MODELING AND SIMULATION APPROACHES FOR DOSE ESTIMATION IN PEDIATRICS

Kwang-il Kwon, Ph.D.
Professor in College of Pharmacy
Chungnam National University, Korea
CONTENTS

• Current aspects in pediatric drug dosing (14 slides)
• Introduction of model based pediatric drug dosing (12 slides)
  Population PK(PD), PBPK, and PK/PD modeling
• Case study: Vincristine and Tacrolimus (9 slides)
Rescue therapeutic orphans

- Medicinal products intended to cure in both adult and pediatric patients, but children are still “Therapeutic Orphans”
  - 75% prescription drugs in children “off-label”
  - Pediatric indications are not profitable for industry.
  - Current Pediatric Dosing: Extrapolated from adults based on weight, body surface area, or age, and the PK/PD relationship is not often considered.
  - Widely varied pharmacokinetics might be related to physical developmental stages.
Physiology in children

- BSA large for weight; susceptible to hypothermia
- All brain cells present at birth; development of nerve fibers occur during first year.
- Head proportionately larger, susceptible to head injury
- Higher metabolic rate, higher oxygen needs, higher caloric needs
- Until about 10 years, there is a faster respiratory rate and less lung volume.
- Susceptible to metabolic acidosis
- Bones are soft and easily bent and fractured
- Water proportion of body weight is larger
- Blood volume is weight dependent: 80mL/kg
- Cardiac output is rate dependent not stroke volume dependent, making heart rate more rapid.
- Abdomen offers poor protection for the liver and spleen, making them susceptible to trauma.
- Kidney do not concentrate urine effectively for electrolyte secretion and absorption

Absorption is reduced in pediatrics in general

Gastric acid secretion, bile salt formation, gastric emptying time, digestive enzymes, and intestinal motility are reduced in neonates.

- BA of acid-labile drugs (e.g., penicillin) can be increased; low acid secretion
- BA of weakly acidic drugs are decreased (e.g., Phenobarbital)
- BA of lipophilic drugs (e.g., diazepam) are decreased; less bile acid
- Time to reach therapeutic concentration may be delayed: Reduced motility

• **Distribution: Increased Vd**
  - Higher level of body water, and immature blood-brain barrier

• **Metabolism and Elimination: Reduced in general**
  Immaturity of liver metabolizing enzymes, and immaturity of renal function could reduce drug elimination.
  - Phase I (oxidation, reduction, hydrolysis) activity is reduced in neonates
  - Renal plasma flow is low at birth (12mL/min) and reaches adult levels of 140mL/min at approximately 1 year of age
  - Phenytoin, barbiturates, analgesics, and cardiac glycosides have plasma half-lives 2 to 3 times longer in neonates than in adults.
Pharmacodynamics in children

- PK-PD relationships **do not differ** between the adult and the pediatric populations, **EXCEPT in neonates.**

- **Differences in toxicity** between adult and pediatric patients:
  - Cyclosporine & Sotalol (QTc interval prolongation in neonates)
  - Acetaminophen (reduced hepatotoxicity),
  - Valproic acid (hepatotoxicity),
  - Chloramphenicol (Grey Baby Syndrome),
  - Inhaled corticosteroids (growth retardation),
  - Aspirin (Reye’s syndrome),
  - Lamotrigine (Hypersensitivity, including Stevens-Johnson syndrome)

**Traditional Methods to Calculate the Optimal Dose in Pediatrics**

- **Pediatric dosing adjustment based on Age**

<table>
<thead>
<tr>
<th>Equation</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cowling equation</td>
<td>( \frac{1 + \text{Age}}{24} \times \text{Adult Dose} )</td>
</tr>
<tr>
<td>Bestedo equation</td>
<td>( \frac{(\text{Age} \times \text{Adult Dose})}{30} )</td>
</tr>
<tr>
<td>Bronton equation</td>
<td>( \frac{\text{Age}}{25} \times \text{Adult Dose} )</td>
</tr>
<tr>
<td>Dilling equation</td>
<td>( \frac{\text{Age}}{20} \times \text{Adult Dose} )</td>
</tr>
<tr>
<td>Starkenstein equation</td>
<td>( \frac{\text{Age}}{18} \times \text{Adult Dose} )</td>
</tr>
<tr>
<td>Young equation</td>
<td>( \frac{\text{Age}}{\text{Age} + 12} \times \text{Adult Dose} )</td>
</tr>
<tr>
<td>Ueno equation</td>
<td>( \sqrt[2]{\text{Age}} \times \text{Adult Dose} )</td>
</tr>
<tr>
<td>Fried equation</td>
<td>( \frac{\text{Month}}{20} \times \text{Adult Dose} )</td>
</tr>
<tr>
<td>Augsberger II equation</td>
<td>( \frac{(\text{Age} \times 4) + 20}{100} \times \text{Adult Dose} )</td>
</tr>
</tbody>
</table>

