Population pharmacokinetics for busy clinicians and active patients: how to get the most out of it?

Alfonso Iorio, MD, PhD
Health Information Research Unit
Hamilton-Niagara Hemophilia Program
McMaster University
• Alfonso Iorio
  – research funding (Baxter, Bayer, Biogen Idec, NovoNordisk, Pfizer)

• WAPPS
  – B-CHERP funding, peer-reviewed grant from the Canadian Hemophilia Society, three years
  – Not supported by any industry funding
WAPPS: vision

Solution: Population PK

Barrier: Number of samples
Population pharmacokinetic
Population pharmacokinetic

Time = 10 hr

Conc

0.53

0.22
Population pharmacokinetic
Single patient data

Web-application

Estimating PK for single individuals on the base of 2-4 samples

Single patient report
Estimating PK for single individuals on the base of 2-4 samples

Online PPK engine (NONMEM)

Web application

Single patient report

Single patient data
Estimating PK for single individuals on the base of 2-4 samples

Online PPK engine (NONMEM)

Control files for bayesian individual estimation

- ADVATE
- KOKENATE
- BENEFIX
- ALPROLIX
- ELOCTATE
- ETC

Brand specific Source individual PK data

Offline PPK modeling

Brand specific PPK models
Web application

Online PPK engine (NONMEM)

Control files for Bayesian individual estimation
- ADVATE
- KOGENATE
- BENEFIX
- ALPROLIX
- ELOCTATE
- ETC

Brand specific Source individual PK data

Brand specific PPK models

Offline PPK modeling

Single patient data

Single patient report

Patients

Patients
Modeling: Base Structural Model

\[ \hat{C}_{pt} = \frac{D}{V} e^{-\frac{CL}{V}\cdot t} \]
Modeling: Base Structural Model

- **Type**: 1-cmt
- **Estimation Method**: FOCE
- **IIV**: Additive
- **Residual Variability**: Exponential, Additive + CCV
- **Model Parameters**: Cl, Vol
- **Assessment**: OBJF Diagnostic plots
The WAPPS network
New Patient Entry

Required Fields
- Gender: M
- Date of Birth:
- Local Patient ID:
- Consent: Informed consent to enter their data into the system

Optional Fields
- Blood Group: N/A
- Baseline Factor Level (U/ml):
- Positive History of Inhibitors:

Save

Patient List

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age</th>
<th>Gender</th>
<th>Blood Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVATE 2</td>
<td>31</td>
<td>M</td>
<td>N/A</td>
</tr>
<tr>
<td>ADVATE 2a</td>
<td>31</td>
<td>M</td>
<td>N/A</td>
</tr>
<tr>
<td>ADVATE1</td>
<td>56</td>
<td>M</td>
<td>N/A</td>
</tr>
<tr>
<td>ADVATE1a</td>
<td>56</td>
<td>M</td>
<td>N/A</td>
</tr>
<tr>
<td>ADVATE1b</td>
<td>58</td>
<td>M</td>
<td>N/A</td>
</tr>
<tr>
<td>Advate3</td>
<td>35</td>
<td>M</td>
<td>N/A</td>
</tr>
<tr>
<td>Advate4</td>
<td>25</td>
<td>M</td>
<td>N/A</td>
</tr>
<tr>
<td>Advate5</td>
<td>53</td>
<td>M</td>
<td>N/A</td>
</tr>
<tr>
<td>Alfonso lori</td>
<td>20</td>
<td>M</td>
<td>N/A</td>
</tr>
<tr>
<td>Alprolix 3</td>
<td>57</td>
<td>M</td>
<td>N/A</td>
</tr>
</tbody>
</table>
### WAPPS: the website

#### Measurement Date/Time
- **Advate**: 45 2000 44.4 2014-09-16 12:00 PM 5 One Stage Coag. (PTT Based) Generic 0

<table>
<thead>
<tr>
<th>Measurement Date/Time</th>
<th>Time Elapsed (h:m)</th>
<th>Concentration</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014-09-16 04:00 PM</td>
<td>4:0</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>2014-09-16 12:00 PM</td>
<td>TBD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Kogenate
- **Kogenate**: 65 3900 60.0 2014-10-02 11:00 AM 0 One Stage Coag. (PTT Based) Drug Specific 0

**Request PK Calculation**
## Pharmacokinetic Estimates

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Half-Life (hr)</strong></td>
<td>10.5 (8 – 13)</td>
</tr>
<tr>
<td><strong>Time to 0.05 IU/ml (hr)</strong></td>
<td>39.5 (36 – 42)</td>
</tr>
<tr>
<td><strong>Time to 0.02 IU/ml (hr)</strong></td>
<td>53.0 (48 – 58)</td>
</tr>
<tr>
<td><strong>Time to 0.01 IU/ml (hr)</strong></td>
<td>63.0 (59 – 67)</td>
</tr>
</tbody>
</table>
# Pharmacokinetic Estimates

## Infusion data used for the assessment:

<table>
<thead>
<tr>
<th>Drug</th>
<th>BW (kg)</th>
<th>Total U</th>
<th>U/kg</th>
<th>Infusion end time</th>
<th>Duration (mins)</th>
<th>Test</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advate</td>
<td>60</td>
<td>2990</td>
<td>49.8</td>
<td>2015-01-23 09:00 AM</td>
<td>0</td>
<td>One Stage Coag. (PTT Based)</td>
<td>Drug Specific</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measurement Date/Time</th>
<th>Time Elapsed (h:m)</th>
<th>Concentration</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-01-23 09:11 AM</td>
<td>0:11</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>2015-01-23 02:10 PM</td>
<td>5:10</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>2015-01-25 07:34 AM</td>
<td>46:34</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

Time to 0.5 PTT (min): (59 – 67)
Disclaimer: This is a research service under development, not yet validated for clinical practice use. Any use of the results of the population pharmacokinetic estimation in the care of individual patients is not recommended and cannot be considered part of the service in this phase. The local investigator is solely responsible for any such use.
Join the WAPPS network at:
www.wapps-hemo.org

Download these slides at:
Hemophilia.mcmaster.ca

Thank you !!!