Pharmacology of Antifungal Drugs in Newborns - Rio de Janeiro August 2014

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Disclosure -  
J. V. Aranda, MD, PhD, FRCPC, FAAP

- Served as an unpaid (pro bono) and paid (grants, small honoraria) consultant on drug and protocol development for various Pharmaceutical companies (Purdue, Farmacon, Mead Johnson, Whitehall Robins, Pfizer, Aventis, Merck, Bristol Myers Squibb-Mead Johnson, Glaxo, AstraZeneca etc)

- > 140 Clinical Trials from Phase 1 to Phase 4 (1999-2008) Support for clinical studies performed independently or with the NIH Pediatric Pharmacology Research Network (NICHD - PPRU)

- Consultant – Educational Program- Ross Abbott (12/05) Ovation Pharma (2006-2007)

- **No conflicts of interest related to the Drugs included in this presentation**
OBJECTIVES: RIO AUG 2014
Antifungal drugs for newborns

- Epidemiology of Neonatal fungal disease
- Pharmacologic Strategies for management of fungal infections in newborns
- Fungal microstructures and sites of drug action
- Clinical pharmacology of antifungals in newborns (PK/PD/dose regimens)
- Monotherapy or combination therapies
Invasive Candidiasis in Newborns

- 10% - 20% of newborns < 1,000 grms develops invasive fungal infections
- 4-18% of ELBW neonates has candidemia
- 20-30% - mortality attributed to candida infection
- 25% of neonates diagnosed with candidiasis will grow candida from other normally sterile sites (meninges, urine) and have negative blood culture
- 30% Candidemia has meningitis also (Benjamin 2006)
- 48% of meningitis has negative blood cultures (Benjamin et al Pediatrics 2006)
Fungal Infections/Colonization in Newborns

• 12% of nosocomial sepsis in 30,993 neonates (27 hospitals in Spain) was due to fungal sepsis (Lopez Sastre et al J Perinat Med 2002:30:149)

• <1,000g: 30/50 (60%) colonized (6wks) reduced to 11/50 (22%) with IV fluconazole. Sepsis: 10/50 (20%) reduced to 0/50 with fluconazole (Kaufman et al NEJM 345:1660,2001 )
Pharmacologic Strategies for management of fungal disease in newborns

1. Prophylaxis of high risk neonates (fluconazole) if NICU > 7% invasive candidiasis
2. Presumptive (empirical) Therapy
3. Definitive Antifungal therapy for proven fungal infections
**Fluconazole Prophylaxis and the Combined Outcome of Invasive *Candida* Infection or Mortality**

(Kaufman D, PEDIATRICS 122 : 2008, pp. 1158-1159)

<table>
<thead>
<tr>
<th>Study</th>
<th>Invasive <em>Candida</em> Infection or Mortality, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluconazole-Placebo Treated Patients Group</td>
</tr>
<tr>
<td>Kicklighter et al</td>
<td>5/53 10/50</td>
</tr>
<tr>
<td>Kaufman et al</td>
<td>19/50 35/50</td>
</tr>
<tr>
<td>Manzoni et al</td>
<td>25/216 22/106</td>
</tr>
<tr>
<td>Total</td>
<td>34/319 (10%)a  51/206 (25%)</td>
</tr>
</tbody>
</table>

a Odds ratio: 0.36 (95% confidence interval: 0.23–0.58; \( P < .0001 \)).

Presumptive or Empirical therapy for neonatal Candidemia

Benjamin et al Pediatrics 2003( 112:543-7 Sept)

- (recommendations based on multivariate analysis of 6,172 neonates < 1250 grams with blood culture (21,233) after day 3)

- Consider presumptive antifungal therapy at the time of blood culture if:
  - <25 wks with thrombocytopenia
  - 25-27 wks with or without thrombocytopenia
  - 3rd generation cephalosporin or carbapenem exposure in last 7 days
Pharmacologic Strategies for management of fungal disease in newborns

1. Prophylaxis of high risk neonates (fluconazole)
2. Presumptive (empirical) Therapy
3. Definitive Antifungal therapy for proven fungal infections
Impact of Presumptive therapy on neonatal outcome
Candida albicans – electron micrograph
Accessed Dec 18, 2012
Fungal structure and targets of drug therapies

http://biochemie.web.med.uni-muenchen.de/Yeast_Bio
accessed June 8, 2008
Fungal structure and targets of drug therapies

