Current challenges in triazole TDM

Isabel Spriet, PharmD PhD
Clinical Pharmacology and Pharmacotherapy, University Hospitals Leuven & KU Leuven, Belgium
• Triazoles are the most widely prescribed antifungals for prophylaxis and treatment of IFI, especially in patients with hematological malignancies

• Triazoles exhibit substantial inter- and intrapatient variability in exposure and PK, especially in patients with mucositis, diarrhea, hypoalbuminemia, sepsis, altered renal function, CYP450 DDIs....

• A growing body of evidence has identified a relationship between triazole plasma exposure and clinical outcome which suggests a benefit for therapeutic drug monitoring (TDM)
### Summary of TDM plasma target level recommendations

<table>
<thead>
<tr>
<th>Triazole</th>
<th>Recommended plasma range*</th>
<th>SOR</th>
<th>Timing of first trough sample</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Voriconazole</strong></td>
<td>Prophylaxis and treatment: Acceptable: 1.6 mg/L; Optimal: 2-5 mg/L</td>
<td>All (efficacy) All (toxicity)</td>
<td>After 2-5 days; (repeat sampling recommended)</td>
</tr>
<tr>
<td><strong>Posaconazole</strong></td>
<td>Prophylaxis: &gt; 0.7 mg/L Treatment: &gt; 1.0 mg/L</td>
<td>BI (efficacy) All (efficacy)</td>
<td>Tablet/IV: after 3 days; Suspension: 5-7 days.*</td>
</tr>
<tr>
<td><strong>Itraconazole</strong></td>
<td>Prophylaxis: 0.5-4 mg/L Treatment: 1.4 mg/L</td>
<td>All (efficacy) BI (toxicity)</td>
<td>7-15 days;*</td>
</tr>
</tbody>
</table>

1. **1st line IA treatment**
2. **1st line IFI prophylaxis**
3. **PK variability?**
4. **Narrow therapeutic window?**
5. **Clear relation between exposure and efficacy/safety?**

→ **Current challenges are highlighted in red**

---

**ECIL-6 guidelines**

Voriconazole – PK variability?

1) Reduced oral bio-availability (60-65%) in some populations
   • co-administration with food/enteral feeding decreases absorption (AUC↓35%)

2) 100- fold intrapatient variability in metabolism/clearance
   • Non-linear saturable elimination in adults
   • Metabolism mediated by CYP2C9, CYP2C19 & CYP3
     • Involved in many drug-drug interactions
     • Genetic polymorphism described for CYP2C19

3) Children < 12 yrs: 3-5 fold greater clearance (FMO3).

---

Voriconazole – PK variability is not fully explained

Impact of Hypoalbuminemia on Voriconazole Pharmacokinetics in Critically Ill Adult Patients

Inflammation Is Associated with Voriconazole Trough Concentrations

AAC 2014; 58: 6782-9

AAC 2014; 58: 7098-101
Voriconazole – not all drug interactions are known
Voriconazole – not all drug interactions are known

VORICONAZOLE AND FLUCLOxacillINE?

In conclusion, the often prescribed combination of flucloxacillin and voriconazole leads to unmanageably low plasma voriconazole concentrations in half of the patients with primary and secondary immune deficiencies.
Evidence on **usefulness of TDM** and **targets** for voriconazole

- Discussed in ECIL-6 and based on a selection of 40 studies on TDM for voriconazole
- **Typically for knowledge on TDM: evidence base is relatively weak**
  - Most studies on TDM are retrospectively designed
  - Limited number of prospective studies are often single centre and characterized by small sample sizes
- **However, specifically for voriconazole**
  - Also 1 RCT
  - 5 post-hoc/meta-analysis

<table>
<thead>
<tr>
<th>Study type</th>
<th>n (%) studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective</td>
<td></td>
</tr>
<tr>
<td>Single-centre studies</td>
<td>21 (53)</td>
</tr>
<tr>
<td>Multicentre studies</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Prospective</td>
<td></td>
</tr>
<tr>
<td>Single centre studies</td>
<td>10 (25)</td>
</tr>
<tr>
<td>Multicentre studies</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Randomized for TDM intervention</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Post-hoc analysis of Phase II/III RCT</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>
**Voriconazole** – target exposure definition for **efficacy**?

