TDM Monograph posaconazole

Indication	All patients treated with posaconazole (suspension, tablets and intravenous solution)
Interpretation	Target exposure depends on the indication of use* - Prophylaxis: ≥ 0,7 - Therapy: ≥ 1.25
Time of sampeling	Trough level
Evidence level	2

* In case of pathogens with higher MIC, higher trough levels might be required, see reference values

Abbreviations

Introduction

Posaconazole is an azole antifungal agent with fungicidal activities against *Aspergillus fumigatus*, *Mucor, Blastomyces dermatitidis*, selected *Candida* species, *Cryptococcus neoformans*, and *Trichosporon*.(1) Like other azole derivatives, posaconazole inhibits the enzyme lanosterol 14α-demethylase, disrupting ergosterol biosynthesis. Ergosterol is a crucial component of the fungal cell membrane. The inhibition leads to an accumulation of methylated sterol precursors and a reduction in ergosterol within the cell membrane, compromising its structure and function, which accounts for posaconazole's antifungal activity.(2)

Posaconazole is highly protein bound in plasma (>98%).(2) Its volume of distribution (Vd) is relatively large 62-181 L.(3,4) It distributes in various human tissues and accumulates in peripheral tissues, especially in lungs, kidneys, liver, and heart (5). 77% of posaconazole is excreted in feces, of which > 66% is unchanged, while 13% of the dose is eliminated in urine, of which < 0.2% is unchanged. (5)The drug is only partially (approx. 17%) metabolized through glucuronidation by UDP-glucuronosyltransferase (UGT) enzymes, particularly UGT1A4.(5) The drug is a substrate for P-glycoprotein (P-GP). Therefore, plasma concentrations may be affected by P-GP inhibitors/substrates. Posaconazole is not a substrate, but a potent CYP3A4 inhibitor and can significantly increase exposure to CYP3A4 substrates.

Formulations and Bioavailability

Posaconazole is available in various formulations: tablets, enteric-coated powder with solvent for suspension, oral suspension and intravenous (IV) injection. These formulations **are not interchangeable** due to substantial differences in absorption and pharmacokinetics (2)

It is crucial that tablets are used whenever possible, as they offer a more stable and predictable pharmacokinetic profile compared to the oral suspension. In children that cannot swallow, it is preferable to use the enteric-coated powder with solvent for suspension.

Oral Suspension

The oral suspension is one of the first formulations of posaconazole, most literature about posaconazole is based on this suspension. It has highly variable and saturable absorption, requiring administration three to four times daily.(6,8–11) Bioavailability is also influenced by food intake, gut motility, and gastric acidity, with significant improvement when taken with a high-fat meal.(12) Co-administration with certain medications, such as proton pump inhibitors or metoclopramide, can lead to subtherapeutic posaconazole levels, making therapeutic levels difficult to maintain. (6) At higher doses, absorption of the suspension is saturated. Therefore, the dosing frequency is increased in cases of low trough levels, instead of only increasing the dose.(13)

Delayed-Release Tablets

The tablets exhibit a more stable and higher bioavailability compared to the suspension, resulting in a more favorable pharmacokinetic profile. High-fat meals can increase the bioavailability and exposure

of the tablet. The effect of high-fat meals on bioavailability and exposure is less relevant with the tablets than what is observed with the suspension. (6) Notably, the tablet's exposure is not significantly affected by drugs that alter gastric acidity or gut motility. There are indications that with the tablets, there is no absorption saturation up to a single dose of 800 mg. However, there is insufficient clinical data to support this. Therefore we also recommend, in cases of low trough levels, to increase the dosing frequency of the tablets.(5)

Enteric-coated powder with solvent for suspension

The effect of food on the pharmacokinetics of the enteric-coated powder with solvent for suspension has not yet been determined. Drugs affecting gastric pH or motility are not expected to significantly alter exposure based on similarity to the delayed-release tablet. The pharmacokinetics of the enteric-coated powder with solvent for suspension have not been directly compared with those of the delayed-release tablets or the immediate-release oral suspension, but it offers the practical advantage of once-daily dosing, making it more patient-friendly. (7)

