Therapeutic drug monitoring for triazoles

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Purpose of review

Invasive fungal infections are a leading cause of morbidity and mortality in immunocompromised patients, and mechanisms to optimize therapeutic outcomes are urgently required. Therapeutic drug monitoring represents an important component for the routine use of the triazoles.

Recent findings

Triazoles have revolutionized the prevention and treatment of invasive fungal infections. Increasing data suggest that this class displays important concentration–effect and concentration–toxicity relationships. There has been an increased understanding of the pharmacokinetics and pharmacodynamics of triazoles, and this has facilitated the identification of concentrations (or drug exposures) that are both effective and nontoxic. This review discusses the application of therapeutic drug monitoring to fluconazole, itraconazole, voriconazole and posaconazole.

Summary

Therapeutic drug monitoring represents an important mechanism to optimize the outcome of immunocompromised patients receiving triazoles.

Keywords

fluconazole, posaconazole, therapeutic drug monitoring, voriconazole

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Introduction

The triazoles available for routine clinical use include fluconazole, itraconazole, voriconazole and posaconazole, with ravuconazole and isavuconazole currently in development. Although triazoles have revolutionized the prevention and treatment of invasive fungal infections, their pharmacological properties and behaviour are complicated. Triazoles display clinically relevant concentration–effect and concentration–toxicity relationships. This review summarizes these relationships and provides practical guidelines for the therapeutic drug monitoring (TDM) of triazoles.

Indications for therapeutic drug monitoring: general principles

The objective of TDM is to maximize the probability of a successful outcome and minimize the probability of toxicity. Specific indications vary according to the agent and the clinical context; these are summarized below:

(1) clinically relevant exposure–response relationships,
(2) clinically relevant exposure–toxicity relationships,
(3) compounds with a narrow therapeutic window,
(4) variable pharmacokinetics,
(5) physiological instability,
(6) drug–drug interactions,
(7) infections at sanctuary sites,
(8) children and neonates,
(9) degree of compliance,
(10) change of dosage,
(11) patient failing therapy and
(12) serious/poor prognostic disease.

An understanding of the relationship between the probability of success and toxicity requires a common measure of drug exposure as the independent variable. In this regard, the most informative measure is the pharmacokinetic–pharmacodynamic variable which is optimally linked to outcome; this is determined in experimental systems, and for triazoles and disseminated candidiasis is the ratio of the area under the concentration–time curve to the minimum inhibitory concentration (AUC:MIC) [1–5]. In clinical contexts, an estimate of the AUC which develops in an *individual* patient is readily possible but resource intensive. Consequently, simpler, but less precise measures of drug exposure are frequently used, and for the triazoles, this is usually the trough concentration. Although the trough is an informative sampling point for estimates of terminal elimination, it provides little information related to the absorption and distribution phases, both of which may contribute significantly to the total AUC.

Variability in drug handling for individual patients receiving the same dosage is a critical determinant of the probability of therapeutic success and toxicity. Such variability may be an inherent manifestation of the drug itself or result from physiological derangement or instability. A portion of the total variance may be attributed to fixed effects (e.g. weight), but after these effects are considered, one is left with residual (or unexplained) variance. For many drugs and drug classes, considerable residual variance makes a-priori predictions of concentration–time profiles in individual patients impossible; hence, the need for TDM.

The timing of samples for TDM is poorly defined. Using Bayesian estimation techniques and population pharmacokinetic models, it is possible to obtain robust estimates of drug exposure (e.g. AUC) in individual patients *before* the onset of steady state. The use of less precise measures of drug exposure, such as trough concentrations, really requires sampling at steady state to enable meaningful interpretation. The time to steady state for drugs with linear pharmacokinetics can be estimated from the half-life alone (4–5 half-lives), but this is not possible for drugs which display nonlinear pharmacokinetics (e.g. voriconazole and itraconazole). For these agents, multiple samples are required to ensure that effective and non-toxic concentrations have been obtained.

Fluconazole

Fluconazole has an excellent long-term safety and efficacy record, with an established role for prophylaxis, empirical therapy and the treatment of both superficial and invasive yeast fungal infections [6,7].