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accessed June 8, 2008
Pharmacologic targets - antifungals

Chitin is β-(1,4)-poly-N-acetylglicosamine

Three membrane-bound synthetases:
- Csh1 Repair enzyme
- Csh2 Involved in septum formation
- Csh3 (Cds2) Cell wall maturation and bud-ring formation

Glucomannoproteins
- β-(1,6)-glucan
- β-(1,3)-glucan

Entrapped mannoproteins

ER = Endoplasmic reticulum
S = Secretory

Cell wall
Periplasm
Plasma membrane
Cytosol
Peroxisome
Vacuole
Mitochondrion
Invagination
Nucleus
Bud scar
Pharmacologic targets - antifungals

Polyenes (Ampho B)

- Polyenes (Ampho B)
- Glucomannoproteins
  - \( \beta-(1,6) \)-glucan
  - \( \beta-(1,3) \)-glucan
- Entrapped mannoproteins
- Chitin
- Plasma membrane

Chitin is \( \beta-(1,4) \)-poly-N-acetylg glucosamine

Three membrane-bound synthetases:
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Pharmacologic targets - antifungals

AZOLES
Polyenes (Ampho B)

Glucomannoproteins
\( \beta-(1,6)-\text{glucan} \)
\( \beta-(1,3)-\text{glucan} \)
Entrapped mannoproteins
Chitin
Plasma membrane
Cytosol

Chitin is \( \beta-(1,4)\)-poly-N-acetylglucosamine
Three membrane-bound synthetases:
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Pharmacologic targets - antifungals

Echinocandins
AZOLES
Polyenes (Ampho B)

Glucomannoproteins
β-(1,6)-glucan
β-(1,3)-glucan
Entrapped mannoproteins
Chitin
Plasma membrane
Cytosol

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Three membrane-bound synthetases:
Csh1 Repair enzyme
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Pharmacologic targets - antifungals

- Echinocandins
- AZOLES
- Polyenes (Ampho B)

5-flucytosine

Echinocandins

AZOLES

Polyenes (Ampho B)

Glucomannoproteins
- β-(1,6)-glucan
- β-(1,3)-glucan

Entrapped mannoproteins

Chitin

Plasma membrane

Cytosol

Chitin is β-(1,4)-poly-N-acetylglucosamine

Three membrane-bound synthetases:
- Csh1 Repair enzyme
- Csh2 Involved in septum formation
- Csh3 (Cds2) Cell wall maturation and bud-ring formation
Proteins forming the beta(1.3)D Glucan synthase complex (FKs1p and FKS2p) are shown with some proteins from regulatory network (adapted from DW Denning, Lancet Oct 4, 2003)
Mechanisms of action: Echinocandin

1. Micafungin Inhibition of 1,3-β-D-Glucan Synthase

## MICs of Micafungin for Clinical Isolates of Yeast

<table>
<thead>
<tr>
<th>Organism (No. of isolates)</th>
<th>Compound</th>
<th>MIC range (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C. albicans</strong> (37)</td>
<td>FK463</td>
<td>$\leq 0.0039$ - 0.0156</td>
</tr>
<tr>
<td></td>
<td>FLCZ</td>
<td>0.125 - 4</td>
</tr>
<tr>
<td></td>
<td>ITCZ</td>
<td>0.0156 - 0.25</td>
</tr>
<tr>
<td></td>
<td>AMPH-B</td>
<td>0.25 - 1</td>
</tr>
<tr>
<td><strong>C. albicans</strong> (FLCZ-resistant) (4)</td>
<td>FK463</td>
<td>0.0156 - 0.313</td>
</tr>
<tr>
<td></td>
<td>FLCZ</td>
<td>16 - &gt; 64</td>
</tr>
<tr>
<td></td>
<td>ITCZ</td>
<td>0.5 - &gt; 8</td>
</tr>
<tr>
<td></td>
<td>AMPH-B</td>
<td>0.25 - 0.5</td>
</tr>
<tr>
<td><strong>C. tropicalis</strong> (20)</td>
<td>FK463</td>
<td>0.0156 - 0.313</td>
</tr>
<tr>
<td></td>
<td>FLCZ</td>
<td>16 - &gt; 64</td>
</tr>
<tr>
<td></td>
<td>ITCZ</td>
<td>0.5 - &gt; 8</td>
</tr>
<tr>
<td></td>
<td>AMPH-B</td>
<td>0.0313 - 0.25</td>
</tr>
<tr>
<td><strong>C. glabrata</strong> (20)</td>
<td>FK463</td>
<td>0.0078 - 0.0156</td>
</tr>
<tr>
<td></td>
<td>FLCZ</td>
<td>4 - &gt; 64</td>
</tr>
<tr>
<td></td>
<td>ITCZ</td>
<td>0.5 - &gt; 8</td>
</tr>
<tr>
<td></td>
<td>AMPH-B</td>
<td>0.0625 - 1</td>
</tr>
<tr>
<td><strong>C. krusei</strong> (11)</td>
<td>FK463</td>
<td>0.125 - 0.25</td>
</tr>
<tr>
<td></td>
<td>FLCZ</td>
<td>16 - 64</td>
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<td></td>
<td>AMPH-B</td>
<td>0.5 - 1</td>
</tr>
</tbody>
</table>
Antifungal drug action- synergisms