IV injection

For hospitalized patients with no oral intake, the IV formulation can be used.(6) The concentrate has a pH ranging from 3.1 to 3.6 after mixing. Therefore, administration via a central venous line is recommended.(2)

In summary, the suspension has inferior and highly variable bioavailability compared to the tablets and should only be considered if the tablets are contraindicated. The oral suspension may still be useful for patients who are unable to take tablets, but dose adjustments are required. In children that cannot swallow, it is preferable to use the enteric-coated powder with solvent for suspension.

Criteria for TDM

Posaconazole meets several criteria for TDM. It exhibits significant interindividual variability in pharmacokinetics, and an association between posaconazole exposure and clinical efficacy has been demonstrated.(6,14–20) Target concentrations have been established for prophylaxis and suggested for the treatment of invasive fungal infections.(14–20)

Once adequate plasma levels are achieved in patients using the tablets or IV formulation, routine follow-up measurements are not required given the more consistent plasma posaconazole concentrations. See the subsection ‘Interpretation results’ for further explanation and exceptions.

Dosing recommendations

The different forms of posaconazole (oral suspension, tablets, IV injection and enteric-coated powder with solvent for suspension) are **not interchangeable**.(2)

It is crucial that tablets are used whenever possible, as they offer a more stable and predictable pharmacokinetic profile compared to the oral suspension. In children that cannot swallow, it is preferable to use the enteric-coated powder with solvent for suspension.

Adults

See www.kennisbank.knmp.nl or Summary of Product Characteristics (SmPC) posaconazole.(2)

Children (2–18 years)

See www.kinderformularium.nl (21)

Reference values

Efficacy

The PK/PD index associated with efficacy of antifungal therapy for treatment of an invasive aspergilloses is the ratio of the Area Under the concentration-time curve (AUC_{0-24}) over the minimum inhibitory concentration (MIC). Because posaconazole trough concentrations correlate strongly with AUC_{0-24}, trough levels are a practical surrogate for exposure in clinical practice.(6,22,23)

It should be noted that above mentioned target trough concentrations are independent of the susceptibility of the fungal pathogen. In case of pathogens with higher MIC, higher trough levels might be required (for example in case of infections with mucormycosis instead of aspergilloses). The development of azole resistance in *Aspergillus fumigatus* is a significant concern. In this context, measuring the MIC values for azole compounds is essential to improve clinical outcomes. According to EUCAST, the proposed MIC breakpoint for susceptible micro-organisms is ≤0.125 mg/L. Seyedmousavi et al. proposed breakpoints for posaconazole between 0.25 and 0.5 mg/L for *Aspergillus fumigatus*, which are higher than the EUCAST breakpoints for *Aspergillus* species.

Posaconazole exposure, measured by the area under the curve (AUC), shows a linear correlation with dosage. Therefore, a higher exposure of the posaconazole is required to achieve similar efficacy when azole-concentration dependent strains are present.(6,22,24)

Prophylaxis

Posaconazole is commonly prescribed for preventing invasive yeast and mold infections, such as invasive aspergillosis, in high-risk immunocompromised patients. There is evidence supporting reference values for posaconazole in a prophylaxis setting. Reference values for prophylaxis indicate serum levels above which fewer breakthrough infections are observed. Multiple studies indicate that maintaining a serum level between 0.5 and 0.7 mg/L should be attained to prevent breakthrough infections in patients receiving posaconazole.(12–15,25) It seems reasonable to assume a reference value for trough concentrations ≥0.7 mg/L should be targeted when used as prophylaxis.

