Therapeutic Drug Monitoring for Antifungal Agents

Denise E. Riccobono, Pharm.D., BCPS
Clinical Coordinator of Infectious Diseases
Kingsbrook Jewish Medical Center
Brooklyn, New York

Objectives

- Briefly review rationale for therapeutic drug monitoring
- Discuss factors that contribute to intra-patient variability in pharmacokinetics of antifungal agents
- Review evidence supporting a “therapeutic range” for antifungal serum drug concentrations
- Recommend practical approaches towards targeted TDM to individualize antifungal dosing
Therapeutic Drug Monitoring (TDM)

- **What is it?**
  - Measuring and interpreting drug concentrations in biological fluids
    - Typically serum
- **Involves**
  - Applying pharmacokinetic principles
  - Taking advantage of pharmacodynamic characteristics of a drug
- **Objective/Goal:**
  - To maximize the probability of a successful outcome and minimize the probability of toxicity for an individual patient

Four Major Criteria for TDM

1. **Valid assay**
   - Accurate, readily available, and cost-effective
   - Able to provide results in a timely manner

2. **Clinical efficacy/toxicity of the drug must be delayed or difficult to directly measure**

3. **Unpredictable/Variable dose-concentration relationship exists**
   - Related to inter/intra patient differences in PK parameters of a specific drug
   - Drug concentration can not be assumed from empiric dosing strategies

4. **Clear relationship between drug concentrations in the body fluid and clinical outcome**
   - Therapeutic efficacy &/or toxicity

Example
Aminoglycosides

✓ Assay

✓ Clinical efficacy/toxicity delayed or difficult to measure
  • Empiric treatment

✓ Variable dose-concentration relationship
  • Distribution
  • Clearance

✓ Relationship between drug concentration and clinical outcomes
  • Efficacy: dose dependant killing
  • Toxicity: nephrotoxicity with high trough

Why is therapeutic drug monitoring conceptually appealing for invasive fungal infections?
**Efficacy**

- Invasive fungal infections are associated with high rates of crude mortality
  - Invasive Candidiasis (38%)\(^1\)
  - Invasive Aspergillosis (60-90%)\(^2\)
- Significant increase in mortality if effective therapy is not administered early\(^3,4\)
- Few, if any, practical intermediate endpoints are available for monitoring response to antifungal therapy
- Many antifungal drugs exhibit marked variability in drug blood concentrations\(^5\)
  - Inconsistent absorption, metabolism, elimination, drug interactions, genetic variability

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5-Andes D et al. AAC. 2009; 53:24-34

### Pharmacogenomic variability

**Gastrointestinal**
- motility (all)
- splanchnic blood flow (all)
- mucosal damage (all)
- physiochemical (itraconazole)
  - pH (itraconazole, posaconazole)

**Intestinal**
- efflux drug transporters (all azoles, flucytosine)
- pre-systemic metabolism (itraconazole, voriconazole, posaconazole)

**Hepatic**
- efflux drug transporters (posaconazole, amphotericin B)
- excretion transporters (azoles, caspofungin)
- metabolism (azoles, caspofungin, micafungin)

**Renal**
- drug transporters (fluconazole, amphotericin B)
- metabolism
  - glomerular filtration (fluconazole, flucytosine, cyclodextrans)

**Drug interactions**
- induction (azoles, caspofungin)
- inhibition (itraconazole, voriconazole, posaconazole)

Lewis R.E.
Do any antifungals TRULY fit the criteria for routine therapeutic drug monitoring?

### Antifungal Agents

<table>
<thead>
<tr>
<th></th>
<th>Signif. Interpt variability</th>
<th>Correlation of serum drug conc &amp; efficacy/tox in humans</th>
<th>Efficacy/toxicity delayed/diff to measure</th>
<th>Assay Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td></td>
<td>Possibly</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Azoles</td>
<td>✔,</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Echinocandins</td>
<td></td>
<td>Possibly</td>
<td></td>
<td>✔</td>
</tr>
</tbody>
</table>
Available Assays

- **Microbiological (Bioassays)**
  - **Advantages:**
    - Simplicity
    - Rapidity
    - Low cost
  - **Disadvantage:**
    - Less precise
    - Includes the presence of active metabolites
      - e.g. Itraconazole
    - Interference with combination antifungal therapy

