Posaconazole: The Case for Therapeutic Drug Monitoring

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Abstract: Invasive fungal infections are associated with high morbidity and mortality. Antifungal therapeutic options remain relatively limited; therefore, optimization of present regimens is essential. Posaconazole is licensed for prevention of invasive fungal infections and oropharyngeal candidiasis and salvage therapy for invasive aspergillosis. Recent data suggest that therapeutic drug monitoring may be an important tool for patient management. Clinical and laboratory animal data suggest that posaconazole demonstrates clinically relevant exposure–response relationships. Higher systemic drug exposure is associated with improved clinical outcomes. Potentially subtherapeutic concentrations are frequently encountered in critically ill patients. Therapeutic drug monitoring provides a way to optimize the use of posaconazole, and this review summarizes the indications and process by which this can be achieved.

Key Words: antifungal, posaconazole, triazole, therapeutic drug monitoring, pharmacokinetics

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BACKGROUND

Invasive fungal infections are associated with high morbidity and mortality, yet therapeutic options remain relatively limited. Therefore, the optimal use of currently available agents is essential. Therapeutic drug monitoring (TDM) and individualization of therapy is a way to maximize the outcomes of vulnerable immunocompromised patients. TDM may be indicated for compounds that exhibit substantial pharmacokinetic variability and clinically important drug exposure–response and/or drug exposure–toxicity relationships.

Posaconazole is currently licensed for prevention of invasive fungal infections for immunocompromised adults, the treatment of oropharyngeal candidiasis, and for the treatment of patients with invasive aspergillosis who are intolerant or refractory to other antifungal agents.[1] Posaconazole is highly active against a wide range of medically important opportunistic fungal pathogens. This, coupled with its excellent safety profile,[2–7] has facilitated its widespread use in the clinic. Increasingly, however, studies suggest that TDM may be an important adjunct to the optimal use of posaconazole. This review summarizes the current evidence and our own perspectives for TDM of posaconazole.

Pharmacology and Clinical Pharmacokinetics of Posaconazole

Posaconazole is a triazole that exhibits structural homology with itraconazole. In common, with other members of the triazole class, posaconazole exerts its antifungal action via the inhibition of the fungal enzyme lanosterol 14α-demethylase. Inhibition of this protein results in reduced synthesis of ergosterol, which is an essential component of the cell membrane. The differential activity of posaconazole against moulds and other triazole-resistant fungal species is conferred by the structure of its side arm, which is thought to be important for orientating the triazole ring to its target.

Posaconazole is relatively insoluble in water. The current formulation is an oral suspension. The development and production of intravenous formulations has been difficult. Newer formulations are currently being studied to further characterize their clinical pharmacokinetics and to identify dosages that result in bioequivalence to the current oral formulation.

The licensed dose for the prevention of fungal infections is 200 mg Q8 hours. For the treatment of established infection, posaconazole is administered as 200 mg every 6 hours for a week followed by 400 mg every 12 hours thereafter. The clinical pharmacokinetics of posaconazole is reasonably well characterized and can be summarized as follows. The oral bioavailability and systemic drug exposure are increased with administration with food and to an even greater extent with fatty food or supplements.[8–11] The oral bioavailability and systemic drug exposure are higher with a lower stomach pH.[12] Posaconazole has a large volume of distribution with (indirect) evidence of extensive distribution to tissues.[13,14] Posaconazole has a relatively long half-life, with a flat concentration–time profile that results in comparable average and trough concentrations (Fig. 1). Posaconazole exhibits saturable absorption with difficulties in increasing systemic drug exposure in a linear manner with progressive dosage escalation beyond 800 mg/d.[3,13] This has been ascribed to the relatively poor

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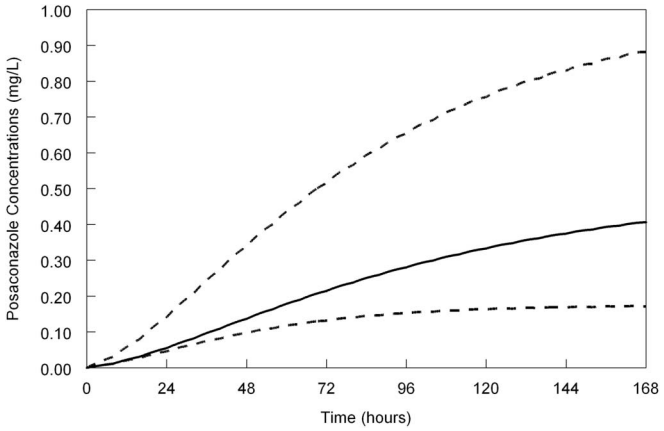

