Individualized treatment for hemophilia: Population pharmacokinetics approach

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I have no personal or financial interests to declare:

I have no financial support from an industry source at the current presentation.
About me

• MSc in Health Research Methodology (2016)
• PhD candidate in Pharmacy (expected 2022)
• Research Coordinator for the WAPPS-Hemo project (PI: Dr. Alfonso Iorio), focusing on our research-related collaborations
• Department of Health Research Methods, Evidence, and Impact (HEI) at McMaster University, Hamilton, ON, Canada
Objectives

• Learn about the scientific background of WAPPS

• Consider why applying popPK is a powerful tool in the treatment of hemophilia

• Understand the benefits of PK-tailored dosing in hemophilia

• See the power of the WAPPS database

• Learn how to use WAPPS and an introduction to myWAPPS
Hemophilia treatment

- Prophylactic factor replacement therapy began in the 1960s
- Was based on the observation that non-severe hemophilia patients do not experience the spontaneous bleeds and joint damage as in severe patients
- No consensus on optimal treatment regimens
PK targets in hemophilia prophylaxis
Patient PK variability

- Because CL and V differ between patients, half-life differs between patients
- Half-life greatly affects the clinically important outcome of
  - Time to 1%
  - Time to 2%
- ‘Time to’ is important because it drives dosing frequency (and dose)

Collins PW et al. Thromb Haemost. 2010;8(2):269-75;
Patient PK variability: half-life differs between patients

Half-lives of FVIII products and their variability

- Xyntha/Refacto: 10.9
- Kogenate: 12.3
- Advate: 10.8
- GreenCross VIII: 13.4
- Fanhdi/Alphanate: 12.4
- Afstyla: 13.3
- NovoEight: 11.8
- Kovaltry: 14.1
Understanding variability to define a dosing strategy

- Patients have similar PK
- Individual PK similar over time

Generic population dose (e.g. 10 mg/kg)

- Maximum concentration
- Minimum effective concentration
Understanding variability to define a dosing strategy

- Patients have different PK
- Individual PK different over time
- Can’t define a safe and effective dose

McMaster Hemophilia Research Group

Closing the Research Gap Drop by Drop
Understanding variability to define a dosing strategy

Patients have different PK
Individual PK similar over time  Individualized dose

Clotting factors

Maximum concentration
Minimum effective concentration

Subject
Why does this matter??

Because knowing a patients’ PK that should be stable over time, we can use it to derive a dose and dosing frequency that will achieve the PK target (e.g., always above 2%)
Once I know a patients’ PK...

• I can simulate what the ideal dose and dosing frequency will be to achieve their PK targets
• I also know that this dosing regimen will be valid for quite a long time (stable PK)
How do we determine a patient’s PK

**Previous ISTH guidelines (dense sampling)**

• Designed to get an understanding of the PK in a population

• Classical study design: 12-15 patients with a crossover design

• 10 or 11 blood samples over a period of 32-48 h after infusing 25-50 IU/kg

• Washout needed

How do we determine a patient’s PK

New ISTH guidelines (popPK + sparse sampling)

- Focus on individual PK estimation
- 2-3 samples for one patient over 48 h
- Use a population pharmacokinetic model and individual samples to derive individual estimates
- No washout necessary, no standard dose needed

How we use popPK models in hemophilia

• Our goal is to get patient-specific estimates of CL and V so that we can use them to adjust dose.

• Our patient is defined by their covariates (BW, Age…) and FVIII or FIX activities as sampled over time.

Bayesian forecasting

Jamal
38 yrs
79 kg
187 cm
Blood group O
Web-Accessible Population Pharmacokinetics Service - Hemophilia

Aims of the service:

• **Empower** hemophilia treatment by facilitating individualized dosing

• **Estimate** individual PK parameters from a reduced number of plasma samples

• **Establish** the largest global repository of factor concentrate PK data
Benefits of PK-tailored dosing in hemophilia: PK-tailored dosing led to...