Traditional Methods to Calculate the Optimal Dose in Pediatrics

- **Optimal pediatric dosing based on weight**
  - Augsberger I equation:
    \[
    \frac{WT(\text{kg}) \times 1.5 + 10}{100} \times \text{Adult Dose}
    \]
  - Clark equation:
    \[
    \frac{WT(\text{pound})}{150} \times \text{Adult Dose}
    \]
  - Ivady & Dirner equation:
    - \( \leq 5\text{yr}, < 20\text{kg} \):
      \[
      \frac{WT(\text{kg}) \times 2 + 5}{100} \times \text{Adult Dose}
      \]
    - \( \geq 5\text{yr}, \geq 20\text{kg} \):
      \[
      \frac{WT(\text{kg}) + 30}{100} \times \text{Adult Dose}
      \]
  - Hamburger equation:
    \[
    \frac{WT(\text{kg})}{70} \times \text{Adult Dose}
    \]

- **Pediatric dosing based on Age & Weight**
  - Lenart equation:
    \[
    \frac{\text{Age} \times 2 + WT(\text{kg}) + 12}{100} \times \text{Adult Dose}
    \]

- **Based on Body surface area (BSA)**
  - Clack equation:
    \[
    \frac{\text{Pediatric BSA}}{\text{Adult BSA}} \times \text{Adult Dose}
    \]
  - Pediatric dosing equation:
    \[
    \left(\frac{WT_{\text{pediatr}}}{WT_{\text{adult}}}\right)^{0.7} \times \text{Adult Dose}
    \]

Pediatric Specific Modeling and Study Design Issues

- Current pediatric specific modeling and study design issues
  - Size vs. Age/maturation effects for pediatrics may not corelated
  - Similar exposure-response relationship in pediatrics and adults
  - Co-linearity and covariate search are necessary
  - Sparse PK/PD sampling strategies are required
  - Model qualification and validation for simulation

# Steps for Pediatric Drug Development

- **Model Based Drug Development program:**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>To develop age appropriate formulations</td>
</tr>
<tr>
<td>Juvenile animal study</td>
<td>To address developmental toxicology issues</td>
</tr>
<tr>
<td>Modeling and Simulation</td>
<td>PK/PD in pediatric patients are simulated based on allometric scaling from PK/PD in adults</td>
</tr>
<tr>
<td>Phase I study (relative bioavailability)</td>
<td>To assess pediatric formulation performance versus adult formulation in healthy adult volunteers</td>
</tr>
<tr>
<td>Phase II study (PK/PD dosing finding)</td>
<td>To assess PK/PD in pediatric patients and to derive dose guidance for Phase III trial</td>
</tr>
<tr>
<td>Phase III study (efficacy &amp; safety)</td>
<td>To assess efficacy and safety in pediatric patients for registration</td>
</tr>
</tbody>
</table>

FDA Pharmacometrics 2020 strategic Goals

**Train 20 Pharmacometricains**
- Technical track
- Disease track
- Drug development track

**International Harmonization**
- Share expertise between global regulatory bodies

**Implement 15 Standard Templates**
- Develop disease specific data, analysis standards
- Expect industry to follow

**Integrated Quantitative CP Summary**
- All NDAs should have exposure response analyses

**Develop 5 Disease Models**
- Create public disease model library

**Design by Simulation for pediatric studies are compulsory.**
- Prior to design pediatric clinical trials

1. Pharmacometrics at FDA (http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm167032.htm)
Guidance for Pediatric Drug Development – USA, Europe, and Korea

FDA (USA)
• Best Pharmaceuticals for Children Act (BPCA) and BPCA of 2007
• Food and Drug Administration Amendments Act (FDAAA) of 2007
• Guidance for Industry “Nonclinical safety evaluation of pediatric drug products” of 2006
• Pediatric Research Equity Act (PREA) of 2003
• Guidance for Industry “Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products “of 1998
• FDA Modernization Act (FDAMA) of 1997