FIGURE 1. A Monte Carlo simulation from the population pharmacokinetic model of AbuTarif[17] showing the median along with the 5th and 95th percentiles for concentration–time profiles of 5000 simulated patients throughout the first week of therapy for patients receiving posaconazole 200 mg every 8 hours. A 2-compartment model with the following parameters was used: Ka 0.0396 h^{-1}, elimination rate constant 0.0198 h^{-1} (between-subject variability 0.221), and V/F 3290 L (between-subject variability 0.156). The simulations were performed using the pharmacokinetic program ADAPT 5.

aqueous solubility of posaconazole and the possibility that posaconazole is a substrate for P-glycoprotein and is therefore continuously pumped from the bloodstream into the gut.[15] Finally, a number of additional factors may have an impact on the pharmacokinetics of posaconazole, with decreased systemic drug exposure observed in older patients and those with elevated gamma-glutamyl transferase.[14,16]

The population pharmacokinetics of posaconazole has been described in a relatively small number of patients. Furthermore, posaconazole is a relatively difficult compound to model mathematically. The 1-compartment pharmacokinetic models that have been (appropriately) used are unidentifiable (ie, one cannot distinguish whether a low serum concentration is due to poor oral bioavailability, a large volume of distribution, or high clearance). The population pharmacokinetic model of AbuTarif et al[17] demonstrates several clinically relevant features of posaconazole pharmacokinetics (Fig. 1). The short dosing interval relative to the long half-life results in a relatively flat concentration–time profile and average and trough concentrations that are similar, and there is relatively slow accumulation throughout the first week before steady state concentrations are reached somewhere toward the end of the first week of dosing. One clinical study showed concentrations associated with a high probability of a successful outcome (circa 1.25 mg/L).[17] These concentrations are higher than the median patient receiving 200 mg every 8 hours, which are approximately 0.5 mg/L (Fig. 1). This suggests that posaconazole could be an even more effective antifungal agent than is currently the case if higher drug exposures are achieved and that this could be potentially achieved with improved formulations and/or TDM.

DRUG EXPOSURE TARGETS ASSOCIATED WITH THERAPEUTIC EFFICACY

Any case for TDM requires an understanding of concentration–effect and concentration–toxicity relationships. Increasingly, such data are available for posaconazole. Arguments for TDM of the oral formulation of posaconazole predominantly rest with optimizing exposure–effect relationships. There are no concentration–toxicity relationships that are apparent for other triazoles such as itraconazole and voriconazole.

Preclinical Models of Disseminated Candidiasis, Aspergillosis, and Invasive Pulmonary Aspergillosis

A preclinical model of disseminated candidiasis suggests that the ratio of the area under the concentration–time curve (AUC) to minimum inhibitory concentration (MIC) is the pharmacodynamic index that optimally links drug exposure with the observed antifungal effect.[18] In common with other triazoles, posaconazole exhibits a postantifungal effect of approximately 20–30 hours,[18] which probably largely reflects persistence of drug at the effect site. The magnitude of the free AUC:MIC that is associated with half-maximal antifungal effect (ie, a 50% decline in the fungal burden in the kidney) is 16.9 for disseminated candidiasis.[18]

There have not been any formal dose fractionation studies to identify the pharmacodynamic index for posaconazole against *Aspergillus* spp. or other medically important moulds. The AUC:MIC has been used in 2 publications that have examined the pharmacodynamics of posaconazole against *Aspergillus fumigatus*.[19,20] A model of disseminated aspergillosis (ie, where conidia are inoculated into the tail vein of a mouse) using survival as the study endpoint demonstrates increasing survival with increasing AUC:MIC.[19] The AUC:MIC values associated with 50% and 100% survival are 321.3 and approximately 1000, respectively. More recently, an inhalational murine model (ie, conidia are nebulized into the lung) of invasive pulmonary aspergillosis with serum galactomannan concentrations as the pharmacodynamic endpoint has been described.[20] In this model, an AUC:MIC of 166.90 and 440.91 is associated with a 50% and 90% maximal antifungal effect, respectively. To place these findings in context, an average patient receiving posaconazole 800 mg/d, who is infected with a strain with an MIC at the upper end of the wild-type distribution (0.125 mg/L), will achieve an AUC:MIC of approximately 100–150.[20] There are no pharmacodynamic models for other medically important fungal pathogens such as Mucorales or *Fusarium* spp, and the magnitude of drug exposure associated with successful outcomes may be different for these organisms.