- Several retrospective and prospective studies have consistently reported that voricin \( C_{min} > 1.5 - 2 \text{ mg/L} \) is associated with maximal clinical response.

**Voriconazole Therapeutic Drug Monitoring in Patients with Invasive Mycoses Improves Efficacy and Safety Outcomes**

Andres Pascual, Thierry Calandra, Saskia Boley, Thierry Buclin, Jacques Bille, and Oscar Marchetti

1 Infections Diseases Service, University Hospital, Geneva, Switzerland.
2 University of Edinburgh, Edinburgh, Scotland, United Kingdom.

ECIL-6 recommendation (AIII): **TARGET TROUGH for prophylaxis and treatment: > 1-2 mg/L**

Higher troughs are recommended for severe infections or treatment with elevated MICs (e.g. > 0.25 mg/L).

Voriconazole – target exposure definition for toxicity?

NEUROTOXICITY

- Patients with vori Cmin > 5-6 mg/L have a higher probability of neurotoxicity and visual hallucinations

Voriconazole Therapeutic Drug Monitoring in Patients with Invasive Mycoses Improves Efficacy and Safety Outcomes


Dolton M J et al. AAC 2012;56:4793-4799
**Voriconazole** – target exposure definition for toxicity?

**HEPATOTOXICITY**

- Some evidence shows relationship between higher vori exposure and hepatotoxicity

![Graphs showing observed weekly occurrences of AST and bilirubin](image)

**Voriconazole** – target exposure definition for **toxicity**?

**HEPATOTOXICITY**

- Despite the presumed association between higher exposure & altered LFT
- No reliable cutoff can be identified to minimize hepatotoxic effects

---

....except in Japanese patients in which hepatotoxicity was more common (34.5%) when Cmin > 3.9 mg/L

---

*Figure 6. ROC curve for predicting AST abnormalities from plasma voriconazole concentrations.*

*Fig. 1. Voriconazole (VRCZ) trough concentration and logistic regression model for hepatotoxicity (absence, n = 19; presence, n = 10).*

---


*Matsumoto K et al. IJAA 2009; 34: 91-94.*
Voriconazole – target exposure definition for toxicity?

How common is subsequent central nervous system toxicity in asymptomatic patients with haematologic malignancy and supratherapeutic voriconazole serum levels?

S.T. Heo 1,3, S.L. Aitken 2, F.P. Tverdek 2, D.P. Kontoyiannis 1,*

In summary, we have detected subsequent CNS toxicity infrequently, in only 16 patients (5%) of 324 receiving VRC therapy with supratherapeutic levels. Given these findings, automatic VRC dose reduction out of concern for impending CNS toxicity may not be justified. However, in elderly patients or those with concomitant neurotoxic agents, vigilant monitoring for CNS toxicity needs to be performed.
Is TDM useful for voriconazole?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Substantial PK variability?</th>
<th>Therapeutic window defined in humans?</th>
<th>Narrow therapeutic window?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole</td>
<td>✔ yes</td>
<td>✔ yes</td>
<td>✔ yes</td>
</tr>
</tbody>
</table>

Start Cmin monitoring at day 2-5 in every patient treated with vori. Cmin should be repeated after 7 days to confirm if patient is in target range (1-6 mg/L). Recheck every 3-5 days if:
- Change in dose
- IV to oral switch
- Change in clinical condition
- Potential DDI

If Cmin < 1 mg/L:
- Check if dose was adequate
- Screen for DDI or low compliance
- If oral R/: weight based dosing
- Consider oral to IV switch or increase dose with 50%

If Cmin > 6 mg/L:
- Check if dose was appropriate
- Screen for DDI
- Consider dose continuation if patient is tolerating vori, under close monitoring
- If dose reduction is needed: reduce with 50% if level is elevated, hold one dose if level is > 10 mg/L
**Posaconazole – PK variability?**

- **Posaconazole – the molecule:** favorable PK properties
  - Wide distribution
    - Highly protein bound (98%), large Vd
    - High intracellular concentrations
  - ‘Easy’ metabolism/clearance
    - No major metabolism by CYP450 enzymes
    - 30% glucuronidation followed by biliary excretion

