



**az sint-jan**  
brugge - oostende av

## ***Therapeutische drugmonitoring van posaconazole: zin of onzin?***

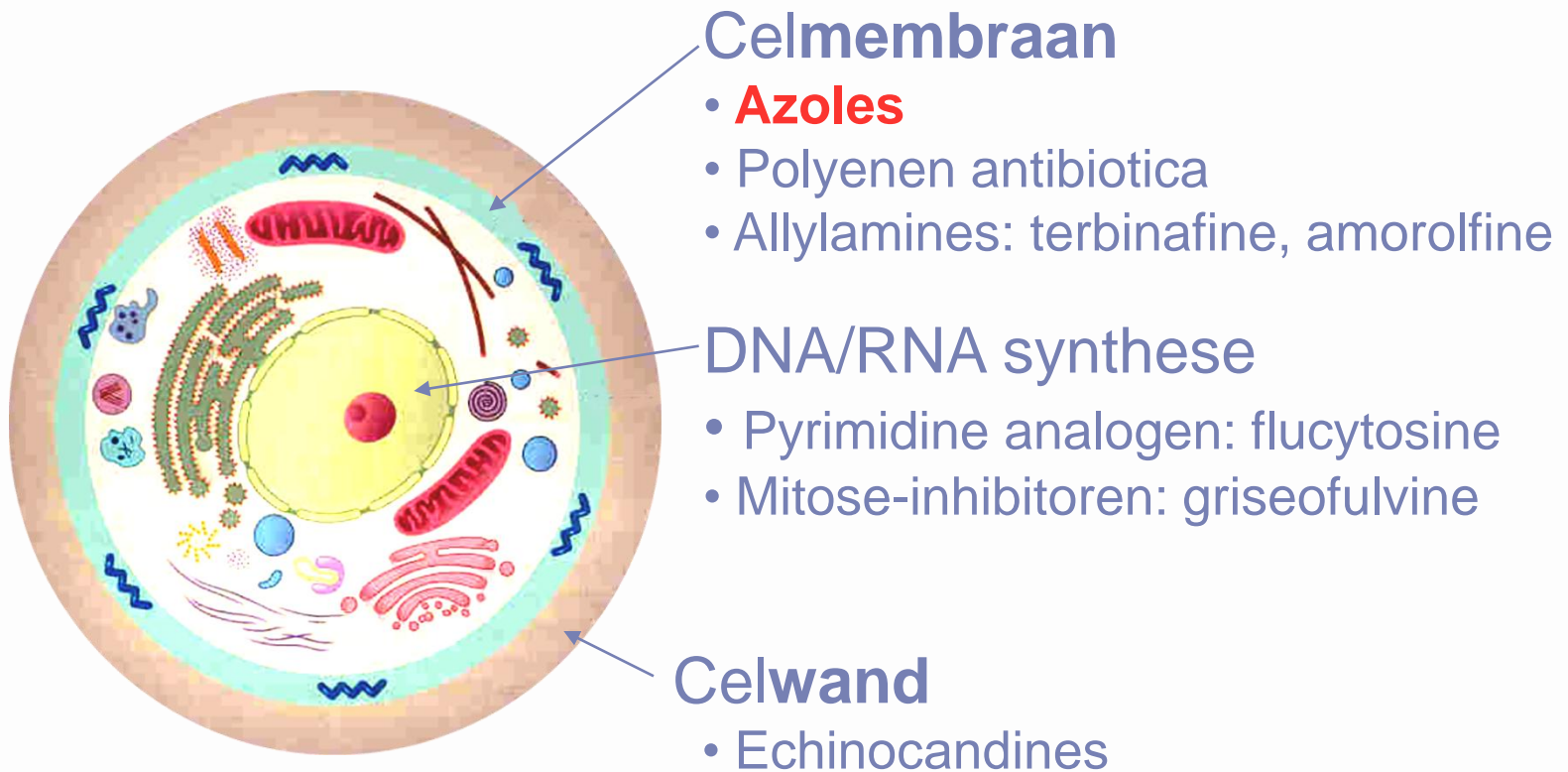
***Timothy Vanwynsberghe***

- ***Azoles***
- ***Posaconazole***
- ***CAT vraagstelling***
- ***1. Wanneer TDM?***
- ***2. Voldoet posaconazole aan criteria?***
- ***3. Hoe kunnen we posaconazole doseren?***
- ***To Do/Actions***
- ***Besluit***