- **POLYENES** - Amphotericin Complexes with membrane sterols (ergosterols) and leads to cell disruption
- **AZOLES** - Fluconazole  Interferes with ergosterol biosynthesis (blocks P450-dependent demethylation step) and leads to accumulation of lanosterol
- **5-Flucytosine**  Is deaminated to 5-Fluorouracil, Incorporated in RNA, inhibits protein synthesis;If converted to 5-Fluorodeoxyuridylate, is incorporated in DNA and inhibits thymidylate synthase
- **ECHINOCADINS** (micafungin, caspofungin ) – inhibits 1,3 glucan synthase and blocks cell wall synthesis
Antifungal Drugs in Newborns 2014

• Polyenes: Amphotericin, Nystatin, Natamycin
• Fluorinated pyrimidines: 5 fluorocytosine (5FP)
• Thiocarbamates: tolfanate
• Azoles (>20): fluconazole,
  – clotrimazole, itraconazole, Ketoconazone
  New: voriconazole, vibunazole, posaconazole, ravuconazole
• Echinocandins: caspofungin, micafungin (FK463), anidalufungin

NB: none approved by FDA for newborns
Antifungal Drugs in Newborns 2014

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Micafungin (Mycamine) FDA approval June 24, 2013 for children > 4 months
Antifungal Drugs in Newborns 2014

- Polyenes: Amphotericin, Nystatin, Natamycin
- Fluorinated pyrimidines: 5-fluorocytosine (5FC)
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  - New: voriconazole, vorunazole, posaconazole, ravuconazole
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Amphotericin B (AMB)

- Everyone is using it….most commonly used and ‘standard of care’ systemic antifungal in newborns
- Polyene with macrocylic lactone ring derived from streptomyces nodosa
- Antifungal action:
  1. Forms AMB bound to ergosterols in fungal cytoplasmic membranes disrupts osmotic integrity allowing leakage of molecules and K
  2. Fungal cell damage caused by auto-oxidation of AMB bound to cytoplasmic membranes forming free radicals, cell injury and cell death
Amphotericin B (AMB)

- Active against almost all fungal organisms:
  - Candida species
  - Cryptococcus neoformans
  - Blastomyces
  - Histoplasma capsulatum
  - Mucormycosis
  - Aspergillus species
AMPHOTERICIN B (AMB)

- Poorly absorbed after oral or intramuscular administration - so always give AMB by IV route
- Eliminated slowly via kidneys, no substantial metabolism
- Toxicity:
  - CNS – seizures
  - Decreased renal function
  - Hypokalemia
  - Anemia
  - Others (fever, chills etc)
Amphotericin B (AMB)

- Formulations-check dose from handbooks
  - Amphotericin B Deoxycholate (Fungisone) usual dose = 1 mg/kg/day IV over 4 hrs
  - Amphotericin B Liposomal (ambisome) usual dose = 3 to 5 mg/kg/day IV over 1 to 2 hrs
  - Amphotericin B Lipid Complex (Abelcet) usual dose = 1- 5 mg/kg/day IV for 2 hrs
  - Amphotericin B Lipid Complex (ABCD) usual dose = 5 mg/kg/day IV over 2 hrs
Comparison of 3 Amphotericins

- Compared effectiveness and tolerability of
  - AmphoB,
  - AmphoB colloidal dispersion (ABCD),
  - Liposomal AmphoB
- 56 newborns with candida sepsis
- NO difference in mortality
- No difference in time to negative blood culture achieved in 67 to 83.3% of babies
The AZOLES

• More than 20azole anti-fungals available
• Newest approved by FDA: voriconazole
• Most used in newborns: FLUCONAZOLE
• Fluorinated bis-triazol
• Highly and selectively Inhibits fungal cytochrome P450 sterol C-14 a-demethylation in cytoplasmic membrane resulting in cell lysis
Fluconazole is a potent Triazole antifungal agent.