Therapy

Posaconazole is used for the treatment of an invasive fungal infection.(26) There is limited evidence regarding TDM reference values for patients using posaconazole as salvage treatment. An open-label, multicenter study indicated that the highest number of responders had posaconazole serum levels of ≥1,25 mg/L at steady-state.(6,17, 27) In the context of first line therapy the 2017 ESCMID-ECMM-ERS guidelines and SWAB Guidelines recommend a trough level of ≥1.0 mg/l for antifungal therapy targeting azole-susceptible *Aspergillus fumigatus*.(26,28) However, clinical studies validating these proposed targets are lacking.

Some studies did not find an association between posaconazole concentration and response to therapy. These studies reported high median posaconazole levels (≥1,25 mg/L), which may have reduced the ability to observe an exposure-response relationship, as most patients had high systemic exposure to the drug.(19) Based on this literature we recommend a reference value for treatment of ≥1,25 mg/L.

In *Aspergillus fumigatus*, MICs of 0.25 and 0.5 mg/L have been proposed. As a result, a higher dose of the azole and a corresponding increase in trough levels are necessary to achieve optimal exposure and therapeutic efficacy.(6,24)

Toxicity

There is no upper plasma target that is associated with toxicity defined in studies. (25) However, a higher likelihood of treatment related adverse events is observed with higher trough levels. (29,30) Several studies failed to show an association between adverse events and serum levels of posaconazole. (20,24,31) Clinical registration studies used a cut-off value of 3.75 mg/L.(23) As posaconazole exposures between 0.7–3.75 mg/L are well studied and considered safe and effective with all formulations, ECMM-ERS guidelines indicate posaconazole serum levels above ≥3.75 mg/L may be associated with toxicity.(28) For patients experiencing adverse drug events with higher exposure, dose reduction may be considered.

Summary target exposure

Efficacy

- Prophylaxis: ≥ 0,7 mg/L
- Therapy: ≥ 1.25 mg/L

Toxicity

- There is no clear evidence for an exposure – toxicity relationship
- Consider dose reduction in patients with high exposure that experience adverse drug events.

When increasing the dosage based on low trough levels, saturated absorption must be taken into account. We advise to divide the doses into multiple administrations rather than increasing the single dose.

Sample collection

Samples must be obtained after the steady state concentration is reached, which is approximately on day 6 of posaconazole treatment with tablets or IV solution and 7-10 of treatment with posaconazole suspension. As a general rule, obtain samples 7 days after start of therapy or dosing alteration.(2) When using Model-Informed Precision Dosing (MIPD), sampling can be carried out earlier.

Trough level sampling is preferred, as most studies have used trough levels in their research. However, since posaconazole has an elimination half-life ranging from 20-31 hours, sampling in the middle of the dosing interval can be considered.(2)

A recent study has demonstrated that MIPD can also be applied.(32)

Interpretation results

The interpretation of plasma concentrations depends on the indication for which posaconazole is used (i.e. prophylaxis or treatment of an invasive fungal infection), as well as on factors such as the pathogen involved, the site of infection, and the pathogen's susceptibility.

Once adequate plasma levels are achieved in patients using the tablets or IV formulation, consider obtaining follow-up plasma level measurements if any of the below stated patient-specific factors change (6,33):

- Defecation patterns (especially diarrhea) (3,34,35)
- Changes in dietary habits (2)
- Change in disease status:
    - Conditions associated with hypoalbuminemia (36)
    - Intestinal mucositis (37)
    - Critically ill ICU patient
- Significant change in body weight (3)
- Suspected azole resistance with or without breakthrough invasive fungal infection
- Active invasive aspergillosis and worsening of symptoms after 7 days
- Start or cessation of interacting medications (e.g., PPI or metoclopramide use) (34,35)
- Suspected non-adherence to therapy

In patients using the oral suspension more routine serum levels are advised due to the intrapatient variability that is described in the literature.(6)

Specific patient groups

<u>Pediatrics</u>

To date little prospective data on the association between posaconazole exposure and treatment outcome in newborns, infants, and children has been published. Adult target trough concentrations are currently used for dose optimization in children.(38)

