supports the routine use of therapeutic drug monitoring for polyenes (amphotericin B), echinocandins, fluconazole or new azoles such as isavuconazole, despite the fact that a better understanding of antifungal exposure may lead to a better response. **Objectives**. The aim of this work is to review published pharmacokinetic/pharmacodynamic data on systemically administered antifungals focusing on those whose monitoring is not routinely recommended by experts. **Sources**. A MEDLINE search of the literature in English was performed introducing the following search terms “Amphotericin B, fluconazole, itraconazole, voriconazole, posaconazole, triazoles, caspofungin, micafungin, anidulafungin, echinocandins, pharmacokinetics, pharmacodynamics, and therapeutic drug monitoring. Review articles and guidelines were also screened. **Content**. This article collects different pharmacokinetic/ pharmacodynamics aspects of systemic antifungals and summarizes recent threshold values for clinical outcomes and adverse events. Although for polyenes, echinocandins, fluconazole and isavuconazole extensive clinical validation is still required for a clear threshold and a routine monitoring recommendation, particular points such as liposome structure or complex pathophysiological conditions, affecting final exposure, are discussed. For the rest, their better-defined exposure-response/toxicity relationship

allow to have useful threshold values and to justify routine monitoring. Additionally, clinical data are needed to better define thresholds that can minimise the development of antifungal resistance.

Implications. General therapeutic drug monitoring for all systemic antifungals is not recommended, however, this approach may help to stablish an adequate antifungal exposure for a favourable response, prevention of toxicity or development of resistance in special clinical circumstances.

Background

For therapeutic drug monitoring (TDM) to be reasonably useful, the following characteristics should be met: availability of a validated assay, demonstrated variable interindividual exposure (pharmacokinetic variability, PKv), high correlation between blood concentration and efficacy/toxicity, and a narrow therapeutic index. Being an intervention method, the main goal is to establish the appropriate exposure of difficult-to-manage medications to improve patient responses to the drugs administered and to avoid adverse drug reactions.

In clinical practice, drug exposure is monitored through measurement of blood trough concentrations (C_{min}), a more reliable index of drug exposure than dosage, which also serve as surrogate markers of area under the curve (AUC).

Systemic antifungal agents for the management of invasive fungal infections (IFIs) include polyenes (amphotericin B), triazoles (fluconazole, itraconazole, voriconazole, posaconazole and isavuconazole), echinocandins (caspofungin, micafungin, and anidulafungin), and flucytosine. For most of them, the PKv is a common issue. An in-

depth understanding of the relationship between antifungal exposure and response is required to establish clinically useful threshold values for clinical outcomes and adverse events, and thus for TDM usefulness. However, the resources used in antifungal TDM, i.e. economical costs, are not always backed by positive results. In most cases, studies analysing the impact of antifungal TDM on efficacy and safety are observational or include a low number of patients. However, most of them have found TDM to be beneficial, particularly with certain types of triazole drugs and flucytosine, due to their large inter- and intra-individual PKv and their high tendency for drug-drug interactions or their toxicity [1]. Furthermore, there is scarce evidence to support the routine use of TDM for polyenes, echinocandins, fluconazole or the new triazole isavuconazole, although a better understanding of antifungal exposure may lead to better response. TDM may be useful in certain circumstances, e.g., when dosing children, adolescents, and critical or older patients, due to scarce exposure information. Conditions that affect absorption of oral formulations (mucositis or vomiting) or distribution (inflammation that leads to increased body fluids) may affect final exposure. Here, data on systemic antifungal TDM are reviewed, focusing on those for which there are not clear expert recommendations. Tables 1 and 2 summarize these data, including a list of available studies and the main pharmacokinetic (PK) and pharmacodynamic (PD) characteristics for each of them.