EMEA (Europe)
• Guidance on reporting the result of population pharmacokinetic analysis (June, 2007)
• Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (June, 2009)
• Role of pharmacokinetics in the development of medicinal products in the pediatric population (June, 2006)
• Investigation of bioequivalence (July, 2008)
• Clinical investigation of medicinal products in the pediatric population (Jan., 2001)

KFDA (Korea)
• Guidance on nonclinical safety evaluation of pediatric drug products (Dec, 2007)
• Clinical investigation of medicinal products in the pediatric population (May, 2007)
• Guidance on exposure-response relationships- study design, regulatory applications (Dec, 2008)
• Guidance on nonclinical investigation of biological products (Dec, 2008)
Model Based Pediatric Drug Development

- **Pediatric Study Decision Tree**
  - The pediatric decision tree established by the FDA
  - Bridge adult and pediatric data
  - Bridge data between different pediatric age groups or subjects

MODEL BASED PEDIATRIC DRUG DOSING AND DEVELOPMENT

1. Population PK model
2. Physiologically based PK model
3. Statistical/mechanical PK/PD model
1. Population Pharmacokinetic Modeling — by NONMEM

- **Structural and covariate model** development
  - PopPK is the finding of the sources and correlates of variability (covariates) in drug concentrations.
  - Interindividual variability in PK can be minimized using covariates compensation.

- **Pop-PK models can be used for**
  - Pediatric dose recommendations for **first-in-children** dose finding studies.

![Diagram](image)

Population PK(PD) model development process

Final population PK/PD model with covariate

Minimize pediatric dosing prediction error
Pop-PK models could incorporate covariate to predict PK in children based on adult PK data of different age subjects.

The covariates for pediatric model can be body weight, age, body surface area, Clcr, Bilirubin etc..

\[ V_c = TVV_c \times \left( \frac{\text{Weight}}{\alpha} \right)^\beta \]
\[ V_c = TVV_c \times \left( \frac{\text{Age}}{\alpha} \right)^\beta \]
\[ V_c = TVV_c \times \left( \frac{\text{BSA}}{\alpha} \right)^\beta \]

\( \alpha = \) population mean
\( \beta = \) covariate model parameter

Population Pharmacokinetic Model in pediatrics

• Example: Gatifloxacin

**Conclusion**

- 82 pediatric patients (6 months ~ 16 years)
- PK model: One-compartment model with first-order absorption and elimination
- Covariate: “CL/F=8.46 (L/h/m²) × BSA (m²), “V/F=2.15(L/kg) × weight (kg)”

2. PBPK model development process

• Allometric scaling methods
  ▫ PBPK model is developed based on physiology including organ size, blood flow rate etc.
  ▫ The body weight varies exponentially across the species and allows scale up and down.  \( Y = aW^b \)
    \( Y = \) PK parameter, \( W = \) body weight, \( a = \) allometric coefficient, \( b = \) scaling exponent
    \( b = 0.25; \) heart rate, circulation time, respiratory rate, \( b = 0.75; \) basal metabolic rate, blood flow, clearance
  ▫ Key point: Flow limited model, Membrane limited model

Log PK = a • BV

Log PK

Log BW
Physiologically Based Pharmacokinetic Model - PBPK model

- Allows predictions of the concentration profiles in different pediatric age groups
- A first-in-children dose could be recommended.
- Promote the understanding of mechanism of ADME.
- Disadvantage: difficulty in extrapolation, estimation of R(partition coefficient), measurement of blood flow, etc.

Physiologically Based Pharmacokinetic Model - PBPK model

- Example: Theophylline and midazolam

Prediction of drug disposition in infants and children by means of physiologically based pharmacokinetic (PBPK) modelling: theophylline and midazolam as model drugs

- The developed PBPK model

- Conclusion
  - The calculated $V_{dss}$ followed the amount of adipose tissue. Higher in neonates for the hydrophillic drug theophylline, and lower for the lipophilic drug midazolam.
  - $CL$ per kg was maximal ($t_{1/2}$ minimal) at 2-5 years.

3. Pharmacokinetic/Pharmacodynamic Model — PK/PD model

- Pharmacokinetic/Pharmacodynamic Model (PK/PD model)
  - To investigate the PK/PD relationship in pediatric patients.
  - Can be used for first-in-children dosing prediction and Clinical study optimization.