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# Azoles



- Azoles
  - Binden aan lanosterol 14 $\alpha$ -demethylase
    - verhinderen ergosterol synthese
  - Breedste activiteitsspectrum onder de anti-fungale middelen
  - Per os, IV of topisch
  - Concentratie-onafhankelijk, wel tijdsafhankelijk (AUC:MIC  $\geq 50$ )
  - Cyt P450!!, leverenzymes

# Azoles

|                       | C. Albicans | C. neoformans | Dermatofyten | A. Fumigatus       | Dimorfe fungi   |
|-----------------------|-------------|---------------|--------------|--------------------|-----------------|
| <b>Imidazoles</b>     | +           | +             | +            | -                  | +               |
| <b>Triazoles</b>      | +           | +             | +            | (+) <sup>***</sup> | +               |
| <b>Amfotericine B</b> | +           | +             | -            | +                  | +               |
| <b>Nystatin*</b>      | +           | -             | +            | -                  | -               |
| <b>Terbinafine</b>    | -           | -             | +            | + <sup>**</sup>    | + <sup>**</sup> |
| <b>Flucytosine</b>    | +           | +             | -            | -                  | -               |
| <b>Griseofulvine</b>  | -           | -             | +            | -                  | -               |
| <b>Echinocandines</b> | +           | -             | -            | +                  | + <sup>**</sup> |

\*Enkel topisch gebruik

\*\* Klinische effectiviteit nog niet bewezen

\*\*\* Itraconazole en Voriconazole actief tegen A. fumigatus, maar Fluconazole niet

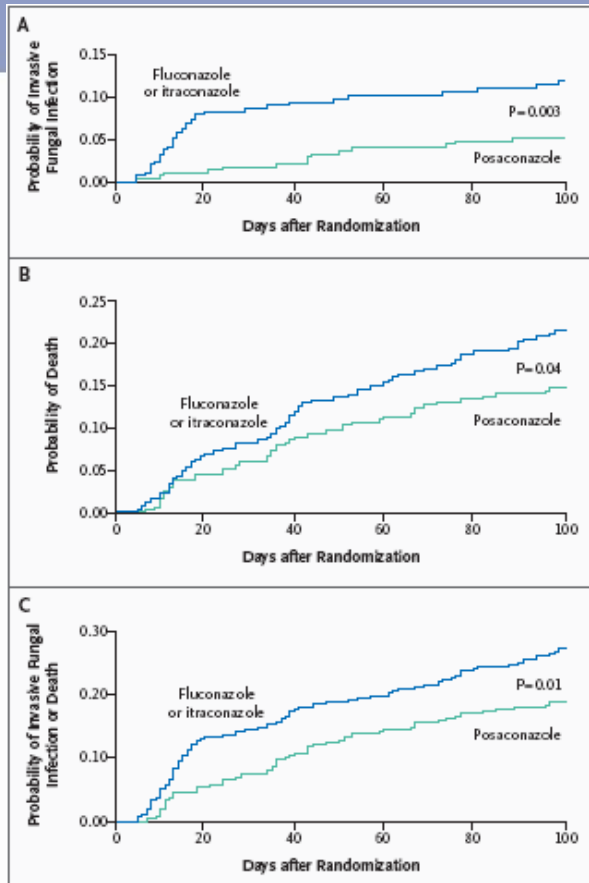
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# Posaconazole

| Parameter        | Posaconazole  |
|------------------|---|
| Formule          | p.o. oplossing  |
| Onderhoudsdosis  | 400mg tweemaal daags  |
| Bio-availability | 8% - 47% (dosis-dependent: beschikbaarheid verhoogd door vetrijke maaltijd) |
| Eiwitbinding     | 98% - 99%   |
| Halfleven        | 25u   |
| Eliminatie       | Faecaal >> renaal: voornamelijk in ongewijzigde vorm                        |
| Metabolisme      | UGT1A4  |
| CYP inhibitie    | CYP3A4  |