Fluconazole prophylaxis has been shown to reduce fungal colonization and systemic infection.

Excellent CSF & tissue penetration.

Low incidence of adverse events.

Well tolerated.

Candida Albicans and Parapsilosis are typically sensitive to fluconazole.

Relatively low cost.

Insufficient Pharmacokinetic information in neonates had led to highly variable dosing practice.
Fluconazole

- Excellent GI absorption – 90% bioavailability
- Negligible metabolism
- Excreted by kidneys = 80% as unchanged drug
- CSF/Plasma ratio: 0.50-0.90
- Drug interactions:
  - Theophylline, phenytoin, cisapride, hydrochlochlorothiazide, zudovudine, etc.
Pharmacokinetics of Fluconazole in VLBW

(Saxen Clin Pharm Ther. 1993;54(3):269-77)

- Mean fluconazole half-lives:
  - Birth: 88.6 hours (n = 7),
  - 1 Week: 67.5 hours (n = 9),
  - 2 weeks: 55.2 hours (n = 4);

- Recommendations:
  - Fluconazole dose (6 mg/kg every 3 days),
    - mean serum peak and trough concentrations increased during the first week but decreased during the second week.
    - After the first week suggested dose is 6 mg/kg every 2 days, or even daily.
Old Dosing Guidelines- Systemic Therapy

- Dosing range 2-50 mg/kg/day
- Most common is 6 mg/kg (IDSA guideline)
  - Near Term infants Q24 hr
  - VLBW infants
    - Q72 hr if <14 days of life, Q48 hr 14-28 days of life, Q24 hr >28 days of life
    - IDSA guideline recommends Q24 despite prolonged early clearance in VLBW infants
- Breakthrough fungemia associated with sub-therapeutic treatment
Simulation fluconazole exposure in infants using population PK model. A.) Simulated 24 hour interval AUC for each day among infants receiving 12 mg/kg/day fluconazole (open circle infants are 23-29 weeks BGA with solid median band, closed circle infants are 30-40 week BGA with dotted median band). B) Median boxplot of predicted dose required to achieve steady state AUC target 800 mg*hr/L in infants stratified by birth gestational age (GA) and post natal age (PNA). (n=55) GA 23-40 weeks, PNA <120 days.

PopPK – Population Pharmacokinetics

- The study of variability in plasma drug concentration between individuals when standard dosage regimens are administered.
- PopPK studies the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest.
- Typically uses sparse sampling.
Simulation fluconazole exposure in infants using population PK model. A.) Simulated 24 hour interval AUC for each day among infants receiving 12 mg/kg/day fluconazole (open circle infants are 23-29 weeks BGA with solid median band, closed circle infants are 30-40 week BGA with dotted median band). B) Median boxplot of predicted dose required to achieve steady state AUC target 800 mg*hr/L in infants stratified by birth gestational age (GA) and post natal age (PNA). (n=55) GA 23-40 weeks, PNA <120 days.

Dosing Guidelines - FLUCONAZOLE

DOSING GUIDELINES
FLUCONAZOLE
PROPHYLAXIS
6 MG/KG/ 2X/WEEK
(TUESDAYS AND FRIDAYS
SYSTEMIC: 12 MG/KG/DAY

• Fluconazole t½ = 24 hours
• Time to achieve desired target AUC > 400 mg/h/L = 5 to 7 days at dose of 12 mg/kg/day
• PK/PD index : AUC/MIC (min inhibitory conc breakpoint <8 mg/mL ) > 50 non-achievable
• Need Loading dose to reach target quickly
Loading dose = desired $C_p \times V_d$

Maintenance dose = desired $C_p \times C_l$

Where:

$C_p$ = plasma drug concentration (mg/L)

$V_d$ = volume of distribution (L/kg)