Antifungals with no routine recommendations for TDM monitoring

Polyenes

Amphotericin B (AmB) is the most commonly used polyene antifungal agent with a broad spectrum of action against yeasts, moulds, and certain protozoa. It remains one

of the most prescribed antifungals for critically ill patients. The initial formulation was amphotericin B deoxycholate (DAmB) and for many decades, it was the only polyene agent available for the treatment of invasive fungal diseases. However, the major dose-limiting toxicity of DAmB (most notably nephrotoxicity and infusion-related reactions) promoted the development of novel less toxic formulations. Different lipid-based formulations have been developed: liposomal, lipid complex and colloidal dispersion [2]. AMB lipid complex (ABLC, the largest of the lipid preparations) is available in the market in few countries, whereas the production of AMB colloidal dispersion, a cholesteryl sulphate complex of AMB, has stopped [3]. Liposomal amphotericin B (AmBisome®; LAmB) is the most frequently used lipid formulation for nearly 30 years to treat a wide range of fungal infections due to its antifungal activity, tolerability and efficacy. AmB retains the antifungal activity after its incorporation into a liposome bilayer and its toxicity is significantly reduced [4]. Studies in animals and humans have shown that LAmB produces higher exposure in blood and tissues than other formulations (LAmB maximum concentration in serum, $C_{max,}$ 22.9 ± 10 µg/ml vs DAmB C_{max}, 1.4 ± 0.2 µg/ml), with clear differences in PK behaviour between these two formulations [5]. Although standard doses of lipid formulations are around five-time higher than those of conventional DAmB (which can explain the high blood levels) it is suspected that, because the structure of the liposome stabilized AmB in blood, the extravascular liberation of AmB from liposomes might be limited. This would explain the high blood levels and reduced distribution in normal organs, including kidneys, helping to increase the safety of liposomal formulations. However, in infected tissues, a gap is formed between vascular endothelial cells due to inflammation and tissues cells affected by fungal invasion. This enhances the permeability of the capillary vascular wall and blood-

tissue barrier [6] leading to higher distribution into the infected organs and increased efficacy with some degree of selectivity. A study showed that in a patient with pulmonary aspergillosis treated with LAmB, drug levels in the infected areas were approximately 3-fold higher in comparison to non-infected areas, confirming that LAmB is more likely to accumulate around infected lesions [7]. Demartini *et al.* also described lower AmB concentrations in plasma than in tissues in 18 patients with lung cancer [8]. However, there are scarce data on the relationship between AmB exposure and clinical outcome, which further complicates the identification of a target therapeutic range. New data regarding a specific pharmacodynamic (PD) target recognize the maximum concentration-to-MIC (C_{max}/MIC) ratio of AmB as the index that best predicts clinical response [9,10]. The C_{max}/MIC ratio required for efficacy remains controversial ranging from 3.8 to 40.2 in animal and human studies [11-14]. Although clinical verification is still required, targeting a C_{max}/MIC ratio 4.5 or higher may serve as an index for predicting the clinical effects of LAmB in order to design treatment regimens. However, little is known if this PD target should be established considering free or total AmB (encapsulated and non-encapsulated in liposomes) [12]. In line with this, liposome structure deserves special attention. As for other liposome formulations, drugs sequestered within this particle cannot achieve diffusional equilibrium with the extravascular compartment. Additionally, the AmB released from a liposome highly binds to plasma protein (>90%, highly dependent on patient clinical status) and this aspect may affect final AMB blood exposure. Thus, the total AmB measured in blood after LAmB administration may not indicate the real exposure [12], and the clinical use of monitoring AmB blood concentration may be questionable. Thus, until a clearer relationship between total AmB exposure and efficacy is established, TDM may be

recommended for toxicity surveillance and treatment optimization but not in routine clinical practice.