- **Chromatographic (HPLC or LC-MS)**
  - **Advantages:**
    - High sensitivity
    - High specificity
    - Rapid analysis
  - **Disadvantages:**
    - Requires expensive equipment
    - Specialized technicians
    - Laborious sample preparation
    - High up-front costs

Flucytosine (5-FC)

- Fluorine analogue of a normal body constituent, cytosine, marketed early 1970’s
- Broad antifungal activity against most *Candida spp.* & *Cryptococcus neoformans*
  - Except *Candida krusei*
- Almost never used as monotherapy due to rapid development of resistance
- **Treatment:**
  - Cryptococcal meningitis - in comb w/ AmB
  - Invasive Candidemia (e.g. endocarditis, meningitis) – in combination w/ AmB
  - Candiduria
Flucytosine (5-FC)

- ADME Patient Variability
  - Absorption: rapid, 80-90%
  - Distribution: <4% protein binding
    - VD 0.6-0.9 L/Kg; widely distributed into body fluids and CSF
  - Metabolized: not significant
- Excretion: Kidney (90%)
  - Reduced 5-FC clearance with renal dysfunction
  - Predominant variable

- Drug concentration vs. toxicity
  - Concentration dependant toxicity (Peak >100 mg/L)
    - Blood dyscrasias, hepatic injury, or GI disturbances
    - Occurs with elevated levels for prolonged period (>2 weeks)

Bennett J.E., et al. NEJME, 1979;301:126-31

Flucytosine Toxicity

% of Patients with 5-FC Toxicity

Flucytosine (5-FC)

- Drug concentration vs. efficacy
  - Optimal antifungal activity
    - Pre-clinical infection models: T>MIC for 50% dosing interval
    - No clinical data
  - Narrow Therapeutic Index (30-80 mg/L)

Hope WW, et al. AAC. 2006; 50: 3680-3688

Flucytosine (5-FC)

✓ Recommendations for drug monitoring
  - Dose adjust for renal impairment
  - Obtain 2 hr post-dose concentrations after 3-5 doses
    - Repeat levels 1-2 times weekly if fluctuating renal function and/or concomitant nephrotoxic drugs
  - Goal drug concentrations
    - Cryptococcal infections: 30-80 mg/L
    - Meningitis due to Candida spp: 40-60 mg/L
  - Monitor blood counts (e.g. CBC, LFTs)

Azoles

<table>
<thead>
<tr>
<th></th>
<th>Signif. Interpt Variability</th>
<th>Correlation of serum drug conc &amp; efficacy/tox in humans</th>
<th>Efficacy/toxicity delayed/diff to measure</th>
<th>Assay Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>— / ✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Biopharmaceutical Differences of the Azoles

**Aqueous solubility**

- Fluconazole pKₐ 2
- Voriconazole pKₐ 1.63
- Itraconazole pKₐ 3.7, log P 9.66
- Posaconazole pKₐ 3.6, log P 3

**Lipid solubility**

Lewis R.E.
## Cytochrome P450 Inhibition Potential

<table>
<thead>
<tr>
<th>Drug</th>
<th>CYP3A4</th>
<th>CYP2C8/9</th>
<th>CYP2C19</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inhibitor</td>
<td>Substrate</td>
<td>Inhibitor</td>
</tr>
<tr>
<td>Fluconazole(^2,3)</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Itraconazole(^2,3,4)</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Voriconazole(^3,5,6)</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Posaconazole(^1)</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* ++ minimal activity
  * ++ moderate activity
  * +++ strong activity

Dodds-Ashley ES et al. CID. 2006; 43(suppl 1):S28-39
**Fluconazole**

- **ADME Patient Variability (minimal)**
  - Absorption: >90%
  - Not affected by food or gastric pH
  - Distribution: 11% protein binding
  - VD 0.6-0.9 L/Kg; widely distributed into body fluids and CSF
  - Metabolized: minimal liver (11%)
  - Excretion: Kidney (80% unchanged)
    - Adjust for renal impairment

- **Drug Concentration vs. toxicity**
  - Not established

- **Drug concentration vs. efficacy**
  - Antifungal Activity
    - AUC/MIC (≥ 25)
    - S-DD
  - Linear kinetics
    - PREDICTABLE

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**Fluconazole S-DD**

Fluconazole: Correlation of dose, peak levels, and breakpoints

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Peak Plasma Level (µg/mL)</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>6</td>
<td>&lt;8</td>
</tr>
<tr>
<td>400</td>
<td>20-30</td>
<td>16-32</td>
</tr>
<tr>
<td>800</td>
<td>40-60</td>
<td>&gt;64</td>
</tr>
</tbody>
</table>


Rex JH et al. *CID*. 1997;24:235-247
Fluconazole- Need to Monitor?