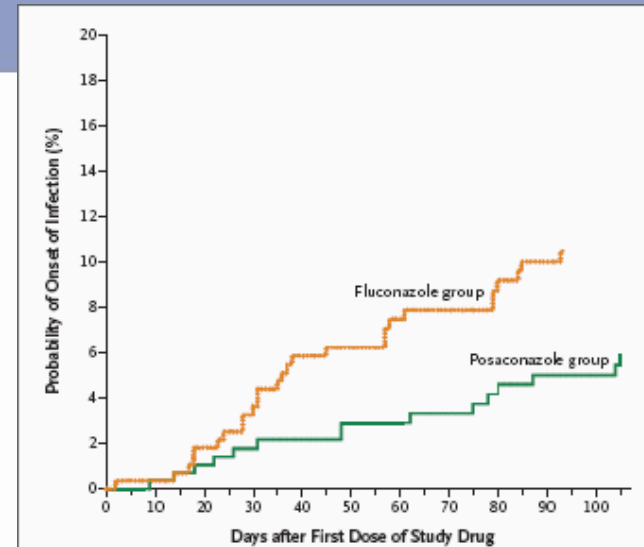


# Posaconazole



**Figure 1.** Kaplan–Meier Curves for Time to Invasive Fungal Infection (Panel A), Death from Any Cause (Panel B), and Invasive Fungal Infection or Death (Panel C) over the 100-Day Period after Randomization.

P values were estimated with the log-rank test. Data were censored on the last date of contact or on day 100 after randomization, whichever was sooner.



**Figure 1.** Time to Proven or Probable Invasive Fungal Infection.

All events not related to invasive fungal infections were considered censored; data on all patients were censored as of the end of the treatment period (day 112). The mean day of the onset of invasive fungal infection was day 102 in the posaconazole group and day 88 in the fluconazole group (P= 0.048).

Ullmann AJ, et al. N Engl J Med 2007; 356: 335-47.

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# CAT vraagstelling

1. Wanneer is therapeutische drug-monitoring (TDM) nodig of aangewezen?
2. Voldoet posaconazole aan TDM criteria?
3. Hoe kunnen we posaconazole doseren?

Met bijzondere aandacht voor de hematologische setting!

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# 1. Wanneer TDM?

- Klinisch relevante dosis-respons relatie
- Klinisch relevante dosis-toxiciteit relatie
- Agentia met een eng therapeutisch venster
- Variabele farmacokinetiek
- Fysiologische instabiliteit
- Geneesmiddeleninteracties
- Moeilijk bereikbare lichaamslocaties
- Kinderen en neonaten
- Compliantie
- Dosisverandering
- Therapiefalen
- Slechte ziekteprognose

# 1. Wanneer TDM?

- Tijd AUC/MIC posaconazole meest gerelateerd met efficiëntie van behandeling in muismodel  
→ onpraktisch!
- TDM makkelijker met dalspiegels bij steady state: na 4-5 halflevens (= 4-5d)

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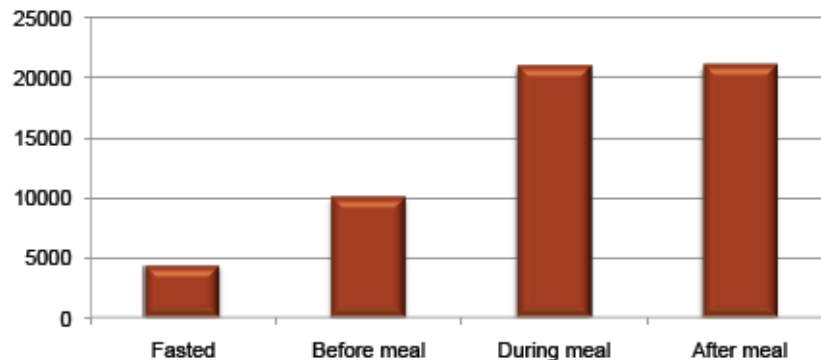
## 2. Voldoet posaconazole aan TDM criteria?