- **Posaconazole – suspension:** difficult absorption
  - Highly dependent on gastric pH, frequency of dosing, administration with (fatty) food
  - TDM highly recommended in patients treated with the suspension

  → In some patients posaconazole concentrations not measurable
**Posaconazole – PK variability?**

- **Posaconazole – new formulations**
  - Tablets: 100 mg, dosing: 300 mg BD as LD, followed by 300 mg OD as maintenance dose
  - IV: 300 mg, dosing: 300 mg BD as LD, followed by 300 mg OD as maintenance dose

- Tablet shows major improvement in absorption
  - not dependent on gastric pH
  - less affected by food

→ tablets are the preferred oral formulation

Kraft W et al. AAC 2014; 58: 4020-5.*
Evidence on usefulness of TDM and targets for posaconazole

- Discussed in ECIL-6 guidelines and based on a selection of 23 studies
- Many real life exposure studies have now been published
- Knowledge is rapidly evolving, gaining new insights on a quick basis
- Unfortunately, none of the real life studies have an ideal design (no RCTs or meta-analyses so far)

<table>
<thead>
<tr>
<th>Study type</th>
<th>n (%) studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective</td>
<td></td>
</tr>
<tr>
<td>Single-centre studies</td>
<td>11 (48%)</td>
</tr>
<tr>
<td>Multicentre studies</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Prospective</td>
<td></td>
</tr>
<tr>
<td>Single-centre studies</td>
<td>6 (26%)</td>
</tr>
<tr>
<td>Multicentre studies</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Randomized for TDM intervention</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Post-hoc analysis of Phase II/III RCT</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Posaconazole suspension – target exposure for efficacy in prophylaxis?

- PK analysis of 2 Phase III trials (suspension): no statistically significant difference in Cavg in patients with vs. without breakthrough IFI

<table>
<thead>
<tr>
<th>Population</th>
<th>Cavg in patients with breakthrough IFI</th>
<th>Cavg in patients without breakthrough IFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSCT-GvHD</td>
<td>0.61 mg/L (n=5)</td>
<td>0.92 mg/L (n=241)</td>
</tr>
<tr>
<td>AML-MDS</td>
<td>0.457 mg/L (n=6)</td>
<td>0.586 mg/L (n=188)</td>
</tr>
</tbody>
</table>

- FDA pharmacodynamic analysis (suspension) – combined endpoint for clinical failure

→ Higher probability for clinical failure with low posa plasma concentrations
→ 0.7 mg/L was proposed as target Cmin for efficacy when used in prophylaxis

Posaconazole suspension – target exposure for efficacy in prophylaxis?

• Several monocentric studies, all investigating PK and TDM using the suspension, reported a relationship between posa plasma trough levels and risk of breakthrough infection –

  all proposing a cutoff for Cmin levels of 0.5-0.7 mg/L

• Bryant AM et al. IJAA 2011; 37: 266-9.
• Elden E et al. EJCMID 2012; 31: 161-7.
• Hoenigl M et al. IJAA 2012; 39-510-3.

ECIL-6 recommendation (BII): TARGET Cmin for efficacy in PROPHYLAXIS: > 0.7 mg/L
Posaconazole suspension – target exposure for efficacy in treatment?

• Open label, externally controlled, study with posaconazole as salvage treatment in patients with IA refractory or intolerant to other antifungals
  - Clinical response improved with increasing Cavg
  - Highest response (75%) observed with Cavg >1,250 mg/L

ECIL-6 recommendation (AII): TARGET Cmin for efficacy in TREATMENT: > 1 mg/L

Should these TDM recommendations, derived from the suspension, also be applied for the new formulations?

**Yes** – efficacy has been extrapolated from the suspension data by aiming comparable exposure (90% of patients with Cavg 0,5-2,5 mg/L) for the new formulations.

**However**…. important remaining questions before recommending TDM for the new formulations:

- In how many patients treated with the new formulations is the exposure < 0,7 mg/L?
- Is serum the right matrix to evaluate posaconazole exposure?
- Should we think about an upper threshold for toxicity as exposure with the new formulations is now much higher?

