Pharmacokinetics of Antifungal Agents in Pediatric Patients

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Pharmacological Effects

Dosage / Dosage Interval

Pharmacokinetics
   Absorption
   Distribution
   Metabolization
   Elimination

Concentration at Target Site

Pharmacological Effects
   Efficacy
   Toxicity

Disease-related Factors

Growth and Development
Changes in body mass and body composition

Maturation processes of excretory organs

Scaling of dosing regimens based on body weight or body surface area generally inappropriate
**Pediatric Antifungal Arsenal**

**Cell membrane**
- Polyenes
  > D-AmB
  > L-AmB
  > ABLC

- Triazoles
  > Fluconazole
  > Itraconazole
  > Voriconazole
  > Posaconazole

**Cell wall**
- Echinocandins
  > Caspofungin
  > Micafungin
  > Anidulafungin

**Nucleic acid synthesis**
> Flucytosine
Caspofungin
Caspofungin:
Dosing Rationale in Adults

Stone et al. AAC 02
Protocol 033: Pediatric Dose-Finding

CAS 1mg/kg

CAS 50 mg/m2
Caspofungin: Pediatric Dosage

- **Children 2 to 11 years** have faster clearance in comparison to adults

- **Children and adolescents 12 to 17 years** have more similar plasma pharmacokinetics

Based on PK, pharmacodynamics and safety of higher exposure in adolescents and adults, **50 mg/m²** (day 1: 70 mg/m²; max. 70 mg/d) selected for further pediatric development
Protocol 042: PK in children 3-24 months

Neely et al. AAC 09
Protocol 058: Neonatal PK study

• **Study Population:** Children ages 0-3 months with documented or highly suspected invasive candidiasis

• **Treatment Regimens:** Caspofungin administered IV as single daily dose (concomitant amphotericin B permitted)
  - 25 mg/m² Single dose (Panel A): 6 patients
  - 25 mg/m² Multiple dose (Panel B): 12 patients

• **Pharmacokinetics:**
  - Peak/trough PK on Day 1 (both panels) and Day 4 (Panel B)
  - results demonstrate that 25 mg/m² results in comparable PK to adults receiving caspofungin 50 mg or children receiving 50 mg/m²

*Saez-Lllorens AAC 09*
Micafungin: Pk-Study in in Children 2–17 Years

- Open-label, sequential, dose-escalation tolerance study
  - Six dose levels of MICA (0.5–4.0 mg/kg); 1-hour infusion once daily
  - Two age groups (2–12 and 13–17 years)
  - Samples for PK analysis were taken on d 1 and 4

- A total of 78 patients with neutropenia (absolute neutrophil count <500 cells/mm3) enrolled; 77 received study drug
Micafungin: Pk-Study in Children 2-17 Years

Seibel AAC 05
### Micafungin: PK Study in Children 2-17 Years

<table>
<thead>
<tr>
<th></th>
<th>Pediatric pts (2-17 yr)</th>
<th>Adults</th>
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<tbody>
<tr>
<td>Dosage</td>
<td></td>
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</tr>
<tr>
<td>1 mg/kg</td>
<td></td>
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<tr>
<td>2 mg/kg</td>
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<tr>
<td>4 mg/kg</td>
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<tr>
<td>50 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg</td>
<td></td>
<td></td>
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<tr>
<td>Cmax (ug/mL)</td>
<td>10.8</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>15.3</td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td>30.3</td>
<td></td>
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<tr>
<td>AUC 0-24h (ugxh/mL)</td>
<td>40.3</td>
<td>33.9</td>
</tr>
<tr>
<td></td>
<td>83.0</td>
<td>59.9</td>
</tr>
<tr>
<td></td>
<td>191.4</td>
<td></td>
</tr>
<tr>
<td>T ½ beta (h)</td>
<td>12.5</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td>13.2</td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td>11.6</td>
<td></td>
</tr>
<tr>
<td>CL (L/h/kg)</td>
<td>0.021</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>0.020</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td>VDss [L/kg]</td>
<td>0.33</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>0.31</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>0.28</td>
<td></td>
</tr>
</tbody>
</table>
Micafungin: Pk-Study in Premature Infants

<table>
<thead>
<tr>
<th>Population</th>
<th>$t_{1/2}$ (h)</th>
<th>$K_e$ (1/h)</th>
<th>$Vd_{ss}$ (L/kg)</th>
<th>Cl (mL/h/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates &gt;1000 g (n = 15)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>8.3</td>
<td>0.088</td>
<td>0.435</td>
<td>38.9</td>
</tr>
<tr>
<td>SD</td>
<td>1.8</td>
<td>0.02</td>
<td>0.111</td>
<td>12.1</td>
</tr>
<tr>
<td>95% CI</td>
<td>7.4–9.2</td>
<td>0.08–0.1</td>
<td>0.378–0.491</td>
<td>32.8–45.0</td>
</tr>
<tr>
<td>Children 2–8 years old (n = 33)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>11.5</td>
<td>0.064</td>
<td>0.335</td>
<td>22.5</td>
</tr>
<tr>
<td>SD</td>
<td>2.9</td>
<td>0.016</td>
<td>0.16</td>
<td>8.6</td>
</tr>
<tr>
<td>95% CI</td>
<td>10.5–12.4</td>
<td>0.059–0.069</td>
<td>0.28–0.39</td>
<td>19.6–25.4</td>
</tr>
<tr>
<td>Children 9–17 years old (n = 32)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>13.4</td>
<td>0.056</td>
<td>0.243</td>
<td>15.1</td>
</tr>
<tr>
<td>SD</td>
<td>3.8</td>
<td>0.018</td>
<td>0.074</td>
<td>6.3</td>
</tr>
<tr>
<td>95% CI</td>
<td>12.1–14.7</td>
<td>0.05–0.062</td>
<td>0.216–0.271</td>
<td>12.87–17.24</td>
</tr>
<tr>
<td>Adults (n = 48)</td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>13.1</td>
<td>0.055</td>
<td>0.256</td>
<td>14.6</td>
</tr>
<tr>
<td>SD</td>
<td>3.0</td>
<td>0.01</td>
<td>0.052</td>
<td>3.4</td>
</tr>
<tr>
<td>95% CI</td>
<td>12.2–13.9</td>
<td>0.052–0.058</td>
<td>0.241–0.271</td>
<td>13.6–15.5</td>
</tr>
</tbody>
</table>