Pharmacology and pharmacokinetics

Fluconazole displays linear pharmacokinetics over dosages ranging from 50–800 mg/day, and probably higher, although this is less well studied [8,9]. Fluconazole is highly bioavailable, exhibits low protein binding and undergoes widespread dissemination to tissues. There is a felicitous relationship between dosage and AUC, in that the AUC is almost identical to the administered dosage (i.e. a dose of 800 mg produces an AUC of 800 mg h/l) [10]. This relationship enables clinicians to quickly check whether a dosage is appropriate to achieve a desired AUC:MIC target.

Evidence for concentration–effect and concentration–toxicity relationships

Exposure–effect relationships have been determined in cohorts of patients with both candidaemia and mucosal candidiasis in which an AUC:MIC of at least 25 [using Clinical and Laboratory Standard Institute (CLSI) methodology] [11] and AUC:MIC of at least 100 [using European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodology] [12] is required to ensure a high probability of successful outcome. Patients infected with isolates with a high MIC and receiving relatively low dosages of fluconazole have poorer outcomes in terms of both therapeutic failure and increased mortality [13].

Fluconazole is remarkably well tolerated, even at higher dosages. The currently recommended dose for the treatment of disseminated candidiasis is 400–800 mg. Although toxic manifestations such as elevated liver function tests (LFTs), nausea, vomiting, erythema multiforme and seizures are observed with higher dosages [9,14,15], quantitative relationships between drug exposure and the probability of toxicity have not been established.

Implications for therapeutic drug monitoring

Routine TDM of fluconazole is not required given its highly favourable pharmacokinetic profile and wide therapeutic index. TDM may be indicated for the treatment of infections in sanctuary sites (e.g. central nervous system), treatment of isolates with reduced susceptibility or patients in whom absorption may be suboptimal. Children and infants are at risk of suboptimal drug exposure, and TDM may be indicated in certain cases. Compliance can be checked with TDM if this is a concern. Target fluconazole trough concentrations have not been defined; a pragmatic solution is to draw four to five samples throughout the dosing interval and calculate the AUC, and ensure that the AUC:MIC is above a desired target [e.g. $\geq$25 (using CLSI methodology) or AUC:MIC of $\geq$100 (using EUCAST methodology)].

Itraconazole

Itraconazole has demonstrated efficacy for the prophylaxis [16–19], and treatment of acute [20–23] and chronic aspergillosis [24] and allergic bronchopulmonary aspergillosis [25]. Itraconazole also has a role in the treatment of fungal skin and nail infections as well as dematiaceous fungi and endemic mycoses, such as coccidioidomycosis, histoplasmosis, blastomycosis and sporotrichosis.

Pharmacology and pharmacokinetics

Pure itraconazole is a highly lipophilic protein-bound compound which is poorly soluble at physiological pH. The solubilization and absorption of the capsule formulation is facilitated by an acidic environment, which is the basis for the administration of itraconazole with food [26] or cola [27]. Absorption is compromised in patients receiving H_2 antagonists or proton pump inhibitors or those with achlorohydria due to critical illness. Generic formulations of itraconazole may be differently bioavailable, often to a clinically significant degree [28]. The oral hydroxypropyl-β-cyclodextrin (itraconazole suspension) formulation has 20–50% higher bioavailability, is

absorbed more rapidly and results in higher systemic drug exposure than capsules [29]. Nausea is more common with the suspension due to the osmotic effects of cyclodextrin; this may affect compliance and is a further indication for TDM (see Indications for therapeutic drug monitoring: general principles). The use of intravenous itraconazole enables target concentrations to be achieved within the first 48 h of therapy [30,31].

Itraconazole displays nonlinear pharmacokinetics [32], but this remains poorly characterized. Recent studies have described concentration–time profiles using linear pharmacokinetic models [29,33,34]; in these particular circumstances, the absence of nonlinearity is probably a function of study design. Oxidative metabolism of itraconazole produces hydroxyitraconazole in a ratio of approximately 1 : 1; the latter has comparable antifungal potency to the parent. The terminal half-life estimated after the onset of linear phase of clearance is 24 h, and steady state is reached after 13–14 days in healthy volunteers [32]. Oral loading doses may be warranted for patients with serious infections. Numerous drug interactions are documented with itraconazole, mostly mediated by cytochrome P450 (CYP)3A4.

Evidence for pharmacokinetic variability for itraconazole

Itraconazole exhibits extensive pharmacokinetic variability in both laboratory animal models [35] and humans [32]. For patients taking capsules, low levels are usually because of poor absorption. This is less of an issue with the suspension, but overall variance is large, and a proportion of patients receiving this formulation will still have low levels. High itraconazole levels probably result from drug accumulation secondary to saturated clearance pathways.

