Clinical Development of Systemic Antifungal Drugs in Pediatrics – Achievements and Challenges

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Invasive Fungal Diseases in Pediatric Patients

• Relative to adults, children and adolescents are similarly vulnerable

• However, differences exist as to:
  – Populations at risk
  – Epidemiology
  – Usefulness of newer diagnostic tools
  – Pharmacology of antifungal agents
Pediatric Populations at Risk for Invasive Fungal Diseases

- AML, ALL during prolonged steroid treatment
- Recurrent leukemias
- Hematopoietic stem cell transplantation
  - During granulocytopenia until engraftment
  - During augmented immunosuppression for GVHD

- Very low and extremely low birth weight infants
- Children with life-threatening problems in the ICU

... chronic granulomatous disease; lung and heart/lung, liver, and pancreas transplantation; metabolic diseases
Antifungal Pharmacology and Pediatric Drug Development
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
PK Challenges in Pediatric Patients

- Distribution: larger Vd
- Metabolism/elimination: greater Cl
- Oral Bioavailability/Absorption:
  - development of a palatable oral solution may be a major challenge to providing oral delivery of an antifungal compound
- Particular challenge: premature neonates
EMA Guidance for Pediatric Drug Development

– clinical studies on pharmacokinetics, safety and tolerance are prerequisite

– if underlying conditions, cause of targeted disease and expected response are similar

Data generated in adults can be used to support documentation of efficacy

However, the regulations stress the importance of post-marketing surveillance to increase the pediatric database

Pediatric Antifungal Arsenal

**Cell membrane**
- Polyenes
  > DAMB
  > LAMB
  > ABLC

- Triazoles
  > Fluconazole
  > Itraconazole
  > Voriconazole
  > Posaconazole

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

**Nucleic acid synthesis**
> Flucytosine
Micafungin
Micafungin: Pk-Study in in Children 2-17 Years

- Open-label, sequential, dose-escalation study in 78 patients with neutropenia requiring antifungal therapy
  - 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 taken on d 1 and 4
Micafungin: Pk in Children 2-17 Years

1) linear PK; 2) age-dependent weight-normalized CL
# Micafungin:
## PK Study in Children 2-17 Years

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Pediatric pts (2-17 yr)</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mg/kg</td>
<td>2 mg/kg</td>
</tr>
<tr>
<td>Cmax (ug/mL)</td>
<td>10.8</td>
<td>15.3</td>
</tr>
<tr>
<td>AUC 0-24h (ugxh/mL)</td>
<td>40.3</td>
<td>83.0</td>
</tr>
<tr>
<td>$T\ 1/2 \ beta$ (h)</td>
<td>12.5</td>
<td>13.2</td>
</tr>
<tr>
<td>CL (L/h/kg)</td>
<td>0.021</td>
<td>0.020</td>
</tr>
<tr>
<td>VDss [L/kg]</td>
<td>0.33</td>
<td>0.31</td>
</tr>
</tbody>
</table>
Micafungin: Population Pk in Children 2-17 Years

- Allometric power model: Clearance in smaller children is higher than predicted on the basis of weight alone, requiring a relative dosage increase to ensure exposure comparable to older children.

Monte Carlo simulations in 9,999 simulated pts showing micafungin dosages in children 10 to 80 kg required to produce a mean AUC 0-24 equivalent to the AUC0–24 observed in adults receiving 100 mg (A) and 200 mg (C) at s/s.

Hope et al. AAC 07
Micafungin Pediatric Program

Pediatric PK Study in Adolescents or Older Children 2-17 Years Old (n = 77)

Dose selection

P III Candida (n = 52)
P III Prophylaxis (n = 39)

P II Candida (n = 53)
P II Aspergillus (n = 70)

Pediatric PK Studies in Premature Neonates (≤ 40 weeks, ≥ 500g) (n = 23)
Micafungin: Pk-study in Premature Infants

- Phase I, single-dose, multicenter, open-label trial
  - Post-gestational age \( \leq 40 \) weeks and body weight \( \geq 500 \) g
  - MICA doses of 0.75, 1.5 and 3.0 mg/kg; single 30-minute infusion

- A total of 23 patients were included; five weighed 500–1000 g, 18 weighed >1000 g

- Micafungin safe and well tolerated
- No serious drug-related AEs
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>8.3</td>
<td>0.088</td>
<td>0.435</td>
<td>38.9</td>
</tr>
<tr>
<td>Mean</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>11.5</td>
<td>0.064</td>
<td>0.335</td>
<td>22.5</td>
</tr>
<tr>
<td>Mean</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>13.4</td>
<td>0.056</td>
<td>0.243</td>
<td>15.1</td>
</tr>
<tr>
<td>Mean</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>
<td>13.1</td>
<td>0.055</td>
<td>0.256</td>
<td>14.6</td>
</tr>
<tr>
<td>Mean</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: Population PK in Premature Neonates

Population PK modeling of the neonatal PK data and Monte Carlo Simulation:

- A larger neonatal dose is required to produce drug exposure comparable to those predicted on the basis of weight in children and adults.

- Additional population PK based on open label PK studies with doses of 7-15 mg/kg/d support the use of 10 mg/kg for neonates.