Pharmacokinetic/Pharmacodynamic Model — PK/PD model

- Pharmacokinetic/Pharmacodynamic Model (PK/PD model)

Pharmacokinetic/Pharmacodynamic Model — PK/PD model

- Example: Argatroban
  - Conclusion
    - Argatroban CL was determined to be dependent upon pediatric patients’ body weight.
    - Hepatically impaired pediatric patients exhibited lower CL
    - Covariate analysis revealed the effect of age, body weight, gender, and hepatic status. And aPTT parameters (ie, $E_{max}$, $E_0$, and $EC_{50}$).
    - Simulations were performed to derive optimal safety starting dose in pediatrics.

Pharmacokinetic and Pharmacodynamic Basis for Effective Argatroban Dosing in Pediatrics

Rajamohan Madabushi, PhD, Donna S. Cox, PhD, Mohammad Hossain, PhD, Dwane A. Boyle, PharmD, Bela R. Patel, PhD, Gary Young, MD, Young-Moon Choi, PhD, and Logan S. Gebbru, PhD

The objective was to characterize the pharmacokinetic (PK) and pharmacodynamic (PD) of argatroban in pediatric patients and derive dosing recommendations. An open-label multicenter trial was conducted in pediatric patients in 1-18 (two to 18 years). A population modeling approach was used to characterize pharmacokinetics and pharmacodynamics of argatroban in pediatric patients. Simulations were performed to derive a dosing regimen for pediatric patients. The estimated clearance of argatroban in pediatric patients was 2-fold lower than that in healthy adults. Body weight was significant predictor of argatroban clearance. The clearance in a typical 20kg pediatric patient was 3.1 L/h. In patients with elevated aPTT or INR levels, the estimated clearance was 0.6 L/h. Effect on activated plasma thromboplastin time (aPTT) was found to be concentration dependent. Simulations suggested that a starting dose of 0.75 mcg/kg/min in pediatric patients was comparable to 2.8 mcg/kg/min approved in adults for achieving target aPTT and INR for bleeding. A dose increment step size of 0.25 mcg/kg/min was suitable for titration. The PK/PD of argatroban was successfully characterized in pediatric. Plasma concentration-aPTT relationship was used to derive a safe starting dose and titration scheme for the first time in pediatric patients and was incorporated into the US prescribing information for argatroban.

Key Words: Hepatic-induced thromboplastic argatroban; pediatric pharmacokinetic/pharmacodynamic; activated plasma thromboplastin time (aPTT) simulation

Journal of Clinical Pharmacology. XXXX/X/xxxx-xxxx © 2010 the American College of Clinical Pharmacology

Case study - Vincristine

- Vincristine
  - Vincristine (Oncovin®), also known as leurocristine, is a vinca alkaloid which enters cell during mitosis and blocks formation of microtubules of the mitotic spindle during metaphase, thus, it finally stops division of cells.
  - Vincristine has been used to treat acute leukemia and all lymphomas.
  - Body surface area (BSA)-based dosing calculation method for vincristine is universally applicable in the clinical situation.

2. www.Google.com
   (https://www.google.co.uk/search?hl=ko&num=10&biw=1000&bih=890&source=lnms&tbm=isch&q=vincristine&sa=X&ved=0ahUKEwiR-i5obqVrAhUSOp8KHdJaBpYQ_AUIEigB)
Factors influencing on dose of vincristine

- Demographic (Age, BSA, Weight, Height) and others (total bilirubin, AST, ALT, serum creatinine, and etc.) were considered as input variables.
- BSA, weight, height, and age have correlation to dose. ($R^2>0.9$)
Case study - Vincristine

- Dosing of vincristine normalized BSA and ages

\[ z = -0.90 + 3.78x - 0.02y - 1.14x^2 \]

\[ R^2 = 0.9738 \]
Demographics and Chemo-regimens

- from May 2006 to October 2009
- 25 Adults and 46 pediatric and adolescence patients with acute lymphoblastic leukemia
- BSA calculation method with DuBois formula was used for the determination of vincristine dosage.
- Complete blood counts and other blood test results were obtained.

Calculating Body surface area

- The Mosteller formula
  \[ BSA(m^2) = \sqrt{\frac{\text{Height(cm)} \times \text{Weight(kg)}}{3600}} \]
- The DuBois formula
  \[ BSA(m^2) = 0.20247 \times \text{Height}(m)^{0.725} \times \text{Weight(kg)}^{0.425} \]

<table>
<thead>
<tr>
<th>Demographics of patients (mean ± SD (median))</th>
</tr>
</thead>
<tbody>
<tr>
<td>variables</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>BSA (m²)</td>
</tr>
<tr>
<td>Vincristine dose (mg)</td>
</tr>
</tbody>
</table>
# Case study - Vincristine

## Demographics and Chemoregimens
- 1.5 mg/m²/day IV vincristine and other anticancer drugs were administered as scheduled.