Exposure–effect and exposure–toxicity relationships

Exposure–response relationships have been established in laboratory animal models of invasive pulmonary aspergillosis. Itraconazole levels (taken 2 h after dose and determined by bioassay) of 6 mg/l induced near-maximal reduction of pulmonary fungal burden [35]. A dose of 40 mg/kg in rabbits resulted in approximately 30-fold variation in peak plasma levels, which had a direct impact upon the therapeutic outcome. A relationship exists between peak itraconazole levels and successful outcome of mucosal candidiasis in patients with AIDS [36].

Adverse events include gastrointestinal intolerance, hypokalaemia, fatigue, ankle oedema, cardiac failure and deranged LFTs. At present, there is no quantitative relationship between drug exposure and the probability of toxicity.

Targets for therapeutic drug monitoring

Itraconazole can be measured by high-performance liquid chromatography (HPLC) or bioassay, but the results are discordant because of the bioactive metabolite. An estimate of total antifungal activity using HPLC requires separate assays for both itraconazole and hydroxyitraconazole. The bioassay simultaneously detects itraconazole and its active metabolite, and estimates for itraconazole levels are 2–10 times higher than those obtained by HPLC [37].

A steady-state itraconazole trough concentration of 0.25 mg/l (HPLC) for 2 weeks was initially considered optimal for the prevention of invasive fungal infections in patients with neutropenia [38]. Subsequently, a target of 0.5 mg/l was proposed on the basis of *Aspergillus* MICs and the demonstration that this higher level provided better protection for patients with neutropenia [39]. The response of patients with AIDS and oesophageal candidiasis is higher in patients with trough levels more than 0.5 mg/l [40]. Collectively, therefore, a reasonable lower therapeutic target is 0.5 mg/l. If concentrations are measured using bioassay, then the lower bound of the therapeutic range is 5 mg/l. Lower TDM targets are likely for mycoses caused by highly susceptible pathogens such as *Sporothrix schenckii* and *Histoplasma capsulatum*, but these have yet to be studied. An upper bound of the therapeutic range is more difficult to establish given the paucity of data.

Patients receiving capsules 200 mg twice daily with low levels should have factors affecting compliance sought and addressed and an enquiry made as to whether capsules are being taken with food or acidic beverage. The specific formulation (i.e. manufacturer) should be recorded and prescribed consistently if adequate concentrations are documented and a switch to another generic formulation considered if concentrations are low. H_2 antagonists and proton pump inhibitors should be stopped if possible, and other potential drug interactions sought and rectified. Capsules can be increased from 200 mg twice daily to 300 mg twice daily or changed to itraconazole suspension 200 mg twice daily. Further increases in dosage directed by serum levels may be appropriate but are often limited by gastrointestinal intolerance induced by the cyclodextrin excipient. Patients with high levels and toxicity should have the drug temporarily stopped and then restarted at a lower dosage; drug may still be detectable for 1–2 weeks following cessation. Following a change in regimen, a repeat level should be obtained, but the nonlinear pharmacokinetics means that a new steady-state concentration may not be achieved for approximately 2 weeks. Compliance and inadvertent drug interactions can also be checked with TDM.

Voriconazole

Voriconazole has demonstrated safety and efficacy for the treatment of disseminated candidiasis [41] and is a first-line agent for the treatment of invasive aspergillosis [42]. Furthermore, voriconazole has a specific role in the treatment of cerebral aspergillosis [43] and *Aspergillus* osteomyelitis [44], in which tissue penetration may be an important determinant of efficacy. Voriconazole has a role in the treatment of chronic pulmonary aspergillosis, especially for patients who have failed or who are intolerant of itraconazole [45]. Voriconazole may also be used for infections due to *Scedosporium* spp. and *Fusarium* spp.