• Cannot be justified because...
  – PK predictable in most patients
  – Inter-patient variability low
  – Relatively wide therapeutic index

• However, appropriate dosing is important
  – S-DD Candida species
  – Weight-based dosing
    • 6 mg/kg/day – 12 mg/kg/day

Itraconazole
Itraconazole

• ADME Patient Variability
  ✓ Absorption ~ 50%
    • Dissolution (inadequate)
      • Highly lipophilic & insoluble in water
      • Weak base – ionized at low pH
    • Pre-systemic Intestinal Metabolism
      • P-glycoprotein (inhibitor & substrate)
      • CYP450-3A4 (inhibitor & substrate)
  ✓ Distribution
    • >99% protein bound
    • Vd: 11 L/kg; extensive tissue distribution
  ✓ Metabolism
    • Liver (extensive) CYP3A4
  ✓ Elimination
    • T1/2  β = 24 ± 9 (and 14 hrs for active metabolite)
    • Excretion: hepatic and urine (inactive metabolites)
    • Self-inhibits own metabolism
      • T1/2 ↑ to >30 hrs after 1 week

Lewis R.E. Itraconazole Monograph. www.aspergillus.org.uk
Buchkowsky. S. Ther Drug Monit. 2005;27:322-333

Differences in Itraconazole Formulations

• Capsule
  – Absorption: erratic and variable
    • pH dependent; requires acidic environment
    • Must administer with meal or acidic beverage

• Oral Solution
  – 40% hydroxypropyl-β-cyclodextrin vehicle
  – AUC ↑ 30% (compared to caps)
    • Absorption enhanced in fasted state
    • Not impacted by gastric pH
    • Not effected by antacids

• Intravenous – no longer available
  – Bypass dissolution/absorption

Lewis R.E. Itraconazole Monograph. www.aspergillus.org.uk
Andes D et al. AAC. 2009; 53(1):24-34
Drug Interactions that Contribute to Suboptimal Concentrations

<table>
<thead>
<tr>
<th>Problem</th>
<th>Mechanism</th>
<th>Suggested Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pH interactions (cap)</strong></td>
<td>Decreased dissolution of capsule results in decreased absorption</td>
<td>- Change to solution formulation</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td></td>
<td>- Avoid taking antacids within 2 hours of itraconazole capsules</td>
</tr>
<tr>
<td>- H2 antagonists, PPI,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>antacids, didanosine tabs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease State</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Chemo-associated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypochlorhydra, GVHD,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>neutropenia/mucositis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Complexation/Chelation</strong></td>
<td>Complexation w/ metal ions ↓ transport across intestinal epithelium resulting in ↓ abs.</td>
<td>- Avoid taking binding agents within 2 hours of itraconazole dose</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Sucralfate, MVI, antacids</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Increased Clearance</strong></td>
<td>Induction of CYP-3A4 metab. results in decrease in plasma Cmax, AUC, &amp; T1/2</td>
<td>- Avoid concomitant use</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td></td>
<td>In con’t tx – ↑ itra dose and monitor levels</td>
</tr>
<tr>
<td>- Rifampin, Rifabutin, CBZ</td>
<td>May last 1-2 wks after d/c</td>
<td></td>
</tr>
<tr>
<td>Phenytion, Phenobarbital,</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Itraconazole

✓ Significant concentration variability
  - Treatment population vs. healthy volunteers
    • Coefficients of variation of 83-115% vs. 47%
  - Lower trough concentrations
    • Acute leukemia, BMT, AIDS

