How to use PK/PD of antifungal drugs in clinical practice?

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How To Use PK/PD Of Antifungal Drugs In Clinical Practice?

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Disclosures

• None

Learning Objectives

• Overview of PK/PD parameters of an antimicrobial agents
• Clinical application, optimization of dose and frequency of administration according to PK/PD of Antifungal agents
• Voriconazole dosing in various patient population
• Need for antifungal TDM in view of variable PK
Background

• Antifungal drug resistance is a big challenge
  • Prior antifungal therapy use, suboptimal drug exposure
  • Agriculture use of antifungals has resulted in environmental reservoirs for some drug-resistant pathogens
  • Global threat of *C. auris* & azole resistant to *A. fumigatus*
• Antifungal PK is challenging due to erratic absorption (ITR, Posa suspension), drug metabolism & drug interaction, efficacy & toxicity


PK/PD

• Pharmacokinetics describes, how human body handles antifungal drug
  • Absorption (Bioavailability)
  • Distribution (Protein bound, penetrations to various body compartments),
  • Metabolism (Cytochrome enzymes, drug-drug interactions)
  • Elimination (Renal, GI)
• Pharmacodynamic is a link between PK, in vitro susceptibility and treatment efficacy
PK/PD: Clinical practice

• PK of antifungal is assessed by estimation of drug levels
• PD is examined by peak concentration in relation to MIC, AUC in relation to MIC, time above MIC, expressed as percentage of the dosing interval (%T>MIC)
• Clinical application
  • Determining dosage and frequency of administration
  • In-vitro drug susceptibility break points
  • Selection of appropriate antifungals according to site (Eye, urinary, CNS)
  • Improve clinical outcome and reduces the risk of emerging resistance

Drug Properties

• Concentration dependent killing ($C_{\text{max}}$/MIC)

Single dose or infrequent dosage

• Time dependent killing property (AUC/MIC)
  • Frequent administration to keep drug level above MIC for longer duration of time (%T/MIC)
  • Many drugs also have a prolonged period of fungal growth inhibition after discontinuation/decreased drug level (PAFE)

Pharmacokinetic/pharmacodynamic relationship of antimicrobial dosing over time relative to organism MIC. The three PD indices are also listed, including $C_{\text{max}}$/MIC, AUC/MIC, and %T>MIC.
PD Properties of Antifungal Agents

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Activity</th>
<th>PAFE***</th>
<th>PD index predictive of efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyenes</td>
<td>CD*</td>
<td>Yes</td>
<td>$C_{\text{max}}/\text{MIC}$</td>
</tr>
<tr>
<td>Triazoles</td>
<td>TD**</td>
<td>Yes</td>
<td>AUC/MIC</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>TD</td>
<td>No</td>
<td>T&gt;MIC</td>
</tr>
<tr>
<td>Echinocandins</td>
<td>CD</td>
<td>Yes</td>
<td>$C_{\text{max}}/\text{MIC, AUC/MIC}$</td>
</tr>
</tbody>
</table>

*CD: concentration dependent, **TD: Time dependent, *** PAFE: Post antifungal effect

The Steady State

Fluconazole

Linear & predictable PK over dose range 50 - 800 mg/day with normal renal function

Wide tissue distribution

- Loading dose required to reach steady state level within 24h
- \( t_{\frac{1}{2}} = 25 - 40 \) hours
- AUC = administered dose, i.e. 800mg produce AUC of 800ml/L
- Predictable blood levels: every 100 mg results in level of 5μg/ml, 800mg = 40μg/ml in healthy volunteers
- Patient receiving CVVH (25ml/min), CVVHD (38ml/min) has higher fluconazole clearance (normal renal function 20ml/min) and requires higher dosage

- A dose/MIC of 50 achieved a response rate above 90% (145 of 159)
- 5 of the 10 cases for which the dose/MIC was exactly 50 failed treatment

The probability of cure was shown to be a function of the dose/MIC and the EC50 was 43.7, but nonetheless, a dose/MIC just short of 100 was required to achieve a probability of cure of 90%
Voriconazole PK

- Adults
  - VCZ has high (96%) oral bioavailability
  - Displays nonlinear PK, with saturable clearance
  - Disproportionate changes when dose altered
  - ~5 days to achieve steady state concentrations

- Children
  - VCZ oral bioavailability is 44.6 – 66%
  - Exhibits linear PK in children
  - Children may metabolise more quickly
  - Higher Dose required


VCZ Trough level and outcome

Treatment success:
Trough level > 1mcg/mL: 88%
Trough level ≤ 1 mcg/mL: 54%

Pascual A et al. CID. 2008; 46:201-11
Inflammation & VCZ trough level

Down-regulation of CYP P450 during inflammation

Marjolijn J. P. van Wanrooy et al AAC 2014

For every 1-mg/liter increase in the CRP concentration, 0.015 mg/liter increase VCZ trough