Pharmacokinetics in children

There are differences in pharmacokinetics in the pediatric population compared to adults. Children show a higher inter-individual variability in apparent clearance compared to that of adults (63.0% vs. 24.2% or 37.9%). This might be partly attributable to differences in hepatic metabolism of children, most likely to the age-associated maturation of hepatic UGT1A4.(12,39,40) Similar to adults, factors such as diarrhea and concomitant proton pump inhibitor use decrease exposure. One retrospective study conducted in children aged <18 years observed lower posaconazole concentrations with increasing CRP concentrations, increasing alanine transaminase (ALT) concentrations and with increasing age.(38)

Target Attainment and Formulation Considerations

A target attainment of 90% of steady state through concentrations above the target of 0,7mg/L is reported for posaconazole delayed-release tablet.(4) In children with cystic fibrosis, the probability of attaining a trough target of 1 mg/L was lower, 77–83% with 300 mg once daily in those aged 6–11 years, and 86–88% with 400 mg once daily in those aged 12–17 years.(41) For a virtual adolescent population (>40 kg body-weight), the standard adult tablet dose of 300 mg once daily was predicted to also reach the target exposures and remain within a safe range.(42)

In children aged 2–17 years with documented or expected neutropenia, IV doses of 4.5 mg/kg/day and 6.0 mg/kg/day achieved the PK target of 90%. The enteric-coated powder for suspension formulation resulted in lower posaconazole exposures compared to the IV formulation across all age groups and doses.(42,43)

There are no pharmacokinetic comparative studies between the enteric-coated powder for suspension and the delayed-release tablet and/or oral suspension. According to FDA Access data drugs affecting gastric pH or gastric motility are not expected to markedly influence exposure of the enteric-coated powder for suspension, but the effect of food has not yet been established.(7) It may offer a pharmacokinetic advantage over the immediate-release suspension, though this has not been formally studied. The once-daily dosing is more patient-friendly. At this time, no clear preference can be stated between these two formulations.

The oral suspension shows even greater variability in bioavailability in children than in adults and should be avoided when the delayed-release tablets can be swallowed.(12,39)

Safety

As in adults, there is no clear exposure–toxicity relationship in pediatric patients. Trough concentrations exceeding 4.0 mg/L have been reported without associated toxicity. (38,44,45)

<u>Liver dysfunction</u>

No dose adjustment is recommended in patients with hepatic impairment.

Posaconazole clearance is slightly reduced in mild to severe hepatic dysfunction (Child–Pugh A–C), likely due to decreased UGT1A4 metabolism. This results in increased AUC values of 36%, 51%, and 23% in respectively mild, moderate, and severe impairment, compared with normal hepatic function. (46) Despite these changes, no dose adjustments are recommended. Further research is needed to fully understand the long-term pharmacokinetics and safety in this population.(46)

<u>Renal dysfunction, dialysis, CVVH</u>

Dose adjustment is not necessary in renal impairment or during hemodialysis, peritoneal dialysis, or CVVH. Renal excretion of posaconazole and metabolites accounts for 14% of the total elimination, making it not the primary route of excretion. Pharmacokinetics are unchanged in mild to moderate renal disease (CLcr 50–80 and 20–49 mL/min). Posaconazole exposure showed more variability in subjects with severe renal disease (CLcr <20mL/min) compared to healthy volunteers and subjects with mild to moderate chronic renal failure. The concentrations before and after dialysis differed 3%, indicating that posaconazole is not removed by dialysis (13) and there is no occurrence of supranormal posaconazole accumulation.(47) Although the SmPC advises preferring oral formulations over IV in moderate to severe renal impairment due to possible accumulation of the sulfobutylether-β-

cyclodextrin (SBECD) excipient, no additional cyclodextrin-related toxicity has been observed, so there is no rationale to avoid IV therapy in these patients.(3, 48-49)