- **A 10% reduction in costs** (drug + bleeding events) as compared to standard prophylaxis treatment (retrospective, n = 6 severe HA children)\(^1\)
- **Reduction in bleeds/yr** (1 yr standard prophylaxis = median 4 [0-30], 1 yr PK-tailored prophylaxis = median 1 [0-11]) and increase in HRQoL scores (prospective, n = 36 severe HA >16 yrs)\(^2\)
- **Tendency towards improvement of ABR** in the adherent group vs non-adherent (not SS), longer times spent above either 1% or 5% were associated with **decrease in AjBR** (prospective, n = 39 severe HA 2-67 yrs)\(^3\)


The power of the WAPPS database

- **Centres:** 412
- **Patients:** 4248
- **Total PK Studies:** 8593
- **PK: Children 6-11:** 2317
- **PK: Children 0-5:** 959
WAPPS inputs and outputs

<table>
<thead>
<tr>
<th>WAPPS ID</th>
<th>15986</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Patient ID</td>
<td>ASH PopPK Case 3</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
</tr>
<tr>
<td>Current Age</td>
<td>21</td>
</tr>
<tr>
<td>Baseline Factor Level (IU/mL)</td>
<td>&lt; 0.0100 IU/mL</td>
</tr>
<tr>
<td>Blood Group</td>
<td>B</td>
</tr>
</tbody>
</table>

**PK Studies**

<table>
<thead>
<tr>
<th>+/-</th>
<th>PK Estimate</th>
<th>ID</th>
<th>Drug</th>
<th>Age</th>
<th>Height (cm)</th>
<th>BW (kg)</th>
<th>LBW (kg)</th>
<th>Tot IU</th>
<th>IU/kg</th>
<th>End of infusion</th>
<th>Opt.</th>
<th>Notes</th>
<th>Flags</th>
<th>Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10037</td>
<td>Benefix</td>
<td>20</td>
<td>170</td>
<td>53</td>
<td></td>
<td>46</td>
<td>2500</td>
<td>47.2 2017-07-01 08:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sampling Date Time</th>
<th>Time Elapsed (hh:mm)</th>
<th>Pre-dose</th>
<th>Plasma Factor Concentration</th>
<th>Notes</th>
<th>Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-07-01 14:00</td>
<td>6:00</td>
<td></td>
<td>0.227 IU/mL (22.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2017-07-02 10:00</td>
<td>26:00</td>
<td></td>
<td>0.081 IU/mL (8.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2017-07-03 17:00</td>
<td>57:00</td>
<td></td>
<td>0.035 IU/mL (3.5%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[Add an infusion] [Merge Infusions]
WAPPS inputs and outputs

Disclaimer: All PK estimates generated by WAPPS, including this report, are to be used as indicated in the user agreement and at the user's sole responsibility.

Approved by Alfonso Iorio
WAPPS inputs and outputs: clinical calculator

<table>
<thead>
<tr>
<th>Dose</th>
<th>Infusion Interval</th>
<th>Peak (IU/mL)</th>
<th>Trough (IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Units</td>
<td>72 hr (3 Days)</td>
<td>0.68</td>
<td>0.050</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weekly Dosage (IU)</th>
<th>10092</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time above 0.01 IU/mL</td>
<td>100%</td>
</tr>
<tr>
<td>Time above 0.03 IU/mL</td>
<td>100%</td>
</tr>
<tr>
<td>Time above 0.15 IU/mL</td>
<td>38%</td>
</tr>
</tbody>
</table>

![Regimen Estimate (Benefix)](image-url)
WAPPS contribution to tailoring treatment in children: How much can real world data add?

Yeung CHT et al. EAHAD oral pres. *Haemophilia* 2019;25(S1):29
The WAPPS Fanhdi/Alphanate project

Chelle P et al. *In revision in Journal of Pharmacokinetics and Pharmacodynamics.*

<table>
<thead>
<tr>
<th>Location</th>
<th>N</th>
<th>Study Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemocentro Unicamp (Sao Paulo, Brazil)</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Complejo Asistencial Dr. Sótero del Río</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>(Santiago, Chile)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital University &amp; Politechnic La Fe</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>(Valencia, Spain)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Centers A to I</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

- **Fanhdi/Alphanate popPK model**
- Yellow: derivation set, grey: evaluation set
- Patients were 1-71 yrs (~40% <20 yrs) with 1-8 samples over 72 hrs
- Objectives: (1) develop a popPK model for Fanhdi/Alphanate using WAPPS data, and (2) evaluate the popPK model for Bayesian forecasting
The WAPPS Fanhdi/Alphanate project


\[
CL = CL_{\text{pop}} \left( \frac{FFM}{50.5} \right)^{\theta_{\text{FFM-CL}}} \left( 1 + \theta_{\text{AGE-CL}} \frac{\max(0, \text{AGE} - 25)}{25} \right) e^{\eta_{CL}}
\]

\[
V1 = V1_{\text{pop}} \left( \frac{FFM}{50.5} \right)^{\theta_{V1}} e^{\eta_{V1}}
\]

\[
Q = Q_{\text{pop}}
\]

\[
V2 = V2_{\text{pop}} \left( \frac{FFM}{50.5} \right)^{\theta_{V2}}
\]
Predicting PK during switching

Factor VIII (FVIII) activity levels of people with hemophilia A (n = 29) was obtained from a phase 3 study.