- Variabele farmacokinetiek
  - Diarree
  - Mucositis
  - Vetgehalte voedsel
  - pH maag



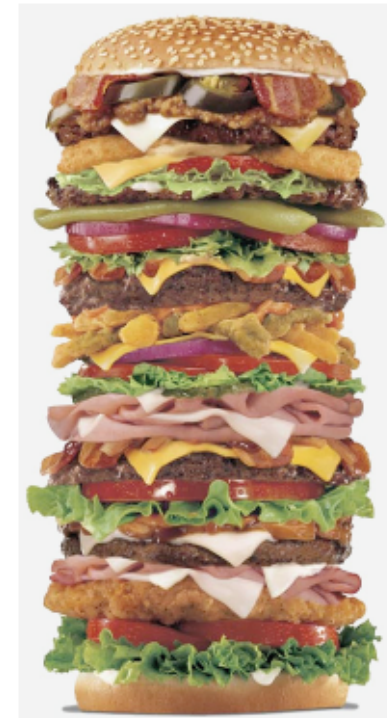
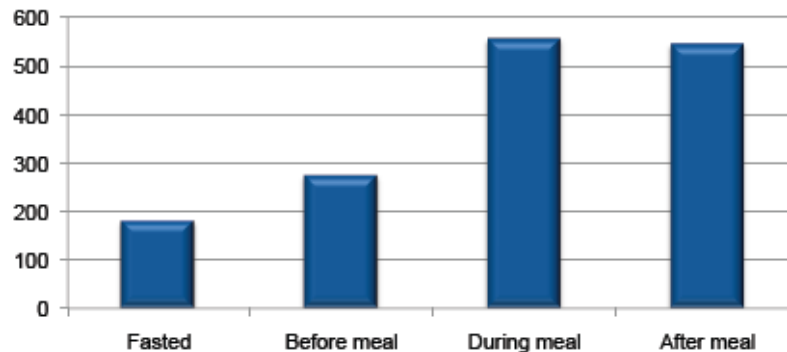
# 2. Voldoet posaconazole aan TDM criteria?

**AUC (ng\*h/mL) after POS 400 mg SD**



Absorption of posaconazole 400 mg single dose relative to meal timing

**Cmax (ng/ml) after POS 400 mg SD**



## 2. Voldoet posaconazole aan TDM criteria?

- Juiste therapeutische concentratie?
  - Andes *et al* (*Antimicrob Agents Chemother* 2009; 53(1): 24-34)
    - Profylaxe: minstens 0,5 µg/ml
    - Therapie: minstens 0,5 µg/ml tot 1,5 µg/ml
  - FDA ([http://www.aapsj.org/abstracts/AM\\_2007/AAPS2007-000993.pdf](http://www.aapsj.org/abstracts/AM_2007/AAPS2007-000993.pdf))
    - Minstens 0,7 µg/ml