Exposure <0.7 mg/L for posa tablet and IV

Real life evidence (17 studies) with posa tablet & iv from 2014-2018

- High interpatient variability in exposure (Cavg, Cmin) reported with new formulations
- Proportion of patients not attaining 0.7 mg/L ranges from 3-29%

*SS= steady state Cmin
Patients at risk for low exposure in prophylaxis

In some studies, several independent risk factors for low exposure were identified:

- Diarrhea (Tang et al, Miceli et al, Leclerc et al),
- Mucositis (Belling et al),
- Age < 60y (Belling et al),
- BW > 90 kg or BMI > 30 (Miceli et al, Tang et al),
- Treatment with a PPI (Tang et al)

However, in other studies no significant correlation was found between these factors and low exposures (Lecefel et al, Jung et al, Pham et al)

→ Up till now: patients at risk for low exposure can not be identified based on clinical risk factors alone

Despite the fact that Cmin is < 0.7mg/L in 3-29%:
Probable IFI breakthrough rate with the tablet is approximately 1-3%
Breakthrough infection is rarely observed in context of low posa serum levels

New insights in posaconazole intracellular concentrations

Steady-State Intrapulmonary Pharmacokinetics and Pharmacodynamics of Posaconazole in Lung Transplant Recipients

John E. Conte, Jr.,1,2,3 a Catherine DeVoe,1 Emily Little,1,3 and Jeffrey A. Golden3
American Health Sciences, San Francisco, California,1 and Department of Epidemiology and Biostatistics2 and Department of Medicine,3 University of California, San Francisco, San Francisco, California

Alveolar cells

Plasma

Epithelial lining fluid

• Very high concentrations in host cell and fungal membrane support efficacy in prophylaxis setting, even if low serum exposure
• Questions if serum is the right matrix for TDM

Adverse events most commonly reported are:
- GI: vomiting, diarrhea, nausea
- (Transient) liver function elevations
- Hypokalemia
- QTc prolongation

Relation between adverse events and posaconazole exposure was addressed in the phase III trial with the tablet formulation

→ Risk for adverse events does not seem to be exposure dependent

**Do we need to define a target for toxicity?**

**Table 7. Summary of treatment-related TEAEs by quartile of pC$_{avg}$ values, all C$_{min}$ PK-evaluable patients: posaconazole 200 mg and 300 mg dose groups combined**

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Posaconazole pC$_{avg}$ mean (ng/mL)</th>
<th>pC$_{avg}$ range (ng/mL)</th>
<th>Number of subjects</th>
<th>Subjects reporting any treatment-related TEAEs, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>860</td>
<td>442–1223</td>
<td>51</td>
<td>29 (57)</td>
</tr>
<tr>
<td>2</td>
<td>1481</td>
<td>1240–1710</td>
<td>51</td>
<td>19 (37)</td>
</tr>
<tr>
<td>3</td>
<td>1979</td>
<td>1719–2291</td>
<td>51</td>
<td>16 (31)</td>
</tr>
<tr>
<td>4</td>
<td>3194</td>
<td>2304–9523</td>
<td>52</td>
<td>20 (38)</td>
</tr>
</tbody>
</table>

pC$_{avg}$, predicted average concentration from C$_{min}$.
AEs occurring in >5% of subjects in each quartile were as follows: quartile 1—diarrhoea 12%, nausea 10%, rash 10%, abdominal pain 8%, hypokalaemia 6%, hypophosphatemia 6%, vomiting 6%; quartile 2—diarrhoea 6%, nausea 10%, abdominal pain 6%, vomiting 6%; quartile 3—diarrhoea 12%, nausea 6%, hypokalaemia 6%, increased ALT 8%, dyspepsia 6%, increased AST 6%; quartile 4—nausea 13%, vomiting 8%.

Do we need to define a target for toxicity?

Real life evidence (17 studies) with posa tablet & iv from 2014-2018:

Hyperbilirubinemia and AST/ALT elevations occur relatively frequently with posaconazole.

Results are conflicting when looking into the relation between liver function test elevations and exposure.

ECIL-6 recommendation: At present, insufficient data to recommend target trough for safety.
Is TDM useful for posaconazole?