VCZ dosage in Obese

Higher chances of supratherapeutic VCZ levels on obese patients when dose at actual body weight.
Posaconazole: Oral solution

- Displays linear PK with dosages of 50-800mg
- Saturation of absorption above 800mg/day
- ~7-10 days to achieve steady state concentrations
- Minimal differences between peak and trough levels
- Similar blood concentrations found in juveniles with comparable efficacy and safety
- Posaconazole has prolong half life (35 hours)

Courtney R et al, Antimicrob Agents Chemother 2003; 47: 2788

Posaconazole: Absorption

- Absorbed in duodenum/jejunum
- Posaconazole Suspension requires dissolution of drug in to stomach
- The rate and extent of Posaconazole dissolution is maximized when the drug is taken as smaller, more frequent doses with a high-fat meal
  - Which lowers gastric pH, prolongs gastric residence time, and stimulates splanchnic blood and bile flow
  - Rapid gastric transit, elevated pH slow down the rate and extent of dissolution & less absorbable drug reaches to duodenum and jejunum
Posaconazole Tablet

- Tablet formulation uses pH-sensitive polymers to release Posaconazole at a controlled rate in the duodenum
- Overcomes issues associated with poor gastric dissolution of the drug
- Important benefits with tablet
  - Patient achieves higher trough level 1400 ng/ml (loading dose of 300 mg BD on day 1 followed by 300 OD) compared to 517 ng/ml with the oral suspension (200 mg 4 times daily) (Ezzet 2005; Duarte 2012)
  - Early steady state level (24 to 48 hours with tablet compared to 7 to 10 days with suspension) (Merck 2014)
  - Co-administration of acid suppressing agents (antacids, H2-receptor antagonists, proton pump inhibitors) does not significantly decrease the bioavailability of the delayed-release tablet while 20% to 40% decrease in mean AUC oral suspension
  - Administration with food increases absorption of tablet


Posaconazole tablets: Limitations

- It can’t be divided or crushed, administered through gastric feeding tubes
- Co-administration of the tablet with the pro-kinetic agent metoclopramide resulted in modest decreases in the $C_{\text{max}}$ (14%) and AUC (7%) of the delayed-release tablet (Kraft 2014)

Posaconazole TDM & outcome

Two clinical trials evaluating Pos for prophylaxis against IFI

Study 1: pts with GVHD after hematopoietic SCT
Study 2: pts with neutropenia after chemotherapy for AML/MDS

Results: Probability of breakthrough infection higher when Posaconazole trough plasma concentrations < 700 ng/mL

Isavuconazole PK/PD

- Oral and IV formulations
  - Highly water soluble ➔ no cyclodextrin vehicle for IV (vs. voriconazole + posaconazole)
- Bioavailability: 98%, IV to oral interchangeable
- Linear kinetics
- Volume of distribution: 450L, > 99% protein bound
- Half-life: 100-130 hours
- Metabolism: liver, CYP3A4 + CYP3A5

5 Flucytosine

- Absorption: rapid, 80-90%
- Penetrates into CNS, eye, and urine
- Excretion: Kidney (90%)
  - Reduced 5-FC clearance with renal dysfunction
- Narrow Therapeutic Index (30-80 mg/L)
- Drug concentration vs. toxicity
  - Concentration dependent toxicity (Peak >100 mg/L)
  - Blood dyscrasias, hepatic injury, or GI disturbances
  - Occurs with elevated levels for prolonged period (>2 weeks)


Echinocandins

- In vitro studies: Concentration dependent killing with prolong PAFE
- In vivo; serum kinetic studies $C_{\text{max}}$/MIC predictive of efficacy and
  tissue kinetic study favors AUC/MIC
- Caspofungin: displayed linear pharmacokinetics
- Caspofungin exposure is lower in ICU patients;
  • Suggested dose of Caspofungin of 1 mg/kg bodyweight for critically ill
    patients

Chemother. 2017;61:e01582–e01616
Amphotericin B deoxycholate

- Concentration dependent killing, $C_{\text{max}}/\text{MIC}$ correlate best with Amphotericin B antifungal activity
- Continuous infusion is better tolerated, less toxicity and less mortality compared to short infusion
- Antifungal activity is adequate with continuous infusion remains to be clarified


Lipid Formulations of Amphotericin B

- Lipid formulations are not as potent as amphotericin B deoxycholate on mg/kg basis
- 3-5mg/kg dosage is required for treatment of most of the fungal infections
- Achieve low serum levels but tissue levels in lung, kidney, liver and brain are high
Summary

• Understanding of antifungal PK/PD parameters are important for dose optimization in various patient population, frequency of administration
• TDM for selected antifungal is required to improve clinical outcome and avoid drug toxicity
• Fluconazole has ideal PK parameters while newer agent Isavuconazole & Posaconazole tablet has also favorable PK

Thank You

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Q&A

Please use a microphone or submit a question card