## 2. Voldoet posaconazole aan TDM criteria?

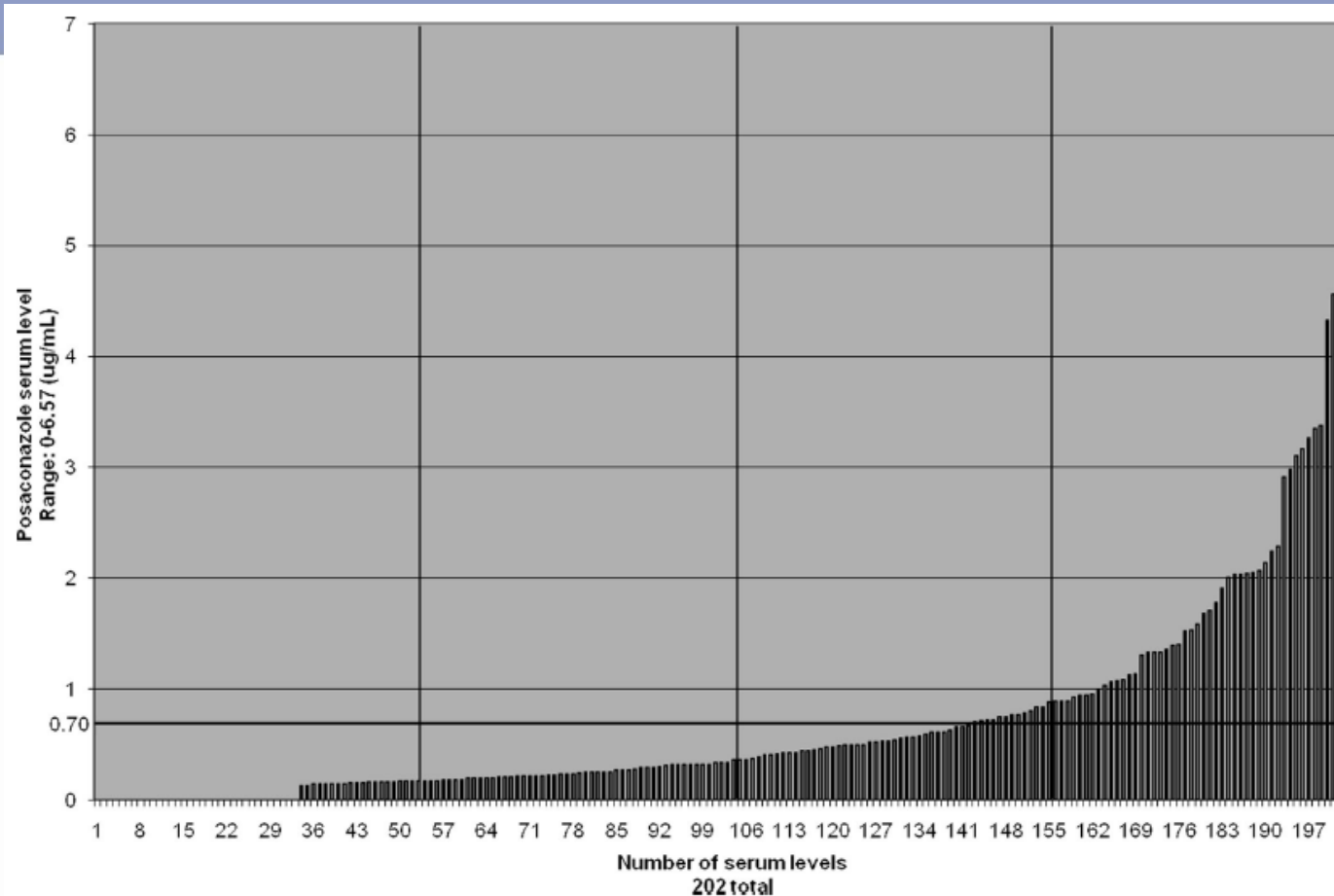


FIG. 1. Distribution of serum posaconazole levels obtained by the Fungus Testing Laboratory, San Antonio, TX, from 26 December 2007 through 30 December 2008.

Thompson GR, Rinaldi MG, Pennick G, Dorsey SA, Patterson TF, Lewis JS. Posaconazole therapeutic drug monitoring: a reference laboratory experience. *Antimicrob Agents Chemother* 2009; 53(5): 2223-4.

# 2. Voldoet posaconazole aan TDM criteria?

- Geneesmiddeleninteracties

|  | Fluconazole | Itraconazole | Voriconazole | Posaconazole |
|--|-------------|--------------|--------------|--------------|
| Ciclosporin  | ↑           | ↑            | ↑            | ↑            |
| Everolimus   | ↑           | ↑↑           | ↑↑           | ↑↑           |
| Sirolimus  | ↑           | ↑↑           | ↑↑           | ↑↑           |
| Tacrolimus   | ↑           | ↑            | ↑↑           | ↑↑           |
| Calcium channel blockers                           | ↑           | ↑            | ↑            | ↑            |
| Antiarrhythmic agents (e.g. quinidine, dofetilide) | ↑           | ↑            | ↑            | ↑            |
| All-trans-retinoic acid                            | ↑           | ?            | ?            | ?            |
| Busulfan   | No          | ↑            | ↑            | ?            |
| Vinca alkaloids                                    | ?           | ↑            | ↑            | ↑            |
| Midazolam  | ↑           | ↑            | ↑            | ↑            |
| Simvastatin  | ↑           | ↑↑           | ↑↑           | ↑↑           |
| Rifampicin   | ↓ FLU       | ↓↓ ITR       | ↓↓↓ VOR      | ↓ POS        |
| Phenytoin  | ↑<br>↓↓ FLU | ↑<br>↓↓ ITR  | ↑↑<br>↓↓ VOR | ↑<br>↓ POS   |
| Omeprazole   | No          | ↓↓ ITR (cap) | ↑ VOR        | ↓ POS        |

cap, capsule; FLU, fluconazole; ITR, itraconazole; POS, posaconazole; VOR, voriconazole. Table adapted from Lipp HP. Mycoses 2008; 51: 7–18, with permission [3].