$t_{1/2}$ indicates half-life; $K_e$, elimination rate constant; $Vd_{ss}$, steady-state volume of distribution; Cl, clearance; SD, standard deviation; 95% CI, 95% confidence interval.
Micafungin: Elevated Dosage in Premature Infants

- Phase I, repeat-dose, single center, open-label trial
  - neonates >48 hrs of age and < 120 d of life
  - MICA doses 15 mg/kg x 5 days / 60 minutes
  - Sparse sampling day 5 / population PK
- 12 patients; seven <1000 g; median birth weight 775 g, median gestational age 27 weeks
  - Micafungin safe and well tolerated
  - Clt and VD greater than in older children
  - 15 mg/kg dosing corresponded to an exposure of approximately 5 mg/kg in adults
Voriconazole
Voriconazole: Pediatric Dose Finding

- Two phase II studies investigating pharmacokinetics of IV VCZ in children 2-12 years at dosages of 2x3 and 2x4 mg/kg
- Combined data on 355 plasma samples in 35 patients

- Linear pharmacokinetics
  Faster clearance

- High interindividual variability (CYP2C19)

Walsh et al. 04
## Voriconazole: Dosage in children 2 to 11 yrs (1)

<table>
<thead>
<tr>
<th></th>
<th>3mg/kg</th>
<th>4mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*Paed.</td>
<td>**Adults</td>
</tr>
<tr>
<td>$C_{ave}$ (ng/ml)</td>
<td>889</td>
<td>1155</td>
</tr>
<tr>
<td>$AUC_\tau$ (ng·h/ml)</td>
<td>10,670</td>
<td>13,855</td>
</tr>
</tbody>
</table>

* 35 subjects from SD and MD PK studies
** 236 healthy volunteers from SD and MD PK studies

Walsh et al. AAC 04
VCZ in children 2-11 yrs: A 1501037

Cohort I
(n=18)
6(iv)- 4(iv)- 6(iv)- 4(po)

Interim analysis
(first 12 subjects)

AUC < 40,000 no safety concerns

Cohort II A
(n = 18)
6(iv)- 6(iv)- 8(iv)- 6(po)

AUC > 40,000 or safety concerns

Cohort II B
(n = 18)
6(iv)- 5(iv)- 4(po)- 5(po)

Walsh et al. ICAAC 06
VCZ in children 2–11 yrs: A 1501037

- Population PK analysis of plasma data from all 3 PK studies of pediatric patients of 2 to <12 years with a range of SD/MD IV and or PO doses
- Final PK model described VCZ elimination by a Michaelis-Menten process and distribution by a two-compartment model. It also incorporated a statistically significant (P < 0.001) influence of the CYP2C19 genotype and of the alanine aminotransferase level on clearance
- Model was used in a number of deterministic simulations (based on various fixed, mg/kg of body weight, and individually adjusted doses) aimed at finding suitable i.v. and p.o. VCZ dosing regimens for pediatric patients

Karlsson et al. AAC 2009
VCZ in children 2-11 yrs:
A1501037

Percent deviations from the reference adult population
AUC distribution (4 mg/kg BID IV; 200 mg BID PO)

Karlsson et al. AAC 09
Voriconazole: Pediatric Dose Finding

Dosage finding of VCZ for pediatric patients 2 to 11 y completed

- 2x7 mg/kg IV without loading
- 2x200 mg PO without loading

Dosage for adolescents ≥12 years

- 2x4 mg/kg IV (2x6 mg day 1)
- 2x200 mg PO (2x400 mg day 1)
VCZ-TDM, case 1:

200 mg BID (20/kgBW) 100 mg BID (10/kgBW)
VCZ TDM, case 2:

- 7 mg/kg BID
- 8 mg/kg BID
- 9 mg/kg BID
- 10 mg/kg BID
- 200 mg BID PO

Voriconazole in Plasma [ug/mL]

Time Course [hours]
Two cases illustrate the high interindividual variability in drug exposure following VCZ therapy pts < 12 years

Indicate the need for further validation of the currently recommended dosage in postapproval studies to better understand the exposure-effect relationships

The AUC may be more adequate than trough or random plasma concentrations to study these relationships