Clinical Data

Posaconazole does seem to exhibit clinically relevant drug exposure–response relationships. Unfortunately, however, the complexity of patients with invasive fungal infections and the absence of concomitantly collected pharmacokinetic data from those patients prevent firm conclusions regarding drug exposure targets for TDM. Nevertheless, some information is available for the prevention of invasive fungal

infections and for the use of posaconazole for salvage therapy for patients with invasive aspergillosis; this can be summarized as follows:

1. Posaconazole is licensed for the prevention of invasive fungal infections in patients with acute myeloid leukemia and persistent neutropenia and for those with hematopoietic stem cell transplantation with graft-versus-host disease. A logistic regression model linking the average posaconazole concentration with the clinical outcome (defined as a composite clinical and microbiologic endpoint) suggests that increasing concentrations are associated with a higher probability of a successful outcome.[21]
2. Posaconazole is licensed for patients with invasive aspergillosis that are refractory or intolerant of other antifungal agents. Despite the fact that this is a difficult patient population to examine pharmacological exposure–response relationships, this study suggests that higher average concentrations are associated with improved clinical outcomes.[1]
3. There is no insight into the relationship between drug exposure and the potential emergence of fungal resistance. Perhaps, this is only relevant for the treatment of chronic pulmonary aspergillosis, but in this patient population, at least, this is a question of considerable clinical importance.
4. There is no information on the pharmacodynamic targets for medically important fungal pathogens other than *Candida albicans* and *A. fumigatus*. Most importantly, there is no information for the Mucorales, which are an important group of pathogens for which posaconazole is frequently used as either a first-line agent or for consolidation therapy after initial therapy with a polyene.

Target Concentrations for TDM

Some have suggested that a reasonable target for TDM is 0.5 mg/L, but this value is lower than suggested by current preclinical and clinical studies.[22] Potential targets for prophylaxis and treatment of invasive aspergillosis are 0.7 and 1.25 mg/L, respectively.[1] Jang et al[21] suggested an algorithm for dose adjustment, with a target of >0.7 mg/L for steady state serum concentrations. The target concentration for optimal treatment of established infection is supported by laboratory animal data. There do not appear to be any clinically relevant concentration–toxicity relationships, although this may change with the advent of newer formulations.

The following are important considerations when attempting to decide on the validity of these targets for patients. There is not a discrete measure of drug exposure (eg, AUC:MIC, average concentration, or trough concentration) that readily enables a patient population to be split into 2 groups each with a high and low probability of a therapeutic response. Rather, higher concentrations are associated with a progressively higher probability of a favorable response. The desired target for an individual patient can, and should, be continuously evaluated by the attending physician, depending on the patient's response to treatment. For example, a critically ill patient with extensive poor prognostic disease needs a higher therapeutic target than those patients with limited disease who are clinically stable. Higher posaconazole exposures are required for patients with established disease compared with those for the prevention of invasive fungal infections.

A PRAGMATIC APPROACH TO THERAPEUTIC DRUG MONITORING OF POSACONAZOLE

Should All Patients Receiving Posaconazole Have Therapeutic Drug Monitoring?

The argument for routine TDM of posaconazole is as follows: (1) invasive fungal infections are rapid life-threatening infections, (2) posaconazole exhibits clinically relevant exposure response relationships, and (3) fixed (as opposed to individualized) regimens frequently result in suboptimal measures of drug exposure. Although such an argument is compelling, it is tempered by a number of considerations. For prophylaxis, a composite endpoint was used by Jang et al.[21] The relationship between measures of posaconazole drug exposure and the prevention of breakthrough fungal infections is not known and would require an extremely large number of patients to definitively answer. The cost-effectiveness of TDM is not known and requires further investigation. The ability to increase serum drug concentrations via dosage escalation or improving oral bioavailability is largely unknown and potentially compromised by saturable absorption for patients receiving total daily dosages >800 mg.[3,13] An interesting recent study by Shields et al[23] nevertheless suggest that dosages as high as 1600 mg/d may result in higher serum concentrations.