$C_l$ = drug clearance (mg/kg/h)
Fluconazole

- 10 newborns – 16 days; gest age 35-38 weeks, birth weight :2.8 kg
- PK study done:
- IV Loading dose: 25 mg/kg infused over 2 hrs
- Maintenance dose : 12 mg/kg/day
- All achieved target trough conc (Cmin) > 8 mg/mL
- Not all achieved target AUC/MIC >400
Voriconazole (Pfizer)

- Second generation triazole (derived from fluconazole) – approved FDA May 2002
- Fungistatic-fungicidal against Aspergillus, candida,
- Rapid oral absorption – bioavailability=96%
- Extensively metabolized by liver (CPY2C19) – watch out for slow and fast metabolizers (5-7% caucasians, 20% Asians- deficient CYP 2C19)
- Plasma half life – variable about 6 hrs, faster clearance in children compared to adults
- Good CSF penetrance (CSF : plasma level = 0.22 to 1.0 (median, 0.46) (Lutsar Clin Inf Dis 2004)).
(birth weight 641 g, 24 wks GA)


**TABLE 1. Pharmacokinetic Profiles for Voriconazole and Micafungin**

<table>
<thead>
<tr>
<th></th>
<th>Voriconazole (4 mg/kg/Dose, every 12 h)</th>
<th>Micafungin (8 mg/kg/Dose, Once Daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day of treatment</strong></td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Serum peak concentration (µg/mL)</td>
<td>0.87</td>
<td>17.3</td>
</tr>
<tr>
<td>Serum trough concentration (µg/mL)</td>
<td>0 (0.1)†</td>
<td>4.8</td>
</tr>
<tr>
<td>Elimination constant (h⁻¹)</td>
<td>0.2</td>
<td>0.058</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>3.5</td>
<td>12</td>
</tr>
<tr>
<td>Maximum concentration (µg/mL)</td>
<td>0.96</td>
<td>17.8</td>
</tr>
<tr>
<td>Minimum concentration (µg/mL)</td>
<td>0.09</td>
<td>4.7</td>
</tr>
<tr>
<td>Volume of distribution (L/kg)</td>
<td>4.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Clearance (mL/h/kg)</td>
<td>858</td>
<td>29.4</td>
</tr>
<tr>
<td>Area under the curve (µg·h/mL)</td>
<td>4</td>
<td>229</td>
</tr>
</tbody>
</table>

*Concomitant medications when the pharmacokinetic analyses were performed included dobutamine, furosemide, hydrocortisone and liposomal amphotericin B.

†For calculation purposes, the trough concentration of 0 µg/mL was assumed to be equal to 0.1 µg/mL with a lower limit of quantitation at 0.2 µg/mL.
Voriconazole

- Available in intravenous and oral formulation
- Loading dose: 6 mg/kg per load x 2 doses
- Maintenance dose: 4 mg/kg BID
- Side effects: visual disturbances (brightness, blurred vision) in ca: 30%; increased liver enzymes
- Drug interactions: cyclosporines, tacrolimus sirolimus
5 Flucytosine (5FU)

- Flourinated pyrimidine related to fluorouracil and floxuridine
- Active against Candida species, cryptococcus
- Rapidly absorbed by gastrointestinal tract
- Plasma t½ normal adults = 3-6 hrs; may be prolonged (>200hrs) in renal failure
- Excreted unchanged in urine (80%); renal clearance equivalent to creatinine clearance
- CSF concentration = 65-90% of plasma
Action of Fluocytosine in Fungi

- 5-Flucytosine is transported into the fungal cell, where it is deaminated to 5-fluorouracil (5-FU). The 5-FU is then converted to 5-fluorouracil-ribose monophosphate (5-FUMP) and then is either converted to 5-FUTP and incorporated into RNA or converted by ribonucleotide reductase to 5-FdUMP, which is a potent inhibitor of thymidylate synthase.
5 Flucytosine

- Flucytosine (ANCOBON);
- Usually used with Amphotericin B
- Limited data in newborns: empirical dose guidelines = 12.5 to 37.5 mg/kg/dose q 6 hrs (increase dosing interval in renal failure)
- Toxicity is related to plasma concentrations
  - (> 100 mcg/ml)
- Adverse effects: severe bone marrow depression, (fluorouracil production), hepatitis, severe diarrhea, rash
- Toxicity increased with Amphotericin B
The New Echinocandins