<table>
<thead>
<tr>
<th>Setting</th>
<th>Substantial PK variability?</th>
<th>Therapeutic window defined in humans?</th>
<th>Narrow therapeutic window?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posaconazole used in prophylaxis</td>
<td>✔ yes</td>
<td>?</td>
<td>? Probably not</td>
</tr>
<tr>
<td>Posaconazole used in treatment</td>
<td>✔ yes</td>
<td>✔ yes</td>
<td>? Probably not</td>
</tr>
</tbody>
</table>

**ECIL-6**

TDM *may be* indicated in patients receiving posaconazole tablets or iv for prophylaxis (CIII) or treatment (BIII)

TDM *is* indicated in the setting of breakthrough infection, resistant pathogens, DDIs, therapeutic failure

**My personal opinion**

TDM when
- Used in treatment
- Used in ICU patients
- Patients with severe mucositis, diarrhea
  - Patients with high BW/BMI
  - Potential toxicity
  - Unknown drug interactions
Importance of correct implementation of TDM

From the PATIENT
1. Prescription for TDM
2. Venipuncture
3. Correct tubes
4. Correct storage on ward
5. Sending sample to lab

to the LAB
1. Correct storage in lab
2. Sample preparation
3. Analysis
   1. Commercial IA
   2. LC-MSMS

and back to the PATIENT
1. Validation of result
2. Advice for dose adaptation based on reference values
3. Actual dose adjustment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole</td>
<td>1-6 mg/L</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>&gt; 0,7 mg/L</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0,5-4 mg/L</td>
</tr>
</tbody>
</table>

ECIL-6 (AIII) recommendation: TDM is a multidisciplinary process, quality should be assured in the pre-analytical, analytical and post-analytical phase.
Importance of correct implementation of TDM: when and how is the sample taken?

- **Trough** level
  just before the next dose

  ✓ Not at 4 am or 6 am when all other blood samples are taken...
  ✓ Not when AF is already infused....

- **Preferably peripheral venipuncture**
Importance of correct implementation of TDM:
accuracy of the analytical method

Five year results of an international proficiency testing programme for measurement of antifungal drug concentrations

V. J. C. Lempers¹, J. W. C. Alffenaar², D. J. Touw²,³, D. M. Burger¹, D. R. A. Uges³, R. E. Aarnoutse¹,³ and R. J. M. Brüggemann¹*

Results: Fifty-seven laboratories (13 countries) reported 2251 results (287 fluconazole, 451 itraconazole, 348 hydroxyitraconazole, 402 posaconazole, 652 voriconazole and 111 fluconosine) in 5 years. Analyses were performed using HPLC (55.0%), LC-MS/(MS) (43.4%), UPLC (1.4%) or GC-MS (0.2%). Overall, 432 (19.2%) analyses were inaccurate. The performing laboratory was the only factor clearly associated with inaccuracies. The questionnaire results indicated that laboratories encounter significant problems analysing low concentrations (15.4% of all inaccuracies).

Conclusions: Results of the PT programme suggest that one out of five measurements is inaccurate. The performing laboratory is the main determinant of inaccuracy, suggesting that internal quality assurance is pivotal in preventing inaccuracies, irrespective of the antifungal drug measured, concentration and analytical equipment.

ECIL-6 recommendation (AIII) to participate in ongoing proficiency testing programs to identify sources of errors and improve analytical methods
Conclusion: current challenges for posa/vori TDM

1. **Variability** in PK and DDI is still not completely understood

2. **Evidence base** on TDM is relatively weak
   - Evidence for triazole TDM is derived from single-centre, retrospective and/or statistically underpowered studies - current evidence provides an *approximate* TDM range

3. For voriconazole
   - Clear relationship between exposure and efficacy: lower efficacy target for Cmin 1-2 mg/L
   - Neurotoxicity and liver injury are well known side effects: upper safety target for Cmin – 5-6 mg/L – dose reduction?

4. For posaconazole
   - Evidence for a clear relationship between exposure and efficacy when used in prophylaxis is weaker
     - **TDM might be carried out, especially in patients at risk, aiming > 0.7 mg/L**
     - When used in treatment, higher targets should be used (1-1.25 mg/L)
     - **Plasma concentrations** may not reflect antifungal activity at the site of infection

5. **Implementation** should be carried out very carefully
   - Education on sampling
   - Participation in quality assurance programs