## 2. Voldoet posaconazole aan TDM criteria?

- Geneesmiddeleninteracties  
– Immuunsuppressiva!!

**Table 6** Posaconazole-triggered drug interactions with immunosuppressive agents and dosage recommendations [modified from References (38–40)].

| Co-administered drug | Effect (posaconazole 400 mg b.i.d)                               | Recommendation  |
|----------------------|--|---|
| Cyclosporin (CsA)    | Decrease in CsA-clearance by 14–29%                              | Use three-fourth of the original* dose; CsA TDM   |
| Tacrolimus           | Increase in $C_{max}$ by 121% and AUC by 358%                    | Reduce tacrolimus* dose to one-third of the planned dose:<br>Consider more intensified tacrolimus TDM     |
| Sirolimus            | Increase in $C_{max}$ and AUC by 6.7- and 8.9-fold, respectively | A dose reduction of sirolimus is needed to avoid overexposure.<br>Consider more intensified sirolimus TDM |
| Everolimus           | Increase in trough levels ( $C_{min}$ ) by 3.8-fold              | A dose reduction of everolimus is needed to avoid overexposure;<br>consider intensified TDM               |

CsA, cyclosporin; TDM, therapeutic drug monitoring.

\*The extent of interaction and dose modification may be dependent on the individual posaconazole plasma concentration.

# 2. Voldoet posaconazole aan TDM criteria?

TABLE 4. Tentative recommendations for monitoring of blood levels during antifungal therapy

| Drug         | Indication  | Time of first measurement after start of therapy (days) | Target blood concn <sup>a</sup> (µg/ml) for:                        |              |
|--------------|---|---|---|--------------|
|              |   |   | Efficacy  | Safety       |
| Flucytosine  | Routine during first wk of therapy, renal insufficiency, lacking response to therapy  | 3–5   | Peak of >20   | Peak of <50  |
| Itraconazole | Routine during first wk of therapy, lacking response, gastrointestinal dysfunction, comedication  | 4–7   | For prophylaxis, trough of >0.5; for therapy, trough of >1 to 2     | NA           |
| Voriconazole | Lacking response; gastrointestinal dysfunction; comedication; children; intravenous-to-oral switch; severe hepatopathy; unexplained neurological symptoms/signs | 4–7   | For prophylaxis, trough of >0.5; for therapy, trough of >1 to 2     | Trough of <6 |
| Posaconazole | Lacking response; gastrointestinal dysfunction, therapy with proton pump inhibitors; comedication   | 4–7   | For prophylaxis, trough of >0.5; for therapy, trough of >0.5 to 1.5 | NA           |

<sup>a</sup> Total or bound and unbound drug concentrations. NA, not applicable.

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# 3. Hoe kunnen we posaconazole doseren?