- Micafungin (FK463)
- Caspofungin
- Anidulanfungin
- Large lipopeptide molecules
- For Intravenous use only (over 1 hr)- poor bioavailability (< 0.2% for caspofungin)
- Incompatible with dextrose
- Activity against Candida species and Aspergillus species
New Echinocandins

• Low CSF drug concentrations but are effective for fungal meningitis
• Mainly degraded in liver by hydrolysis and N-acetylation
• Plasma beta t½ in adults:
  – 11 hrs (caspofungin),
  – 11-17 hrs (micafungin)
Echinocandins

ADVERSE EVENTS ARE FEW……

(Agent subjects and children)

- Headache (caspo > mica)
- Fever (caspo> mica)
- Increased liver enzymes (caspo > mica)
- Phlebitis (caspo> mica)
- Rash
- Hypercalcemia in a preterm newborn (Smith PB, J Perinatology 2007)
Micafungin Pharmacokinetics in Newborns (2003 NIH-PPRU)

- 23 neonates given 3 dose levels of Micafungin (FK463) 0.75, 1.5, 3.0 mg/kg
- Preterm (500-1000 grams)
- > 1,000 grams
- < 40 weeks gestation
## TABLE 3. Comparison of Micafungin Pharmacokinetic Parameters Between the Present Neonate Cohort and Populations of Children and Adults

<table>
<thead>
<tr>
<th>Population</th>
<th>( t_{1/2} ) (h)</th>
<th>( K_e ) (1/h)</th>
<th>( V_d_{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>
<td></td>
</tr>
<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>
<td></td>
<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>
<td></td>
<td></td>
<td></td>
<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; \( V_d_{ss} \), steady-state volume of distribution; Cl, clearance; SD, standard deviation; 95% CI, 95% confidence interval.

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Predicted mean ± SD area under the time-concentration curve (AUC)0–24 at steady state for neonates receiving 3 and 9 mg/kg, compared with children aged 2–17 years receiving 2 mg/kg and adults receiving a daily dose of 150 mg. A larger neonatal dose is required to produce drug exposures comparable to those predicted on the basis of weight in children and adults.
Micafungin- Dose considerations


• (1) a neonatal dose of 9 mg/kg results in a similar mean AUC0–24 at steady state to an adult dose of 150 mg and to 2 mg/kg in children aged 2–17
• (2) micafungin has a favorable safety profile, suggesting that the use of higher doses may be possible
• (3) simulations suggest that near-maximal effect is observed with neonatal doses of 12–15 mg/kg
• These data suggest that an appropriate dose of micafungin to induce near-maximal effect in a majority of infants with meningo-encephalitis could be between 9 and 15 mg/kg.
DOSE - NEWBORN: MICAFUNGIN 10 MG/KG/DAY
**Pharmacokinetics of an Elevated Dosage of Micafungin in Premature Neonates** (Smith BP Ped Inf Dis J May 2009) n=12

**TABLE 3. Pharmacokinetic Profile of Micafungin** (Mean, SD)

<table>
<thead>
<tr>
<th></th>
<th>Cohort &lt;1000 g</th>
<th>≥1000 g</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 12</td>
<td>(n = 7)</td>
<td>(n = 5)</td>
<td></td>
</tr>
<tr>
<td>AUC (ug/h/mL)</td>
<td>437.5 (99.4)</td>
<td>412.7 (121.4)</td>
<td>472.2 (49.6)</td>
</tr>
<tr>
<td>CL (mL/min/kg)</td>
<td>0.575 (0.196)</td>
<td>0.622 (0.250)</td>
<td>0.510 (0.054)</td>
</tr>
<tr>
<td>Cmax (ug/mL)</td>
<td>38.4 (8.8)</td>
<td>38.6 (11.6)</td>
<td>38.2 (3.3)</td>
</tr>
<tr>
<td>Vdss (L)</td>
<td>1.5 (0.5)</td>
<td>1.2 (0.5)</td>
<td>1.8 (0.3)</td>
</tr>
<tr>
<td>Vdss (L/kg)</td>
<td>1.515 (0.516)</td>
<td>1.637 (0.657)</td>
<td>1.344 (0.141)</td>
</tr>
<tr>
<td>Vdβ (L/kg)</td>
<td>0.613 (0.282)</td>
<td>0.636 (0.370)</td>
<td>0.581 (0.106)</td>
</tr>
</tbody>
</table>

Vdβ indicates volume of distribution in the elimination phase.