Azoles

Fluconazole (FLC)

Fluconazole is a common antifungal option for managing *Candida* infections. It is available in oral and intravenous formulations. TDM is currently not recommended since appropriate antifungal exposure has been correlated with favourable outcomes in patients receiving this azole. However, in spite of its favourable PK behaviour, FLC exposure and toxicity (hepatic) may be affected by complex pathophysiological conditions, e.g. renal insufficiency, requiring dosage adjustment for better outcome. Sinnollareddy *et al* described how fluconazole exposure was highly variable in critical patients compared with healthy volunteers [15]. Thus, TDM-guided dosing adaptation may optimize drug exposure in selected patient populations (ie, pediatric patients or those undergoing renal replacement therapies) [16]. The PD index that best relates to the outcome is the AUC_{0_24}/MIC (or dosage/MIC, as the AUC and the dosage are highly correlated). PD values ranging between 50-100 were generally associated with favourable clinical outcomes [16-18]. This target corresponded with a C_{min} at around 10–15 mg/L [17]. In adult liver transplant recipients receiving FLC for invasive candidiasis, TDM showed that a FLC C_{min} > 11 mg/L significantly correlated with clinical success [18]. However, several reports have shown that not many patients achieve the desired index required for optimal outcome, which contributes to the emergence of FLC resistance. Further data on exposure-resistance relationships may provide a role for FLC TDM for a more rational use of this antifungal agent.

Isavuconazole (ISZ): Isavuconazonium sulfate is the most recently approved triazole for the treatment of adults with invasive aspergillosis and invasive mucormycosis [19]. It is a water-soluble prodrug that is rapidly hydrolysed by esterases to the active moiety, ISZ. Data from healthy volunteers and animal models allow concluding that ISZ PK is linear and dose-proportional with dosages up to 600 mg/day, which is useful for predicting blood concentrations in humans. Although the clinical experience with ISZ is limited in comparison to other triazoles, the IDSA and ECIL-6 guidelines recognize lower rates of adverse effects (photosensitivity, skin disorders, hepatobiliary or visual disorders) and a better safety profile compared with other triazoles [20,21]. Additionally, ISZ has a lower predisposition for drug-drug interactions mediated by cytochrome P_{450} in comparison to VRC [22]. A relevant covariate that affects ISZ exposure is ethnicity [23]. Although animal studies show a very strong relationship between the AUC_{0_24}/MIC ratio and treatment outcome, there is little evidence in humans regarding concentration-dependent efficacy or failure to establish a true PD target. No exposure-response relationship was found in the SECURE study, suggesting that the achieved ISZ exposures by clinical dosage regimens were near maximal and enough for treating the infecting organisms [23], concluding that routine ISZ TDM is not recommended. However, ISZ is a relatively new antifungal, and clinical evidences are still needed in selected patient populations. Subjects with critical illness, sepsis, low or high body weight, polypharmacy, hepatic impairment, renal replacement therapy or other extracorporeal devices, long-term administration (which is usually required in proven invasive fungal disease), and on oral treatment may benefit from ISZ exposure monitoring. Data from real-world experiences and clinical trials revealed a low percentage of patients (<10%) showing exposures <1 mg/L, which represents the highest value for a recently established clinical

breakpoint for this compound. Newly reported mean values for ISZ blood concentrations range between 2.98 and 3.30 mg/L [24].

Echinocandins

Echinocandins (caspofungin, micafungin and anidulafungin) are valued antifungals due to their potent activity and lower rates of toxic events in comparison to azoles and polyenes [25]. They act as fungicidal drugs to *Candida* spp., including triazole-resistant isolates, showing a fungistatic activity against *Aspergillus* [26]. Current guidelines recommend echinocandins as first-line therapies for most types of invasive candidiasis [27], although microbiologic resistance to this class of antifungal agents has emerged and can result in clinical failure [28]. Echinocandins display a relevant post-antifungal effect and therefore a concentration-dependent activity. C_{max}/MIC and AUC_{0_24}/MIC (measured as total drug concentrations) ratios are considered relevant PD indices for these drugs [29]. A trough concentration of at least 1 mg/L has been proposed as the target concentration in invasive infections (derived from in vitro susceptibility testing of *Candida* spp.), since a robust PD target is yet to be identified via clinical studies (most data from animal studies were found to be highly variable). This value is described as safeguard of efficacy for the management of *Candida* spp infections. These levels exceed by far the MIC_{90} for the usual strains of *Candida spp*; although they would be insufficient for the management of *C. parapsilosis* [30]. It is worth mentioning the considerable interindividual variability observed in a series of cases including critically ill patients described by Sinnollareddy *et al*. [15]. Other factors such as obesity, age and clinical status may affect exposure, and contribute to substantial PK differences between them. Variability has been established as a source of underexposure and development of