✓ Drug concentration vs. efficacy
  - Optimal antifungal activity: AUC/MIC
  - Higher probability of treatment response w/ ↑ trough
    • Treatment
      - Bioassay: trough > 6 mcg/mL
      - HPLC: trough > 1-2 mcg/mL (> 0.5 mcg/mL oral candidiasis)
    • Prophylaxis
      - HPLC: trough > 0.5 mcg/mL

Hardin TC. et al. AAC. 1988; 32:1310-1313
Andes D. et al. AAC. 2009; 53:24-34
Itraconazole
Antifungal Prophylaxis in Neutropenic Patients

Concentration / Toxicity Relationship

• Drug concentration vs. toxicity (?)
  – Bioassay serum concentrations > 17 mcg/mL associated with increased risk of toxicity (86% vs. 31%)
    • GI and peripheral edema

• Adverse Effects
  – Common:
    • GI: N/V/D, abdominal pain, anorexia (esp. soln.)
    • Skin rash
    • Reversible increase in hepatic enzymes
  – More severe:
    • CHF
    • Idiosyncratic hepatic failure

Lestner JM et al. CID. 2009; 49: 928-930
Lewis R.E. Itraconazole Monograph. www.aspergillus.org.uk

Itraconazole Concentration/Toxicity

Lestner JM et al. CID. 2009; 49: 928-930
Optimizing Itraconazole Therapy

Loading Dose
- Yes
  - Itra soln: 200mg Q12H AC
  - PLUS
  - Itra caps: 200mg Q6H with meal x 7 days

- No
  - Itra oral soln: 200mg q12

Oral Maintenance:
- Soln: 200mg BID
- Cap: 200mg BID

When should we monitor?

CONSIDER CHECKING PLASMA CONCENTRATIONS:
- Trough concentration after 4-7 days of therapy and thereafter
- Breakthrough fungal infection expected or lack of tx response
- New med started that may alter Itra metab (3A4 inducer)
- Change of Itra formulation during maintenance therapy
- During or immediately following chemo cycles
- Poor oral absorption expected
- GVHD or mucocytis

Voriconazole
Voriconazole

- ADME Patient Variability
  - Absorption
    - Rapid
    - BA: 96% (1 hr before or after meals)
    - Pre-systemic Intestinal Metabolism
      - P-glycoprotein (substrate)
      - CYP450 (inhibitor & substrate)
  - Distribution
    - 58% protein binding
  - Metabolism
    - Intestine (CYP450)
    - Liver (extensive)
      - CYP 2C19 (major), 3A4, 2C9
  - Elimination
    - $T_1/2 = 6-7$ hrs (dose dependent)
    - Non-linear PK
    - Excreted in urine and feces


Genetic Polymorphism

- CYP 2C19 Metabolism
  - Extensive Metabolizers
    - Homozygous
      - 4-fold lower drug exposures compared to poor
    - Heterozygous
      - 2-fold lower drug exposures compared to poor
  - Poor Metabolizers
### Genetic Polymorphisms

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Caucasian</th>
<th>Black</th>
<th>Japanese</th>
<th>Chinese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous poor metabolizer</td>
<td>2%</td>
<td>2%</td>
<td>19%</td>
<td>14%</td>
</tr>
<tr>
<td>Heterozygous extensive metabolizer</td>
<td>26%</td>
<td>28%</td>
<td>46%</td>
<td>43%</td>
</tr>
<tr>
<td>Homozygous extensive metabolizer</td>
<td>73%</td>
<td>70%</td>
<td>35%</td>
<td>43%</td>
</tr>
</tbody>
</table>


### Non-linear PK

Purkins L et al. AAC. 2002;46 (8):2546-2553.
Voriconazole

✓ Significant concentration variability
  – In both treatment population and healthy volunteers
    • IV and oral formulations
  – Lower trough concentrations (higher doses necessary)
    • BMT, solid transplant patients, hematologic malignancies

✓ Drug concentration vs. efficacy
  – Optimal antifungal activity: AUC/MIC
  – Higher probability of treatment response w/ ↑ trough
    • Treatment
      – HPLC: trough > 1-2 mcg/mL
    • Prophylaxis
      – HPLC: trough > 0.5 mcg/mL