<table>
<thead>
<tr>
<th>chemoregimens</th>
<th>For pediatrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>0601</td>
<td>Prednisolone (60mg/m²), Vincristine (1.5mg/m²), L-asparaginase (6000U/m²), Daunorubicin (25mg/m²), Ara-C, Methotrexate</td>
</tr>
<tr>
<td>1952</td>
<td>Prednisolone (40mg/m²), Vincristine (1.5mg/m²), L-asparaginase (6000U/m²), Ara-C, Methotrexate</td>
</tr>
<tr>
<td>106B</td>
<td>Prednisolone (60mg/m²), Vincristine (1.5mg/m²), L-asparaginase (6000U/m²), Daunorubicin (25mg/m²), Cyclophosphamide (1200mg/m²), Ara-C, Methotrexate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>chemoregimens</th>
<th>For Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPDL</td>
<td>Prednisolone (40mg/m²), Vincristine (1.5mg/m²), L-asparaginase (6000U/m²), Daunorubicin (45mg/m²)</td>
</tr>
<tr>
<td>VPD</td>
<td>Prednisolone (60mg/m²), Vincristine (1.5mg/m²), Daunorubicin (90mg/m²(45mg/m²)), Methotrexate (15mg)</td>
</tr>
<tr>
<td>VPDC</td>
<td>Prednisolone (40mg/m²), Vincristine (1.5mg/m²)</td>
</tr>
<tr>
<td>VP</td>
<td>Prednisolone (60mg/m²), Vincristine (1.5mg/m²), Methotrexate</td>
</tr>
<tr>
<td>ADVP</td>
<td>Prednisolone (40mg/m²), Vincristine (1.5mg/m²), L-asparaginase (6000U/m²), Daunorubicin (45mg/m²)</td>
</tr>
</tbody>
</table>
Case study - Tacrolimus

- Tacrolimus has become an effective as a component of primary immunosuppression in pediatric transplantation patients.
- **Pharmacokinetic studies on the juvenile animals** carried out by grouping according to the developmental stages paired with humans to characterize the pharmacokinetic properties of tacrolimus.
- Population PK(PD) approaches to get population and individual parameters as well as intra-and inter-subject variability to detect covariates.
Case study - Tacrolimus

- Method – Data
  - Pharmacokinetic data
    - Plasma concentration data of tacrolimus in juvenile rats are collected as scheduled

<table>
<thead>
<tr>
<th>Rat</th>
<th>Neonate</th>
<th>Infant</th>
<th>Child</th>
<th>Adolescent</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>11</td>
<td>24 (6 months)</td>
</tr>
<tr>
<td>No. of subject</td>
<td>30</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

- Time tables for pharmacokinetic study
  - 1 mg/kg IV injection, 5 mg/kg PO administration
  - Pharmacodynamic data – pathophysiological biomarkers (eg. bilirubin, ALT, AST, etc), are to be obtained.
Case study - Tacrolimus

• During modeling, typical population values for kinetic parameters are estimated, together with interindividual and residual (unexplained) variability in juvenile animal model.

• The influence of multiple factors (covariates) which are existed especially in pediatrics on PK parameters can also be examined.

\[ TVCL = \theta_{CL} \cdot [1 + \theta_{CL}^{Age} \times (Age - 2.25)] \]
\[ TVV = \theta_V \cdot [1 + \theta_V^{BSA} \times (BSA - 0.49)] \]
\[ TVF = \theta_F \cdot [1 + \theta_F^{WT} \times (WT - 11.4)] \cdot [(1 - Y) + Y \cdot \theta_F^{TOTBIL}] \]

**Fig. 3** Longitudinal assessment of the predictive performance of the final population model in 2 representative patients from the validation dataset: (a) 1 year-old male (b) 1 year-old female. (●) observed and (■) model-predicted whole blood tacrolimus concentration.

**Fig. 4** Profile of age-normalized clearance (predicted by the population model) vs. age of patient.

In Conclusion

For the Modeling and Simulation Approaches for Dose Estimation in Pediatrics

1. Population PK model
2. Physiologically based PK model
3. Statistical/mechanical PK/PD model

* PK/PD modeling using population analysis using NONMEM is the most useful for the simulation of dose estimation in pediatrics.
THANK YOU

kwon@cnu.ac.kr