resistance. A recent study modelling *Candida glabrata* gastrointestinal colonization and dissemination in mice, suggests that echinocandin-resistant isolates recovered from blood or other internal organs may have originated in the gut where sub-therapeutic drug concentrations might have led to the development of resistant organisms [31]. Most experts consider that the data regarding the relationship between blood echinocandin concentrations and therapeutic outcome is insufficient to support the routine use of TDM for these agents. However, it seems reasonable that monitoring exposure should be considered for patients in whom PK is unpredictable or still unknown [32]. Inadequate antifungal dosing contributes not only to suboptimal outcomes but also to the emergence of resistance.

Antifungals with routine recommendations for TDM monitoring

Azoles

Voriconazole (VRC): TDM should be routinely performed in most patients receiving VRC. This azole exhibits highly variable intra- and inter-individual PK, attributed to different factors, such as pharmacogenetic polymorphisms, drug-drug interactions, altered gastrointestinal absorption, and even inflammation and body weight (Table 2). The optimal VRC trough concentration for clinical response/safety is controversial [16,20,33,34]. Two recent meta-analysis suggest a VRC C_{min} target for TDM between 1 and 6 mg/L when the drug is used to treat an established invasive infection [35,36]. For prophylactic use, the target concentration is less clear. Ashbee et al. recommend that the target should be the ratio between C_{min} and MIC if VRC susceptibility (MIC value) of the invading pathogen is known [16]. The primary metabolic pathway of VCR involves fluoropyrimidine N-oxidation to produce the inactive metabolite VRC N-oxide. Regular

238 VRC N-oxide blood level monitoring is not routinely indicated, although determination
239 of the VRC N-oxide/voriconazole ratio may provide information about the patient's
240 metabolic phenotype and may play a role in VRC associated toxicity. Exposure-
241 dependent hepatotoxicity has been convincingly shown for VRC only [36], although
242 phototoxicity associated to VRC treatment is probably related to its metabolite [37]. In
243 special circumstances such as cystic fibrosis (CF) or treatment in children [38], TDM is
244 required to maintain blood concentrations between 1 and 6 mg/L.
245 **Itraconazole (ITC)**: While newer antifungal agents are currently recommended for
246 management of deep fungal infections, ITC is still used for the treatment of allergic
247 mycosis and remains a key agent in cases of endemic mycosis worldwide [39]. It is
248 available in oral and intravenous formulations (the latter not available in all countries).
249 However, ITC has shown unpredictable oral bioavailability and clinically important drug-
250 drug interactions, making it difficult to determine the optimal dosing regimen. This is
251 the main reason for ITC TDM in clinical practice. A trough level range of 0.5-1 mg/L is
252 generally used as PD target. A minimum concentration below 0.5 mg/L has been
253 associated with an increased likelihood of breakthrough infections [40,41]. According to
254 a recently published meta-analysis, the use of this azole is restricted because of its
255 adverse reactions compared to new safer and more effective antifungals [42]. ITC
256 exhibits dose-dependent PK and is partially eliminated by CYP3A4 oxidation to
257 hydroxyitraconazole (OH-ITC), a metabolite with similar antifungal properties.
258 Concentrations of OH-ITC are around two-fold higher than those of the parent
259 compound in healthy volunteers [43]. Its concentration should be measured as ITC TDM,
260 since several studies show that the metabolites contribute to CYP3A4 inhibition and
261 need to be considered in the quantitative rationalization of the treatment [44], although

there is not a common criteria about this point (Table 2). It is worth noting that ITC bioassay concentration measurements are typically 2-10 times higher than those estimated using HPLC (due to the active metabolite). When measured by bioassay, a reasonable lower limit for TDM is approximately 5 mg/L [39].

