Voriconazole Paediatric Dose: an Example

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Outline of Presentation

• Current voriconazole (Vfend®) adult dosing

• Derivation of paediatric doses
  – data gathered
  – analyses performed
  – interpretations drawn
  – mechanistic implications

• Current voriconazole (Vfend®) paediatric dosing within EU
Vfend® Adult Labelling

- **Adult dosing for invasive aspergillosis**
  - 6 mg/kg IV q12h for first 24h as loading dose
  - 4 mg/kg IV q12h as maintenance dose
  - 200 mg PO q12h as maintenance dose

- **Adult dosing for candidemia**
  - 6 mg/kg IV q12h for first 24h as loading dose
  - 3-4 mg/kg IV q12h as maintenance dose
  - 200 mg PO q12h as maintenance dose

- PO maintenance dosage adjustment possible to 300 or 100 mg q12h

- Voriconazole (Vfend®) is a valuable but complex and challenging compound, from a PK perspective
# Pfizer Paediatric Model Derived Dosing Approach

## Adult data analysis
- N=11 P1 studies
- N=236 subjects
- N=2313 samples
- Completed in 2000

**Non linear PK**
- Intrinsic PK for label
  - CYP2C19 (most influential), gender and age important
  - High Bioavailability
- Japan bridging

## Ped. data analysis
- N=2 studies
- N=35 subjects
- N=355 samples
- Completed in 2001

**Linear PK**
- Intrinsic PK for label
  - Comparable dose to adult 3 mg/kg
  - CYP2C19 (most influential), liver enz. weight important
(Predicted) PK Exposures in Paediatrics and Adults

<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>

* model based analysis of 35 subjects from SD and MD PK studies
** model based analysis of 236 healthy volunteers from SD and MD PK studies

1.33 fold dose inc.

1.33 fold

2.78 fold
Some Pharmacokinetic Principles

- Intravenous

\[ CL = \frac{Dose}{AUC} \]

CL = clearance, F = bioavailability, AUC = area under the curve
Dosing Strategy for Subsequent Paediatric Study

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

**Interim analysis**
(minimum 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)
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### Adult data analysis
- Non linear PK
- Intrinsic PK for label CYP2C19 (most influential), gender and age important
- High Bioavailability
- Japan bridging

### Ped. data analysis
- Linear PK
- Intrinsic PK for label CYP2C19 (most influential), liver enz. weight important
- Comparable dose to adult 3 mg/kg

### Ped. data analysis
- Non linear PK
- Cohort 2 1037
- KM different
- CYP2C19 (most influential), liver enz. weight important
- Less Bioavailability
Model predicted voriconazole AUC\(\text{tau}\) given nominal dosing schedules (n=47)

<table>
<thead>
<tr>
<th>Median AUC(\text{tau}) (ng(\cdot)h/ml)</th>
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<tr>
<td><strong>Cohort I</strong></td>
</tr>
<tr>
<td>(6, 4, 6, 4)*</td>
</tr>
<tr>
<td>13410</td>
</tr>
<tr>
<td>24710</td>
</tr>
<tr>
<td>5710</td>
</tr>
<tr>
<td><strong>Cohort IIA</strong></td>
</tr>
<tr>
<td>(6, 6, 8, 6)*</td>
</tr>
<tr>
<td>24730</td>
</tr>
<tr>
<td><strong>Cohort IIB</strong></td>
</tr>
<tr>
<td>(6, 5, 4, 5)*</td>
</tr>
<tr>
<td>18060</td>
</tr>
<tr>
<td>5710</td>
</tr>
<tr>
<td>7350</td>
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*Denotes the mg/kg q12h doses Day 1 (iv), days 2-4 (iv), days 5-8 (iv/po) and days 8-12 (po)
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- **Non linear PK**
  - Intrinsic PK for label CYP2C19 (most influential), gender and age important
  - High Bioavailability
  - Japan bridging

- **Linear PK**
  - Intrinsic PK for label CYP2C19 (most influential), liver enz.
  - weight important

- **Non linear PK**
  - Cohort 2 1037
  - KM different
  - Comparable dose to adult 3 mg/kg
  - CYP2C19 (most influential), liver enz.
  - weight important
  - Less Bioavailability

- **Non linear PK**
  - Comparable dose to adult 4mg/kg
  - IV and 200mg PO
  - KM different
  - CYP2C19 (most influential), liver enz.
  - weight important
  - Less Bioavailability
  - Variance structure
Analysis Concentration Data (1)
Analysis Concentration Data (2)
Adult Reference Distribution – Different Criterion Required?
Criteria Adopted to Assess Dosing Recommendations

• In broadening criteria from median to the entire distribution the dosing recommendations had to balance the following:
  - maintaining concordance with ICH guidelines which seeks comparable AUC in children and adults at the central tendency (median)
  - *but* not over or under exposing individuals at other points of the distribution relative to adults
  - recognizing differing degree of confidence in the predictions of medians compared to tails
• What can be defined as “over” or “under” exposure in this case?
  - sought consistency with the adult label
    - largest magnitude of a change in AUC resulting from co-administration of another compound that *did not* warrant a dosage alteration 41%
    - smallest magnitude of a change in AUC resulting from co-administration of another compound that *did* warrant a subsequent dosage alteration 70%
  - led to a “single point” criteria of 50% used to evaluate effects upon AUC distribution
• In the reference adults (n=236) 4 mg/kg IV bid has CV 83% n AUC
  - achieving concordance for across percentiles of the entire paediatric AUC distribution is very challenging
7 mg/kg IV provides acceptable concordance
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- **Non linear PK**: Intrinsic PK for label, CYP2C19 (most influential), gender and age important.
- **High Bioavailability**: J apan bridging.
- **Linear PK**: Intrinsic PK for label, Comparable dose to adult 3 mg/kg, CYP2C19 (most influential), liver enz. weight important.
- **Comparable dose to adult 4mg/kg**: IV and 200mg PO.
- **KM different**: CYP2C19 (most influential), liver enz. weight important, Less Bioavailability.
- **Less Bioavailability**: Variance structure, Complex Bioavailability.
- **EU approval**:
Oral mg/kg does not provide acceptable concordance
Fixed mg does provide acceptable concordance
Oral dose Justification

• An age/weight interaction on bioavailability exists
• Some potential explanations why such an effect may be most pronounced in children, but not adults:
  – Children have a higher Km than adults
    • less saturation of metabolism at similar concentrations compared to adults
  – The hepatic blood flow (per kg bodyweight) is higher in children than in adults
    • for the same mg/kg oral dose, the concentration entering the liver from the absorption site will be lower in children
• 200mg bid oral dosage applicable across the entire weight range
  – For higher body weight subjects, with high bioavailability (consistent with adults), an oral dose of 200mg bid is equivalent to adults
  – For lower body weights subjects, with low bioavailability (inconsistent with adults), the 200mg bid dose provides a higher “effective mg/kg dose” compensating for the low bioavailability in these individuals
Vfend® Paediatric Dosing Recommendations

• From previous analysis of voriconazole paediatric data 4mg/kg q12h IV comparable to 3mg/kg q12h IV in adults
  - Higher IV maintenance dose due to higher elimination capacity in paediatric patients (greater liver mass to body mass ratio)
• 7mg/kg q12h IV comparable to 4mg/kg q12h IV in adults
  - Larger dose differential due to different degree of non-linearity in voriconazole pharmacokinetics
• 200mg q12h PO comparable to 200mg q12h PO in adults
  - For oral administration in paediatrics, an additional consideration (lower oral bioavailability)