The case for routine TDM in patients with established infection is stronger. By definition, the use of posaconazole as a salvage agent means that there are a few, if any, available alternatives if posaconazole fails. Pharmacodynamic targets derived from laboratory animal models and clinical studies seem largely concordant and higher than those required for prophylaxis. A trough (or average) concentration of 1.25 mg/L is a reasonable target, although this may be difficult to reliably achieve for many patients with mucositis.[2,5] If an increase in serum concentrations is not possible, then there is the option to add or change to another antifungal compound.

In summary, the requirement for TDM varies according to the clinical context. The potential indications for TDM are summarized in Table 1. In some cases, it is imperative and should be considered a standard of care. In other cases where the risk is suitably low, patients may be reasonably managed without TDM. Some may argue that the efficacy of posaconazole was originally demonstrated without resorting to TDM. A counterargument to this is that even better clinical responses may have been observed in clinical trials if dosing was individualized and serum concentrations optimized.

Sample Times: When Should They Be Taken and How Many Are Required?

The interpretation of a single serum concentration value is best made at steady state. However, the half-life of posaconazole is approximately 31 hours; therefore, steady state is not reached until the end of the first week of therapy, which has implications for the timely individualization of dosing if guided by steady state concentrations.[13,22] The

TABLE 1. Indications for Therapeutic Drug Monitoring

Therapeutic Drug Monitoring Highly Desirable	Therapeutic Drug Monitoring Potentially Useful
Salvage therapy	Prophylaxis
Treatment of extensive infection or poor prognostic disease	Patients receiving H2 antogonists or proton pump inhibitors
Treatment of infection at sanctuary sites	Assessment of complicance
Patients with mucositis, diarrhea, or intolerant of fatty food/supplements	Treatment of limited disease with good prognostic features
Patients with non-*Aspergillus* mould infections	—
Children and neonates (not currently approved)	—

simulation in Figure 1 shows the slow accumulation of serum concentrations throughout the first week of therapy. Jang et al[21] have considered this problem and suggested that a serum concentration of approximately 0.35 mg/L after 2 days can be used as a surrogate for concentrations observed at steady state. In a critically ill patient, in whom it is imperative to optimize drug concentrations as quickly as possible, it may be reasonable to obtain several samples in the first week of therapy and at regular intervals thereafter.

Management of Patients With Subtherapeutic Concentrations

There are no studies that have systematically examined management of subtherapeutic concentrations. The first step in the assessment of a patient with lower than ideal serum concentrations is to address compliance and other factors that may have an impact on oral bioavailability.[24] The coadministration of compounds that cause accelerated clearance of posaconazole should be discontinued if possible (eg, rifampin, carbamazepine, and phenytoin).[25,26] Posaconazole should be administered with food, preferably fatty food (eg, milk, ice cream, or nutritional supplements).[9,10] Such an intervention is a relatively simple but an important initial step. As with itraconazole capsules, the oral bioavailability of posaconazole may be improved by acidic conditions.[12] Cessation of histamine antagonists or proton pump inhibitors may be an important yet simple way to improve oral bioavailability.[23,27]

The utility of dosage escalation is less certain. The pharmacokinetics of posaconazole is linear for dosages $<$800 mg/d, suggesting that dosage escalation is likely to be successful in these circumstances.[13] A question remains however as to whether dosage escalation for patients already receiving 800 mg/d results in a significant increase in drug exposure. A recent study suggests that an increase to 1600 mg/d may be a potential option.[23] An alternative approach is the administration of posaconazole in a more fractionated regimen (eg, 200 mg every 6 hours rather than 400 mg every 12 hours). A total daily dosage of 800 mg administered as 200 mg every 6 hours results in a significantly higher serum AUC.[3]

FUTURE STUDIES AND CONCLUSIONS

Increasing data suggest that fixed posaconazole regimens frequently result in lower than anticipated serum concentrations. Posaconazole shows significant intrapatient variability, particularly in critically patients, presumably primarily due to erratic absorption. The drug also exhibits a concentration–effect relationship. This indicates that TDM may be a useful tool in the management of these patient cases.

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