Posaconazole (PSC): PSC is structurally similar to ITC. Some of its main PK peculiarities are summarized in Table 2. Currently, PSC plays an important role in the prophylaxis of IFI. Three formulations are available in most countries: two oral formulations, a solid delayed release tablets and an oral suspension, and the intravenous formulation with significant differences regarding bioavailability (tables higher than oral suspension). Experts recommend the use of PSC oral tablets in prophylactic regimens over any other formulation, particularly during induction chemotherapy [45]. However, PSC oral suspension is still widely used and available worldwide. This formulation is a good option for patients with nasogastric tubes or those unable to take tablets. Thus, when PSC oral suspension is used, TDM is mandatory if there are concerns regarding gastrointestinal absorption, uncertainty about compliance or suspicious of breakthrough IFI. It is important to consider that the two oral formulations are not interchangeable because they have different doses and PK. Further exposure-toxicity data are needed to fully assess potential dose-dependent hepatic adverse effects for the new formulations and possible influence of drug-drug interactions. A trough level should be measured seven days post-initiation of the therapy or after dose adjustment, although a lower target has also been proposed after 48 h of treatment [16]. A trough level higher than 0.5 mg/L has been proposed in a recent meta-analysis [46], although despite clinical evidence, a consensus of 0.5-0.7 mg/L is accepted as the lower bound in prophylactic regimens.

Several reports conclude that PSC tablet form increases the possibility of achieving this target due to high bioavailability, so whether TDM is useful in this case needs future investigation with large sample size, also exploring the relationship between PSC exposure and adverse events.

Pyrimidines

5-Flucytosine

The antifungal drug 5-flucytosine (5FC) is a synthetic compound originally assessed for the treatment of tumours [47] and then fungal infections. 5FC containing combination therapy remains an efficient option in the treatment of cryptococcal meningitis [48]. Although it is on the WHO essential medicines list, 5FC is currently unavailable in low- and middle-income countries where the disease burden is greatest [49]. This compound exhibits significant inter-patient PKv. Furthermore, PD studies show a correlation between serum concentration and toxicity, particularly renal and marrow toxicity [50,51]. TDM is mandatory for this antifungal agent to prevent serious toxicity [52]. Serum concentration should be determined 72 hours post-initiation of therapy, after dose adjustment, if there is uncertain compliance with oral therapy, or if there are signs of clinical or laboratory toxicity. To date there is no agreement on a precise PD target. Recommendations are based on in vitro evidence in which yeast exposed to concentrations <20-40 mg/L (C_{min}) developed resistance and C_{max} (peak) >100 mg/L are most frequently associated with toxicity.

In summary, in spite of close monitoring of systemic antifungal treatments is not universally recommended, recently studies provide new evidences of the usefulness of

establishing an adequate antifungal exposure for adequate response, prevention of toxicity or development of resistance. TDM should guide dosage to achieve adequate PD target in cases of therapeutic failure, serious toxicity, important PKv due to certain morbidities, obesity, non-compliance, interacting medication, or to provide data on new treatments without sufficient clinical evidence. The high degree of PKv in children and infants (largely excluded from clinical trials) and in any other cases makes TDM an essential procedure to ensure adequate therapeutic exposure in these special circumstances [53]. A less explored application related to TDM is the ability to ensure optimal exposures for reducing the emerging problem of antifungal resistance. Clinical data are urgently needed to define thresholds that can minimise resistance and whether they are safe for patients. This particular connexion has already been described for antifungals such as echinocandins or fluconazole [18,31]. However, TDM requires continuous clinical input. While it may be ideal to have assays performed on site, the cost of developing and running assays may mean that many TDM services are only available in specialist centres. Hitherto, measurements of antifungal concentrations in body fluids are easily accessible to clinical laboratories by bioassay (except for itraconazole) or the new simple, low-cost enzyme immunoassays using automated clinical chemistry analyzers [54].

Transparency declaration

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Conflicts of Interest

The author declares that there is no conflict of interest.

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