Are We Really Going to Buy Into

Individualized Dosing?

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One of my patients...

- 45 year-old HIV+ woman
- Long history of medication intolerance
- Started a fos-amprenavir containing regimen (without ritonavir), 2 x 700 mg tablets twice daily (total 2800 mg/day).
  - Daytime fatigue, which she attributed to the morning dose
  - Enquired about taking the entire dose at night, otherwise does not wish to continue.
Patient 1 Options

• Tell her the problem is in her head and press on.
• Change to 4 tablets every evening, informing her that you hope it is sufficient to maintain virologic control without new (worse?) side effects.
• Change medications, yet again.
• Measure amprenavir concentration(s) and attempt rational drug management
Patient 1 Data

- On the standard dose of 1400 mg bid, a serum amprenavir concentration of 1.4 mg/L was measured 4.5 hours after her previous dose (1 week turnaround time).
- Resistance testing indicated no resistance to amprenavir.
- Target amprenavir trough for wild-type virus suggested to be 0.23 to 0.4 mg/L.
- Can she take all 4 pills at night???
First fit

0.27 mg/L
Once daily dosing

43.5 grams
Every 12 h

2100 mg

700 mg

0.11 mg/L
Every 10, 14 h
Results!

0.26 mg/L
A second patient...

- 18 year old woman, taking atazanavir 400 mg once daily
- Repeatedly swears that she is taking it
- Yet bilirubin is normal, viral load is 30,000 copies/mL, CD4+ cell count is <20 cells/mL
- Level 18 hours after dose is <10 ng/mL. Could she have taken it?
No way!
Overcoming Challenges to Precision Dosing
Patient-Level Challenges

- 30% vancomycin troughs are appropriately timed
- All undetectable voriconazole was after outpatient dosing
- 98% inter- and 66% intra-individual variability in voriconazole AUC among children <2 years of age
"Clinical Pharmacometrics" is the application of quantitative modeling and simulation tools for the purpose of optimizing therapy in an individual patient.
Patient-Level Solutions – Clinical PMx

- Robust to timing of samples
- Model probability of adherence
- Control inter- and compensate for intra-individual variability
Process challenges

- Rapidly available drug concentrations
- Poorly defined concentration targets
- Reimbursement
- Formulation restrictions
- Software tools
- Lack of expertise
Process solutions

HPLC, immuno, LC-MS, field sampling, wearables

Studies, package insert

Novel formulations

More on this...

More on this...

Training
Payment (USA)

- Z51.81 – Any therapeutic drug monitoring
- Z79.xxx – Specific long term therapy
  - E.g. Z79.2 long term (current) use of antibiotics
- Code for underlying diagnosis
- Must be in the context of a face-to-face encounter with the patient
  - Physicians use Evaluation/Management (E/M) codes
  - Pharmacists use Medication Therapy Management (MTM) codes
Regulation

Path for software marketing approval

Approved doses or exposures?
Current thinking

  • Section IV, A: Examples of CDS Functions that are not Devices
    • Line 290: Software that provides health care professionals with recommendations on the use of a prescription drug that are consistent with the FDA-required labeling.
Predicting/forecasting
Optimizing/recommending
How do we change the label?

“Patients may require dosages other than those listed in Sections 2 (Dosage and Administration) and 8 (Use in Specific Populations) to achieve acceptably safe and effective concentrations within the range of those studied and reported in Section 12 (Clinical Pharmacology). Dosage adjustments should be based upon measured drug concentrations and/or relevant patient characteristics.”
What PK data should be in PI?

• CFR § 201.57(c)(13)(i)(C) governing content of PK section for package inserts:
  • 12.3 Pharmacokinetics. This subsection must describe the clinically significant pharmacokinetics of a drug or active metabolites, (i.e., pertinent absorption, distribution, metabolism, and excretion parameters). Information regarding bioavailability, the effect of food, minimum concentration (Cmin), maximum concentration (Cmax), time to maximum concentration (Tmax), area under the curve (AUC), pertinent half-lives (t1/2), time to reach steady state, extent of accumulation, route(s) of elimination, clearance (renal, hepatic, total), mechanisms of clearance (e.g., specific enzyme systems), drug/drug and drug/food (e.g., dietary supplements, grapefruit juice) pharmacokinetic interactions (including inhibition, induction, and genetic characteristics), and volume of distribution (Vd) must be presented if clinically significant.
What PK data ARE there?

<table>
<thead>
<tr>
<th></th>
<th>Adult n=50</th>
<th>Peds n=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax*</td>
<td>40</td>
<td>7</td>
</tr>
<tr>
<td>Cmax*</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>AUC*</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Vd*</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Time-con curve</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Cmin*</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>CL*</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>Thalf*</td>
<td>44</td>
<td>23</td>
</tr>
</tbody>
</table>

*Named in CFR

• Reviewed package inserts of 50 drugs for which FDA granted pediatric exclusivity under BPCA and relabeled
• Excluded topical agents and those with no discussion of pediatric dosing
• Abstracted from the pharmacokinetics sub-section in the clinical pharmacology section
What guidance is there?