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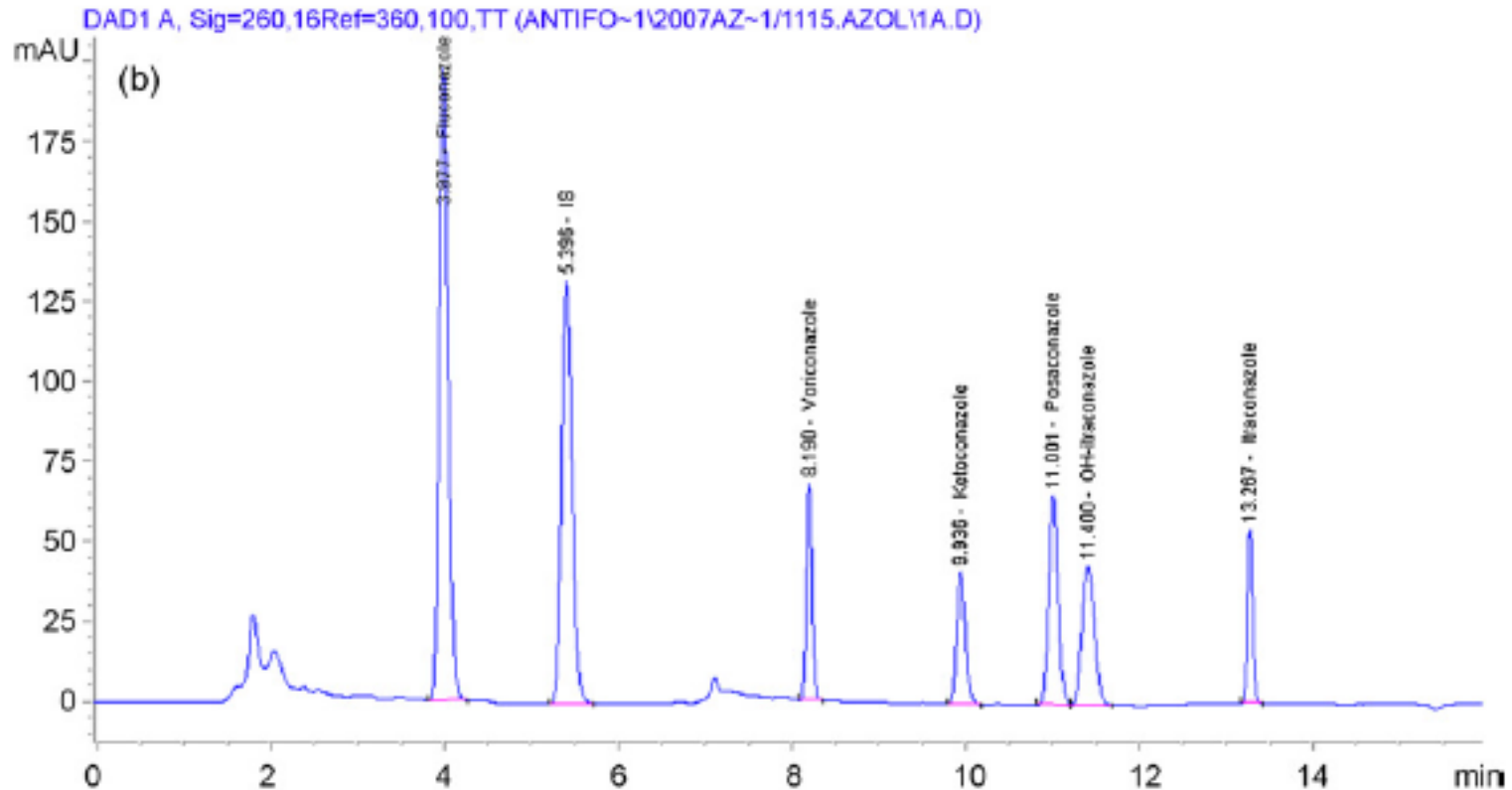
- Chromatografie met HPLC
- Detectie met DAD of tandem-MS



# 3. Hoe kunnen we posaconazole doseren?

- HPLC-DAD
  - Meeste ervaring mee
  - Zowel SPE als LLE
  - Posaconazole +-255nm
  - Detectie meerdere azoles mogelijk
  - Isocratisch of gradiënt?
  - IS keuze?

# 3. Hoe kunnen we posaconazole doseren?



IS = linezolid

# 3. Hoe kunnen we posaconazole doseren?



- LC-MS/MS
  - Ook meerdere azoles te kwantificeren
  - Snelle detectie na eenvoudige LLE
  - Know how
  - Isotoop-gelabelde standaarden

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# To Do/Actions

1. Methode optimalisatie + validatie om posaconazole te doseren in combinatie met voriconazole
2. SOP opstellen
3. Labogids bijwerken

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- TDM posaconazole aangewezen bij:
  - GI dysfunctie
  - Geneesmiddelen-interacties
  - Onvoldoende klinische respons
- HPLC of LC-MS/MS



"I'd say it's a fungal infection."