Pharmacology

Voriconazole is a structural congener of fluconazole, which was specifically engineered for anti-*Aspergillus* activity. The extended spectrum comes at a cost of reduced solubility, less favourable pharmacokinetics and a raft of CYP-dependent drug interactions. Bioavailability is 96% in healthy volunteers, but the extent of absorption in critically ill patients is less well defined. Variability in the rate of absorption influences the time to peak concentration. For the intravenous formulation, voriconazole is solubilized using a sulphobutylether-β-cyclodextrin excipient. Voriconazole exhibits nonlinear pharmacokinetics, which manifests as disproportionate changes in drug exposure following dosage alterations. Voriconazole is principally metabolized by CYP2C19 and CYP3A4, with a smaller contribution from CYP2C9. CYP2C19 displays clinically relevant polymorphisms, including poor metabolizers and extensive metabolizers, and heterozygotes that have reduced, but measurable enzyme activity. The proportion of poor metabolizers within a population depends on the racial composition; the incidence is 3–5% in whites but as high as 15–20% in Asian patients [46]. Because the CYP2C19 genotype only explains a portion of overall variance, dosing cannot be individualized on the basis of pharmacogenetic data alone.

Evidence for variability of voriconazole

Voriconazole exhibits approximately 100-fold variability in drug levels for individuals receiving the same dosage, which is only partly accounted for by sex, age and CYP2C19 genotype. For adults, weight is not a covariate that explains observed variability (website: www.fda.gov/ohrms/dockets/AC/01/briefing/3792b2_01_Pfizer.pdf). In contrast, however, weight is an important determinant of drug exposure in paediatric patients [47]. A recent study has suggested that approximately 15% of bone marrow transplant recipients receiving standard voriconazole dosages have undetectable trough voriconazole levels [48]; the reasons for this are not clear, as this was not observed in the drug development programme. One possibility is that loading dosages (oral or intravenous) are used less frequently in routine clinical practice, but poor compliance, drug interactions and incomplete absorption (e.g. gut graft versus host disease) are possible additional explanations. High voriconazole levels are seen in patients with poor hepatic function, critical illness, poor metabolizer CYP2C19 genotype and the elderly. The coadministration of omeprazole increases voriconazole levels [49••] and the AUC increases by approximately 41%.

Evidence for exposure–effect relationships

Voriconazole exposure–response relationships have been established in experimental models of disseminated candidiasis and invasive aspergillosis. A phase II study suggested that levels of less than 0.25 mg/l are associated with a suboptimal outcome [50]. A compilation of clinical data suggests that patients with higher mean voriconazole concentrations tend to have better responses, with optimal outcomes observed with mean concentrations of 3–4 mg/l (website: www.fda.gov/ohrms/dockets/AC/01/briefing/3792b2_01_Pfizer.pdf). Random concentrations of less than 2.05 mg/l have been associated with a suboptimal therapeutic outcome in patients with invasive aspergillosis [51]. The relationship between trough concentrations and successful outcome was recently defined using a logistic regression model in which a trough level of 1 mg/l was associated with a 70% probability of a successful outcome, with only marginally higher responses predicted with higher trough concentrations [49••].

Patients with high mean voriconazole levels have an increased probability of elevated aspartate aminotransferase, alkaline phosphatase and bilirubin but not of alanine transaminase; of these, the relationship with bilirubin elevation is the strongest [52]. There is not an obvious cut-off that separates the population into groups with high and low probability of toxicity; instead, one sees a gradual increase in the probability of an adverse event as drug exposure increases. The probability of visual adverse events also increases with increasing trough concentrations, although the clinical significance is less important as this phenomenon is transitory and does not require cessation of therapy. More importantly, however, is the relationship between high trough concentrations and central nervous system (CNS) toxicity [49••,53–55]. A logistic regression model suggests that a trough concentration of 6 mg/l results in approximately 20% probability of CNS toxicity [49••]. Other potential dose-related toxicities, which include hypoglycaemia, hypotension, pneumonitis, electrolyte disturbance and arrhythmia, have been reported in a small number of patients [54].

Targets for therapeutic drug monitoring and therapeutic intervention

There is continuing uncertainty regarding precise therapeutic targets for voriconazole. The logistic regression model developed by Pascual *et al.* [49••] suggests that the

lower end of the therapeutic range should be approximately 1 mg/l, and certainly no lower, as a less than 70% probability of a successful outcome for patients with a life-threatening infection is unacceptable. Higher trough levels are associated with only an incremental increase in the probability of a successful outcome. The upper range is probably 5–6 mg/l; trough levels higher than this are associated with an unacceptably high probability of both CNS toxicity and hepatitis. For patients receiving long-term therapy, compliance and inadvertent administration of interacting drugs can be monitored with TDM.