Andes D. et al. AAC. 2009; 53(1): 24-34

Concentration/Clinical Efficacy

• Denning et al.
  – 122 immunosuppressed patients
    • Plasma concentrations obtained
  – Results:
    • 5 patients – mean plasma conc <250 ng/ml
      – 1/5 stable response
      – 3/5 failed to respond
      – 1/5 deteriorated
      » Improved upon dose escalation achieving partial response
    • 6 patients – mean plasma conc 250-500 ng/ml
      – 1/6 Complete response
      – 2/6 partial response
      – 2/6 stable response
      – 1/6 failed to respond
      80% success
    • Found broad trough conc range
      – <100-9700 ng/ml in different patients

Denning W. et al. CID. 2002;34:563-71
Voriconazole Concentration/Efficacy

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

Concentration / Toxicity Relationship

- Correlation between drug conc and toxicity
  - Adverse Effects
    - Visual disturbance (reversible, self-limited)
      - Enhanced light perception, blurred vision, photophobia, or color vision changes
      - Occur w/in 30 min of dose during the first week of therapy
    - Hepatic enzyme elevation
      - Risk ↑ 7-17% for every 1 mcg/mL increase in vori conc
    - Neurologic symptoms (reversible)
      - Recent review identified 4/52 patients developed encephalopathy due to elevated vori conc > 5.5 mcg/mL
Voriconazole Monitoring

- Trifilio S. et al.
  - Retrospective analysis (Nov 2002-Nov 2003)
    - 25 patients (all PO)
      - 22 pts: 200mg PO BID
        » 4/22 dose increased to 300 mg PO BID
      - 2 pts: LD 400mg PO BID, MD 200mg PO BID
      - 1 pt: 300mg PO BID
  - Results:
    - High patient variability
    - Disproportional dose-concentration relationship
    - Correlation between Vori levels and AST and Alk Phos
    - No correlation between Vori levels and Scr
  - Conclusion:
    - It is desirable to have trough levels >0.5 μg/ml
    - Additional work required to address issue
      - Could not show obvious relationship between mg/kg dose and levels


Voriconazole Levels
(Pts with >1 level assessed)

## Voriconazole Levels

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Initial 200mg BID</th>
<th>300mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>41</td>
<td>25</td>
<td>34</td>
</tr>
<tr>
<td>Range</td>
<td>0.2-6.8</td>
<td>0.2-6.8</td>
<td>0.6-6.6</td>
</tr>
<tr>
<td>Median</td>
<td>1.6</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Mean</td>
<td>2.1</td>
<td>1.9</td>
<td>2.0</td>
</tr>
<tr>
<td>S.D</td>
<td>1.8</td>
<td>1.6</td>
<td>1.8</td>
</tr>
<tr>
<td>&lt;0.5μg/ml</td>
<td>6 (15%)</td>
<td>3 (12%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>&lt;1.0μg/ml</td>
<td>15 (37%)</td>
<td>10 (40%)</td>
<td>14 (41%)</td>
</tr>
</tbody>
</table>


## Effect of Voriconazole on AST and Alk. Phos.

Voriconazole Monitoring

• Smith J., et al.
  – Retrospective review from 2002-2005
    • 28 patients
      – Received ≥1 Voriconazole concentration
      – Received a LD and subsequent MD of 200mg PO BID
      – Reasons for concentration determinations
        » 17 pts: disease progression
        » 11 pts: toxicity
  – Results:
    • Pts with disease progression:
      – All 17 pts had serum concentrations <2.51 μg/ml
        » 8/17 pts died of IA
        » 11/17 dose inc. (8 survived)
    • Breakpoint determination: 2.05 μg/ml
      – >2.05 μg/ml: positive response 10/10 (100%)
      – <2.05 μg/ml: positive response 10/18 (55%)
  – Conclusion:
    • Clinical failure may be related to sub-therapeutic drug exposure
    • Escalate dose for conc <2.0 μg/ml

Smith J. et al. AAC. 2006;50(4):1570-1572

Voriconazole Monitoring
Who should be targeted?