Critically ill patients and ICU patients

Therapeutic drug monitoring is essential in critically ill patients and should be performed at least weekly, or more frequently when clinically indicated. It is important to note that the current one-dose-fits-all approach for posaconazole may not be suitable for critically ill patients. Therapeutic levels might be harder to obtain in critically ill patients due to alterations in clearance and Vd and a higher inter-individual variability, necessitating therapeutic drug monitoring to ensure adequate exposure and optimize clinical efficacy. Dosing simulations demonstrated that an increased BMI was associated with a decreased probability of attaining target total and unbound posaconazole concentrations. In contrast, lower serum albumin concentrations were associated with a reduced probability of achieving target total, but not unbound, posaconazole levels.(11,50) In 8 ICU patients the clearance and Vd were more than twice the value reported in healthy volunteers 16.8 L/h vs. 6.9 L/h and 529 L vs. 236 L, respectively.(51,52) One study showed that extracorporeal membrane oxygenation did not influence posaconazole exposure.(53) More frequent therapeutic drug monitoring, i.e. once a week, is advised in all critically ill patients until ICU discharge.(19,52–54) For guidance about the frequency of monitoring, see ‘Interpretation result’.

Obese patients

Be cautious of subtherapeutic concentrations in obese patients. According to the SmPC of posaconazole, patients weighing more than 120 kg are at increased risk of lower posaconazole exposure.(3) Obese patients have an increased clearance and Vd, which can lead to a lower posaconazole exposure and a prolonged half-life.(55–57) Lower trough concentrations have been observed in patients ≥90 kg (0.65 vs. 1.31 mg/L).(58) A population pharmacokinetic study reported that a dose increase (at least 400 mg) is required for therapeutic use in patients above 140 kg and that 300 mg is an adequate dose as prophylaxis.(55)

Chronic Pulmonary Aspergillosis

Be cautious of supratherapeutic concentrations in chronic pulmonary aspergillosis (CPA) patients. CPA patients may have a better drug absorption and therefore achieving higher posaconazole levels, because they generally do not have diarrhoea or mucositis. However, no specific dosing guidelines exist for this patient group. A retrospective study on the evaluation of posaconazole delayed-release tablet tolerance and in a cohort of patients with CPA found that a daily dose of 200 mg achieved therapeutic levels and was better tolerated when compared to the standard 300 mg dose.(59)

CF-population

Be cautious of subtherapeutic concentrations in patients with cystic fibrosis. Achieving target levels is generally more difficult in this population due to reduced absorption, larger Vd, and increased drug clearance of certain drugs. (60) CF lung transplant recipients have shown lower trough levels with oral suspension (0.19 vs. 0.47 mg/L) and with delayed-release tablets (1.1 vs. 1.9 mg/L) compared to non-CF patients. (60)

Interactions

Posaconazole is a substrate of UGT, particularly UGT1A4, and P-GP. It inhibits CYP3A4 strongly, this results in various interactions.(2) For information on drug-drug interactions with posaconazole, consult the KNMP Kennisbank.(2)

Pharmacokinetic parameters

Steady state plasma concentration is reached 7-10 days after administration of multiple doses of the suspension, and 6 days after administration of the tablets and the IV infusion. The elimination half-life averages 35 hours (range 20-66 hours) for the suspension, averages 29 hours (range 26-31 hours) for the tablets, and averages 27 hours for the IV infusion.(2)

Population models

Several population PK models have been published in recent years across various target populations. The review by Chen et al. provides an overview of these models in both adult and pediatric populations.(12) It is important to note that selecting an appropriate population PK model depends on the targeted population, patient characteristics, and the specific formulation of posaconazole being used. A recent study externally evaluated several existing population PK models for posaconazole tablets and identified one model with adequate predictive performance for clinical application, enabling individualized dosing based on a single concentration measurement.(32,61)

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Colophon

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Under the auspices of Working Group Therapeutic drug monitoring, Toxicology and Pharmacogentics (TTF) of the Dutch Association of Hospital Pharmacists (NVZA). In collaboration with the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT).

Appendix

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