15 mg/kg/day Achieved Cp = 5 mg/kg/d in adults Tolerated and No AE
Micafungin in Newborns

Efficacy/safety data limited

Potential adverse effects (but unlikely based on children and adult data)

- increase liver enzymes
- phlebitis
- AE: (from brochure) vomiting (31%), diarrhea (22%), pyrexia (22%), nausea (19%), abdominal pain (16%) and thrombocytopenia (15%)
Caspofungin in Newborns

Natarajan G et al_ J Perinatol 2005

- Caspofungin: started at a median age of 44 days, after 6 to 30 days of persistent candidemia despite of conventional antifungal therapy.
- 11/13 infants cleared the infection,
  - median time to achieve sterilization = 3 days
- median duration of treatment of 18 days (range, 2-43 days).
- 2/13 infants died from candidemia; (had only 2 doses of caspofungin before death.)
Caspofungin PK and dose- newborns?

- Loading dose: 100 mg/m^2 (8 mg/kg) followed by a maintenance dose of 70 mg/m^2/day (6 mg/kg/day). (Smith PB et al J Perinatol. 2007 Feb;27(2):127-9)

- 1 to 1.5 mg/kg/day (n=13) (Natarajan G et al J Perinatol. 2005 Dec;25(12):770-7)

- 1-2 mg/kg/day (n=10) (Odio CPediatr Infect Dis J. 2004 Dec;23(12):1093-7.)
Caspofungin

• NEEDED DATA IN THE NEWBORN:
  – Efficacy and safety
  – Dose finding and tolerability studies
  – Pharmacokinetic data
  – Comparative Efficacy and Safety
  – Drug Combination Studies
Refractory neonatal candidemia and high-dose micafungin pharmacotherapy


- 29/450 (6.4%) VLBW screened had Candida bloodstream infection and received at least a dose of antifungal.
- Refractory (n=19) candidemia and Early responder (n=10) groups = comparable mean (±s.d.) gestation, 27(±3.1) vs 27.8 (±2.7) wks
- Refractory group:
  - had antibiotics for a longer duration, 14.5 (±10.3) vs 7.1 (±5) d
  - more non-albicans infections, 11 (57.9%) vs 1 (10%)
  - were on less enteral feeds > 20ml/kg/day less often (21 vs 70%).
  - Higher Mortality (53 vs 20%)
  - lower fungal clearance rates lower (63.1 vs 90%),

C. Glabrata susceptibility pattern by centers (Columbia Presbyterian, Johns Hopkins, U Mich, Henry Ford, U Florida, U Pittsburg, Auckland City Hosp, Westmead Australia. Resistance breakpoint > 0.5 ug/mL (7 centers, 2,897 isolates)
Combination Therapy-synergism?

5-flucytosine

Echinocandins

AZOLES

Polyenes (Ampho B)

Glucomannoproteins
- β-(1,6)-glucan
- β-(1,3)-glucan
- Entrapped mannoproteins

Chitin

Plasma membrane

Cytosol

Chitin is β-(1,4)-poly-N-acetylglucosamine
- Three membrane-bound synthetases:
  - Csh1 Repair enzyme
  - Csh2 Involved in septum formation
  - Csh3 (Cds2) Cell wall maturation and bud-ring formation
Antifungal drug therapy in the newborn:

- Echinocandin + azole
- Echinocandin + ampho B
- Azole + AmphoB
- Triple therapy: azole + echinocandin + ampho B
Invasive fungal disease – newborns

1. Remove intravascular lines!!!!
2. Start antifungal as soon as possible - BE aggressive.
3. Watch out for other end organ damage (fungal balls - kidneys, eyes, CNS, heart)
Summary-2014

- Invasive Candida infection in newborns - Poor outcome - immediate and long term
- Newer antifungals increase choices for pharmacotherapy of invasive fungal disease.
- Efficacy, safety, PK/PD and other pharmacologic data are needed for the neonatal population
- Aggressive therapy is justified
- Adequate doses should be used, watch out for the next recommendation
- Combination therapy for potential synergism requires randomized trials
Central Park viewed from top of the Rock

Thank you!!!
QUESTIONS???????