• Voriconazole PO
  – Poor absorption
    • Mucositis, GVHD
  – IV to PO switch (weight based dose to fixed dose)

• Voriconazole IV or PO
  – Determine if measurable concentrations are present
    • High risk pts: BMT, solid organ transplant, hematologic malignancies
  – Lack of treatment response / breakthrough fungal infection
  – Concomitant therapy w/ CYP450 inducers
    • CYP2C19, 3A4, or 2C9
  – Monitoring “chronic” therapy in outpatient setting (?)
  – Persistent increase in serum transaminases
  – Unexplained neurologic symptoms
Posaconazole

• ADME Patient Variability
  ✓ **Absorption** (only PO)
    • Dissolution
      • Highly lipophilic & insoluble in water
      • Weak base – ionized at low pH
    • Saturable absorption (800 mg/day)
      • ↑ dosing frequency
      • Requires high fat meal
  • Distribution
    • >98% protein bound
  • Metabolism
    • Liver (minimal ~ 15%)
    • UDP Glucuronidation
    • Inhibits CYP3A4
  • Elimination
    • $T_{1/2 \beta} = 35$ hrs
    • Excreted feces (71%), urine (14%)
      • Majority eliminated as parent drug (66%)

Saturable Absorption


Effect of Food

- Courtney et al.
  - 20 healthy male patients
    - Received 200mg/5ml suspension
      - High fat breakfast (841 cal, 52% fat)
      - Non-fat breakfast (461 cal, 0% fat)
      - Fasting (10hrs)
  - Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>High Fat Meal</th>
<th>Non-Fat Meal</th>
<th>Fasted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>512</td>
<td>378</td>
<td>132</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>4.8</td>
<td>4.1</td>
<td>5.0</td>
</tr>
<tr>
<td>AUC (0,72 hr)</td>
<td>13885</td>
<td>9511</td>
<td>3553</td>
</tr>
<tr>
<td>(ng/ml/hr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1/2 (hr)</td>
<td>23.0</td>
<td>22.2</td>
<td>23.5</td>
</tr>
</tbody>
</table>

Optimizing Posaconazole Absorption


Posaconazole

- Significant concentration variability
  - More pronounced in treatment population
    - Gastric mucosal alteration, ↓ food intake (mucositis), acid-suppression
  - Lower trough concentrations
    - Concentrations 52% lower in allogeneic BMT patients
    - Large coefficient of variation

- Drug concentration vs. efficacy
  - Optimal antifungal activity: AUC/MIC
  - Higher probability of treatment response w/ ↑ trough
    - Treatment
      - Trough > 0.5 – 1.5 mcg/mL
    - Prophylaxis
      - Trough > 0.5 mcg/mL
Concentration / Toxicity Relationship

- Drug concentration vs. toxicity
  - Not been identified

- Adverse Effects
  - Common
    - GI: nausea, vomiting, diarrhea, abdominal pain, anorexia
  - Less common
    - Rash
    - Increased hepatic liver enzymes
    - Headache, dizziness, fatigue


Posaconazole Concentration/Efficacy

- Walsh T. et al (open label salvage trial)
  - 67 patients
    - Available posaconazole plasma concentrations
  - Results
    - Higher plasma conc associated w/ higher response rates
    - Differences between the highest and lowest quartile
      - Proportion of pts w/ GI dysfunction, TPN use, impaired dietary intake, missing >10% dose

<table>
<thead>
<tr>
<th>Quartile</th>
<th>No. of Subj.</th>
<th>Plasma Cmax Mean ng/ml</th>
<th>CV, %</th>
<th>Plasma Cave Mean ng/ml</th>
<th>CV, %</th>
<th>No. (%) Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>142</td>
<td>51</td>
<td>134</td>
<td>45</td>
<td>4 (24)</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>467</td>
<td>27</td>
<td>411</td>
<td>21</td>
<td>9 (53)</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>852</td>
<td>15</td>
<td>719</td>
<td>12</td>
<td>9 (53)</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>1480</td>
<td>16</td>
<td>1250</td>
<td>28</td>
<td>12 (75)</td>
</tr>
</tbody>
</table>

Walsh T.J. et al. CID. 2007;44:2-12
Posaconazole Concentration/Efficacy

- 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 plasma concentrations < 700 ng/mL

**Table 1.** Posaconazole steady-state average plasma concentrations (C_{avg}) vs. clinical failure rate following administration of POS 300 mg q.d. in hematopoietic stem cell transplant recipients also receiving immunosuppressive therapy for graft-vs.-host disease (study 1) and in patients undergoing chemotherapy for acute leukemia or myelodysplastic syndromes (study 2)