• FDA Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format, December 2016
  • Descriptive and generally without specific data items, e.g. guidance on Absorption section does not mention either Tmax or Cmax
### Table 1. Mean (Standard Deviation) Pharmacokinetic Parameters of Linezolid in Adults

<table>
<thead>
<tr>
<th>Dose of Linezolid</th>
<th>$C_{\text{max}}$ $\mu$g/mL</th>
<th>$C_{\text{min}}$ $\mu$g/mL</th>
<th>$T_{\text{max}}$ hrs</th>
<th>AUC $\upmu$g$ \cdot$ h/mL</th>
<th>$t_{1/2}$ hrs</th>
<th>CL $\text{mL/min}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>400 mg tablet</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>single dose</td>
<td>8.10</td>
<td>---</td>
<td>1.52</td>
<td>55.10</td>
<td>5.20</td>
<td>146</td>
</tr>
<tr>
<td></td>
<td>(1.83)</td>
<td>(1.01)</td>
<td></td>
<td>(25.00)</td>
<td>(1.50)</td>
<td>(67)</td>
</tr>
<tr>
<td>every 12 hours</td>
<td>11.00</td>
<td>3.08</td>
<td>1.12</td>
<td>73.40</td>
<td>4.69</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>(4.37)</td>
<td>(2.25)</td>
<td></td>
<td>(33.50)</td>
<td>(1.70)</td>
<td>(49)</td>
</tr>
<tr>
<td><strong>600 mg tablet</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>single dose</td>
<td>12.70</td>
<td>---</td>
<td>1.28</td>
<td>91.40</td>
<td>4.26</td>
<td>127</td>
</tr>
<tr>
<td></td>
<td>(3.96)</td>
<td>(0.66)</td>
<td></td>
<td>(39.30)</td>
<td>(1.65)</td>
<td>(48)</td>
</tr>
<tr>
<td>every 12 hours</td>
<td>21.20</td>
<td>6.15</td>
<td>1.03</td>
<td>138.00</td>
<td>5.40</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>(5.78)</td>
<td>(2.94)</td>
<td></td>
<td>(42.10)</td>
<td>(2.06)</td>
<td>(29)</td>
</tr>
<tr>
<td><strong>600 mg IV injection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>single dose</td>
<td>12.90</td>
<td>---</td>
<td>0.50</td>
<td>80.20</td>
<td>4.40</td>
<td>138</td>
</tr>
<tr>
<td></td>
<td>(1.60)</td>
<td>(0.10)</td>
<td></td>
<td>(33.30)</td>
<td>(2.40)</td>
<td>(39)</td>
</tr>
<tr>
<td>every 12 hours</td>
<td>15.10</td>
<td>3.68</td>
<td>0.51</td>
<td>89.70</td>
<td>4.80</td>
<td>123</td>
</tr>
<tr>
<td></td>
<td>(2.52)</td>
<td>(2.36)</td>
<td></td>
<td>(31.00)</td>
<td>(1.70)</td>
<td>(40)</td>
</tr>
<tr>
<td><strong>600 mg oral suspension</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>single dose</td>
<td>11.00</td>
<td>---</td>
<td>0.97</td>
<td>80.80</td>
<td>4.60</td>
<td>141</td>
</tr>
<tr>
<td></td>
<td>(2.76)</td>
<td>(0.88)</td>
<td></td>
<td>(35.10)</td>
<td>(1.71)</td>
<td>(45)</td>
</tr>
</tbody>
</table>

* AUC for single dose = AUC$_{\text{ss}}$; for multiple-dose = AUC$_{\text{D}}$.

† Data dose-normalized from 375 mg

‡ Data dose-normalized from 625 mg. IV dose was given as 0.5-hour infusion.

$C_{\text{max}}$ = Maximum plasma concentration; $C_{\text{min}}$ = Minimum plasma concentration; $T_{\text{max}}$ = Time to $C_{\text{max}}$; AUC = Area under concentration-time curve; $t_{1/2}$ = Elimination half-life. CL = Systemic clearance.
Figure 1. Plasma Concentrations of Linezolid in Adults at Steady-State Following Oral Dosing Every 12 Hours (Mean ± Standard Deviation, n=16)
Table 2. Pharmacokinetic Parameters of Linezolid in Pediatrics and Adults Following a Single Intravenous Infusion of 10 mg/kg or 600 mg Linezolid (Mean: (%CV); [Min, Max Values])