  

  age-dependent serum protein binding – 8-fold higher unbound fraction (f(u)) in neonatal serum

Hope et al. JID 08; Benjamin et al. AAC 10; Smith et al. PIDJ 09; Hope et al. AAC 10; Yanni et al. BDD 11
Micafungin: Antimicrobial Bridging

- Characterization of pharmacokinetics and pharmacodynamics of micafungin in a rabbit model of neonatal hematogenous Candida meningoencephalitis
- Bridging of the results to neonates by use of population pharmacokinetics and Monte Carlo simulation

An experimental dose–microbiological response relationship was apparent in the brain, and near-maximal effect was apparent with doses of 8 mg/kg

Monte Carlo simulations revealed that near-maximal antifungal effect was attained at human neonatal doses of 12–15 mg/kg

Hope et al. JID 08
Voriconazole
Voriconazole

- Non-linear pharmacokinetics
- Complex hepatic metabolization
  - Substrate/inhibitor of CYP2C9, 3A4, 2C19
  - Genetic polymorphisms of CYP2C19
- Number of relevant pharmacokinetic interactions
- Toxicity issues with link to exposure
Voriconazole:
Pediatric Development

• Two phase II studies investigating the PK of IV VCZ in children 2-12 years at dosages of 2x3 and 2x4 mg/kg
• 355 plasma samples in 35 patients

  ➣ High interindividual variability
  ➣ faster clearance / linear pharmacokinetics

Walsh et al. 02; Walsh et al. 04
Voriconazole:
Dosage in children 2 to 11 yrs (1)

<table>
<thead>
<tr>
<th>Medians</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

1.3 -fold dosage

1.3 -fold dosage

2.8 -fold dosage

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

Chart Title

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

Interim analysis
(first 12 subjects)

AUC < 40,000 no safety concerns

AUC > 40,000 or safety concerns

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

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

Walsh et al. AAC 2010
VCZ in children 2-11 yrs: A 1501037 Pop-PK Analysis

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

Karlsson et al. AAC 09
Voriconazole: Initial Pediatric Dose

Dose recommendation for pediatric patients 2 to 11 yrs
- 2x7 mg/kg IV without loading
- 2x200 mg PO without loading

Dosage for adolescents ≥12 yrs
- 2x4 mg/kg IV (2x6 mg day 1)
- 2x200 mg PO (2x400 mg day 1)

Dosage validation (exposure and safety) in two subsequent pediatric PK trials
Voriconazole: Pediatric Dose Finding

40 immunocompromised children 2 to <12, 7 mg/kg IV BID, switched to 200 mg PO BID

IV doses higher than 7 mg/kg are needed to closely match adult exposures, and a weight-based oral dose may be more appropriate.

Driscoll et al. AAC 2011
Voriconazole: Pediatric Dose Finding

26 immunocompromised adolescents 12 to <17 years, IV to PO switch, 6 mg/kg IV BID (d1), then 4 mg/kg IV BID, then 300 mg PO

Exposures in adolescents overall comparable to those in adults. Young adolescents 12-14 with low body weight may need higher doses

Driscoll et al. AAC 2011
VCZ in pediatric patients 2-17 years: Population PK Analysis

- Pooled data from 112 immunocompr. children (2 to <12 yrs), 26 immunocompr. adolescents (12 to <17 yrs), and 35 healthy adults
  - Different maintenance doses (i.e., 3, 4, 6, 7, and 8 mg/kg BID IV; 4 mg/kg, 6 mg/kg, and 200 mg BID PO) evaluated in the children
  - The adult dosing regimens (6 mg/kg i.v. BID on day 1, followed by 4 mg/kg BID, and 300 mg orally BID) evaluated in the adolescents

- Two-compartment model with first-order absorption and mixed linear and nonlinear (Michaelis-Menten) elimination developed

- Deterministic simulations based on individual parameter estimates from the final model to derive dosage

Friberg et al. AAC 2012
VCZ in children 2-11 yrs: Predicted comparative exposures

Friberg et al. AAC 12
VCZ in adolescents: Predicted comparative exposures

a) Day 1 IV – 9 or 6 mg/kg

b) Day 7 IV (Steady State) – 8 or 4 mg/kg

c) Day 7 Oral (Steady State) – 200 mg or 9 mg/kg (max of 350 mg)
Voriconazole:
Current dosage recommendation

*Children 2 to 11 years and adolescents 12-14 years and <50 kg*
- 2x8 mg/kg IV (day 1: 2x9 mg/kg)
- 2x9 mg/kg PO (max: 2x350mg)

*Adolescents ≥12 to 14 years and > 50 kg and those 15 years and beyond:*
- 2x4 mg/kg IV (2x6 mg day 1)
- 2x200 mg PO (2x400 mg day 1) (adult dose)
VCZ TDM in Immunocompromised Pediatric Patients

74 pts (0.2-18y; mean: 10.2y) / 101 courses of VCZ IV (4) and (15)/or (82) PO at median of 4.8 mg/kg BID (r, 2.2-17.4) for a median of 40 days (r, 6-1002)

<table>
<thead>
<tr>
<th>Voriconazole trough [mg/L]</th>
<th>No. (%) of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.2</td>
<td>56 (22.3)</td>
</tr>
<tr>
<td>0.2 – 0.5</td>
<td>50 (19.9)</td>
</tr>
<tr>
<td>&gt; 0.5 – 1.0</td>
<td>39 (15.5)</td>
</tr>
<tr>
<td>&gt; 1.0 – 2.0</td>
<td>36 (14.3)</td>
</tr>
<tr>
<td>&gt; 2.0 – 5.0</td>
<td>50 (19.9)</td>
</tr>
<tr>
<td>&gt; 5.0</td>
<td>20 ( 8.0)</td>
</tr>
</tbody>
</table>

- no predictable dose-concentration relationships
- TDM recommended in guidelines (not in SPC)
Conclusions
Much has been achieved in the field of pediatric antifungal pharmacology
- Drug- and age-dependent differences in plasma pharmacokinetics and dosing
- No apparent differences in safety and tolerance relative to adults

Increasing number of population PK studies to guide dose finding
- work well for drugs with robust PK, less well for more complex drugs

Still very limited number of phase II and IV pediatric validation studies