To achieve therapeutic concentrations as quickly as possible, a loading dose should be administered; this can be achieved orally (400 mg twice daily for two dosages) or intravenously (6 mg/kg for two dosages, then 4 mg/kg). The dosage may be increased from 200 mg twice daily to 300 mg twice daily if clinically indicated, and a recent study suggests that dosage escalation is frequently required to achieve therapeutic targets [49••]. In a proportion of patients, dosage escalation will saturate clearance mechanisms and cause a dramatic increase in serum concentrations; assiduous monitoring is required to prevent inadvertent toxicity.

For patients with high levels, dose reduction may prevent toxicity. Voriconazole can either be temporarily stopped or the dose reduced to 150 mg twice daily. For those patients receiving omeprazole, this agent may be temporarily ceased. The time taken for levels to fall will vary from patient to patient, and continuous monitoring is required to ensure that levels do not inadvertently become subtherapeutic. The nonlinear pharmacokinetics means that there may be an unexpected disproportionate fall in drug exposure following dosage reduction.

Posaconazole

Although posaconazole has a very wide spectrum of antifungal activity, its primary clinical indications are for salvage therapy for patients with invasive aspergillosis and for prophylaxis for patients with neutropenia and haematopoietic stem cell transplant recipients [56,57]. Posaconazole also has a role in the treatment of the zygomycoses, either as primary therapy or for patients intolerant or refractory to therapy with the polyenes.

Pharmacology

Posaconazole is currently available only as an oral formulation; an intravenous formulation is in development. Posaconazole is administered as a loading dose of 200 mg four times daily for 1 week, followed by a maintenance dose of 400 mg twice daily [58]. Linear pharmacokinetics are observed with dosages between 50–800 mg, with saturation of absorption at dosages more than 800 mg/day [59]. Systemic exposure increases substantially following administration of divided dosages [58] and may be lower in patients with mucositis [60]. Administration with a high-fat meal increases systemic exposure by approximately four-fold with respect to the fasted state [61]. The concentration–time profile is relatively flat, with minimal variation in peak and trough concentrations. Posaconazole has a prolonged half-life of approximately 19 h and takes approximately 100 h to reach steady state, but adequate therapeutic levels are established in 1–2 days in the majority of patients. Unlike other triazoles, interpatient variance has not been robustly quantified using population pharmacokinetic models.

Evidence for exposure–effect relationships

Exposure–response relationships for posaconazole have been defined in a murine model of disseminated candidiasis and a rabbit model of invasive pulmonary aspergillosis [1,62]. In the context of salvage therapy for invasive aspergillosis, a higher proportion of clinical responses are observed in patients with higher mean and peak serum concentrations [63•]. Posaconazole is associated with gastrointestinal intolerance and deranged LFTs, but there is no evidence that these side effects are dose dependent.

Targets and therapeutic intervention

Data from Walsh *et al.* [63•] do not suggest that there is an obvious target concentration which readily separates a population into groups with a high and low probability of success; in contrast, one sees a progressively higher rate of response with higher drug exposures. A peak and average concentration of 1.50 and 1.25 mg/l, respectively, is associated with a 75% response rate [63•].

A paucity of data makes firm recommendations for TDM difficult. TDM should certainly be considered for patients failing therapy, the treatment of infections at sanctuary sites, treatment of resistant organisms, patients with mucositis or malabsorption and those unable to take drug with high-fat food. As there is only limited experience with posaconazole for children, TDM is probably indicated in all paediatric cases. TDM may also be used to monitor compliance in the setting of long-term therapy.

For patients with low posaconazole levels, an assessment should be made as to whether the drug is being administered with food (and preferably high-fat food). Dosage escalation beyond 800 mg/day is unlikely to be useful, but an attempt may be made to fractionate the total dosage. An intravenous preparation, if made available, will facilitate the attainment of therapeutic concentrations at the earliest possible time.

Conclusion

Triazoles have a critical role in the prevention and treatment of invasive fungal infections. Accumulating

evidence suggests that routine monitoring should be considered for itraconazole and voriconazole. Further clinical data are required before recommendations can be made for posaconazole although this agent appears to exhibit important concentration–effect relationships and variable pharmacokinetics. Development of antifungal resistance on azole therapy has been documented and may be more frequent if triazole concentrations are low; additional data are required to establish whether this is relevant to the current understanding of TDM targets. TDM targets for less common drug–pathogen combinations, such as posaconazole and Zygomycetes, may differ from those established for *Candida* and *Aspergillus* infections. For all triazoles, there are specific indications for which determination of drug levels should be considered as an integral component of optimal patient care.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 685–686).

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