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Posaconazole C_{avg} (ng/mL)</th>
<th>Clinical failure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Q</td>
<td>21.5-55.7 (289)</td>
<td>44% (26/60)</td>
</tr>
<tr>
<td>2nd Q</td>
<td>57.7-91.5 (189)</td>
<td>21% (13/63)</td>
</tr>
<tr>
<td>3rd Q</td>
<td>91.5-156 (1339)</td>
<td>18% (11/63)</td>
</tr>
<tr>
<td>4th Q</td>
<td>1,563-3,650 (2,967)</td>
<td>18% (11/63)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study 2 (N = 215)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Posaconazole C_{avg} (ng/mL)</td>
<td>Clinical failure rate</td>
</tr>
<tr>
<td>89.65-322 (306)</td>
<td>55% (26/60)</td>
</tr>
<tr>
<td>322-490 (406)</td>
<td>37% (20/54)</td>
</tr>
<tr>
<td>490-733.5 (612)</td>
<td>46% (25/54)</td>
</tr>
<tr>
<td>733.5-2,200 (1,667)</td>
<td>28% (15/54)</td>
</tr>
</tbody>
</table>

Cornely OA et al. NEJM. 2007; 356:348-359
Ullman AJ et al. NEJM. 2007; 356:335-347

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Optimizing Posaconazole Therapy

**Posaconazole**
- **Susp:** 200mg q6hrs
- **Soln:** 400mg q12hrs

- Poor oral intake
- Pt stable or D/C home and has adequate oral abs
- YES - high fat meals

When should we monitor?

**Consider checking plasma concentrations:**
- Trough concentration after 4-7 days of therapy and thereafter
- Lack of treatment response / breakthrough fungal infection
- Poor oral absorption suspected (mucositis, GVHD, vomiting)
- Impaired dietary intake
- Change in dosing regimen
- Addition of an interacting medication, e.g. acid-suppressant

Andes D. et al. AAC. 2009; 53:24-34
Serum Drug Monitoring
Azoles Summary

<table>
<thead>
<tr>
<th>Azole</th>
<th>Target Range</th>
<th>Timing of Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>Treatment: &gt; 1 µg/ml&lt;br&gt;Prophylaxis: &gt; 0.5 µg/ml</td>
<td>Trough after 4-7d of therapy</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Treatment: &gt; 1-2 – 6 µg/ml&lt;br&gt;Prophylaxis: &gt; 0.5 – 6 µg/ml</td>
<td>Trough after 4-7d of therapy</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Treatment: &gt; 0.5- 1.5 µg/ml&lt;br&gt;Prophylaxis: &gt; 0.5 µg/ml</td>
<td>Trough or Random after 4-7 d of therapy</td>
</tr>
</tbody>
</table>

Andes D. et al. AAC. 2009; 53:24-34

<table>
<thead>
<tr>
<th>Azole</th>
<th>Lab</th>
<th>Location</th>
<th>Assay Type</th>
<th>Turn Around</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>Mayo Med Labs</td>
<td>Rochester, MN</td>
<td>HPLC</td>
<td>4-7 days</td>
<td>$150.20</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Mayo Med Labs</td>
<td>Rochester, MN</td>
<td>LS-MS</td>
<td>4-7 days</td>
<td>$159</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Mayo Med Labs</td>
<td>Rochester, MN</td>
<td>LC-MS</td>
<td>4-7 days</td>
<td>$159</td>
</tr>
</tbody>
</table>
Conclusions

• Due to high rates of mortality with invasive fungal infections, it is imperative to utilize antifungal agents appropriately
  – Optimize dose per PK/PD indices
• Therapeutic drug monitoring can aid the clinician in individualizing drug therapy and reduce risk of failure
• Data supports targeted TDM for 4 antifungal agents
  – Flucytosine, Itraconazole, Voriconazole, Posaconazole
• Currently there are limited amount of specialized labs that perform these assays
• Further studies are needed to
  – Identify optimal timing of antifungal drug monitoring
  – Better delineate targeted monitoring for specific populations and infection sites

Questions