Yu JK et al. EAHAD poster pres. *Haemophilia* 2019;25(S1):29

1. No covariates
   \[ \begin{align*}
   CL &= CL_{pop} \\
   V1 &= V1_{pop} \\
   Q &= Q_{pop} \\
   V2 &= V2_{pop}
   \end{align*} \]

2. With covariates
   \[ \begin{align*}
   CL &= CL_{pop} \times f_{CL}(FFM, AGE) \\
   V1 &= V1_{pop} \times f_{V1}(FFM) \\
   Q &= Q_{pop} \\
   V2 &= V2_{pop} \times f_{V2}(FFM)
   \end{align*} \]

3. Octocog alfa information
   \[ \begin{align*}
   CL &= CL_{pop} \times f_{CL}(FFM, AGE) \times e^{h\text{CL}} \\
   V1 &= V1_{pop} \times f_{V1}(FFM) \times e^{h\text{V1}} \\
   Q &= Q_{pop} \\
   V2 &= V2_{pop} \times f_{V2}(FFM)
   \end{align*} \]

Predicting PK during switching

Yu JK et al. EAHAD poster pres. *Haemophilia* 2019;25(S1):29

<table>
<thead>
<tr>
<th>PK outcomes (units)</th>
<th>Absolute Mean [range]</th>
<th>Relative Error in %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Method 1</td>
<td>Method 2</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>31.3 [1-155]</td>
<td>29.2 [2-129]</td>
</tr>
<tr>
<td>V1 (L)</td>
<td>14.9 [1-37]</td>
<td>12.5 [0-29]</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>21.3 [2-68]</td>
<td>18.7 [2-66]</td>
</tr>
<tr>
<td>Time to 5% (h)</td>
<td>21.6 [0-62]</td>
<td>19.8 [0-60]</td>
</tr>
<tr>
<td>Time to 1% (h)</td>
<td>21.3 [1-64]</td>
<td>19.3 [2-63]</td>
</tr>
<tr>
<td>[ ] at 24h (IU/mL)</td>
<td>26.0 [1-83]</td>
<td>24.8 [3-83]</td>
</tr>
<tr>
<td>[ ] at 48h (IU/mL)</td>
<td>46.5 [1-240]</td>
<td>43.6 [2-235]</td>
</tr>
<tr>
<td>[ ] at 72h (IU/mL)</td>
<td>61.0 [2-323]</td>
<td>57.5 [1-314]</td>
</tr>
</tbody>
</table>

- **Method 3** had the **lowest mean relative error (%)** and **smallest range** across all PK outcomes.
- Regression line for all PK outcomes produced by **method 3** was **most similar to all observed PK outcomes**.
New patient app: myWAPPS

What is myWAPPS?

myWAPPS enables you to view real-time estimates of your factor level at any time, online or offline, based on your individual pharmacokinetic (PK) study. Your personalized PK information in WAPPS-Hemo is linked to myWAPPS by a healthcare professional at your hemophilia treatment centre, and your treatment regimen is set using the WAPPS-Hemo clinical calculator. myWAPPS also comes with an estimator function that allows you to see the forecast of your predicted factor levels.

WITH myWAPPS YOU CAN:

✓ Monitor factor levels, including estimated future levels
✓ Receive reminders when it is time for an infusion
✓ Receive notifications when factor levels drop to the low zone
New patient app: myWAPPS
Thank you

- PI: Dr. Alfonso Iorio
- Dr. Andrea Edginton
- Dr. Pierre Chelle
- Mohamed Elliethy
- Arun Keepanasseril
- Sydney MacLeod
- Alanna McEneny-King
- Tamara Navarro-Ruan

- Dr. Dagmar M Hajducek
- Cindy HT Yeung
- Jacky K Yu
- Chris Cotoi
- Dr. Gary Foster
- Nicholas Hobson
- Michael Sevestre

www.wapps-hemo.org
www.mywapps.org