<table>
<thead>
<tr>
<th>Age Group</th>
<th>$C_{\text{max}}$ µg/mL</th>
<th>$V_{\text{ss}}$ L/kg</th>
<th>AUC∗ µg*h/mL</th>
<th>$t_{1/2}$ hrs</th>
<th>CL mL/min/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal Patients</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pre-term**&lt; 1 week (N=9)*</td>
<td>12.7 (30%)&lt;br&gt;[9.6, 22.2]</td>
<td>0.81 (24%)&lt;br&gt;[0.43, 1.05]</td>
<td>108 (47%)&lt;br&gt;[41.1, 191]</td>
<td>5.6 (46%)&lt;br&gt;[2.4, 9.8]</td>
<td>2.0 (52%)&lt;br&gt;[0.9, 4.0]</td>
</tr>
<tr>
<td>Full-term***&lt; 1 week (N=10)†</td>
<td>11.5 (24%)&lt;br&gt;[8.0, 18.3]</td>
<td>0.78 (20%)&lt;br&gt;[0.45, 0.96]</td>
<td>55 (47%)&lt;br&gt;[19, 103]</td>
<td>3.0 (55%)&lt;br&gt;[1.5, 6.1]</td>
<td>3.8 (55%)&lt;br&gt;[1.5, 8.8]</td>
</tr>
<tr>
<td>Full-term***≥ 1 week to ≤ 28 days (N=10)‡</td>
<td>12.9 (28%)&lt;br&gt;[7.7, 21.6]</td>
<td>0.66 (29%)&lt;br&gt;[0.35, 1.06]</td>
<td>34 (21%)&lt;br&gt;[23, 50]</td>
<td>1.5 (17%)&lt;br&gt;[1.2, 1.9]</td>
<td>5.1 (22%)&lt;br&gt;[3.3, 7.2]</td>
</tr>
<tr>
<td>Infant Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 28 days to &lt; 3 Months (N=12) †</td>
<td>11.0 (27%)&lt;br&gt;[7.2, 18.0]</td>
<td>0.79 (26%)&lt;br&gt;[0.42, 1.08]</td>
<td>33 (26%)&lt;br&gt;[17, 48]</td>
<td>1.8 (28%)&lt;br&gt;[1.2, 2.8]</td>
<td>5.4 (32%)&lt;br&gt;[3.5, 9.9]</td>
</tr>
<tr>
<td>Pediatric Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months through 11 years** (N=59)</td>
<td>15.1 (30%)&lt;br&gt;[6.8, 36.7]</td>
<td>0.69 (28%)&lt;br&gt;[0.31, 1.50]</td>
<td>58 (54%)&lt;br&gt;[19, 153]</td>
<td>2.9 (53%)&lt;br&gt;[0.9, 8.0]</td>
<td>3.8 (53%)&lt;br&gt;[1.0, 8.5]</td>
</tr>
<tr>
<td>Adolescent Subjects and Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 through 17 years (N=36) ‡</td>
<td>16.7 (24%)&lt;br&gt;[9.9, 28.9]</td>
<td>0.61 (15%)&lt;br&gt;[0.44, 0.79]</td>
<td>95 (44%)&lt;br&gt;[32, 178]</td>
<td>4.1 (46%)&lt;br&gt;[1.5, 8.1]</td>
<td>2.1 (53%)&lt;br&gt;[0.9, 5.2]</td>
</tr>
<tr>
<td>Adult Subjects‡ (N=29)</td>
<td>12.5 (21%)&lt;br&gt;[8.2, 19.3]</td>
<td>0.65 (16%)&lt;br&gt;[0.45, 0.84]</td>
<td>91 (33%)&lt;br&gt;[53, 155]</td>
<td>4.9 (35%)&lt;br&gt;[1.8, 8.3]</td>
<td>1.7 (34%)&lt;br&gt;[0.9, 3.3]</td>
</tr>
</tbody>
</table>

∗ $AUC_{\text{ss}}$ = Single dose $AUC_{\text{ss}}$

** In this data set, “pre-term” is defined as <34 weeks gestational age (Note: Only 1 patient enrolled was pre-term with a postnatal age between 1 week and 28 days)

*** In this data set, “full-term” is defined as ≥34 weeks gestational age

† Dose of 10 mg/kg

‡ Dose of 600 mg or 10 mg/kg up to a maximum of 600 mg

§ Dose normalized to 600 mg

$C_{\text{max}}$ = Maximum plasma concentration; $V_{\text{ss}}$ = Volume of distribution; AUC = Area under concentration-time curve; CL = Systemic clearance normalized for body weight
The Future: Emphasize exposure

- Doses in PI sections 2 and 8 become starting doses
- Standardize reported PK characteristics
- Mandate exposure-response section
- Link to de-identified subject-level data in FDA repository
  - Sponsor companies must share after approval
  - Reasons to withhold are reduced
- Flexible dosing is permissible
Call for a Precision Dosing Advisory group

- **Mission:** To provide regulatory support for precision dosing
- **Method:** Revise/create relevant FDA guidance documents and package insert content
- **Composition/representation**
  - Physician/Pharmacist organizations
  - Academia
  - Medical Software industry
  - Pharmaceutical industry
  - Electronic medical record vendors
  - Insurers
  - Government (regulatory, quality, medical, scientific)
Citations

