Consideration of PK/ PD studies

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FDA-University of Maryland CERSI
Analgesic Clinical Trial Designs, Extrapolation, and Endpoints in Patients from Birth to Less Than Two Years of Age
Oct 13-14, 2021
Why MIDD useful in analgesic development for pediatric especially between birth to Less than 2yrs?

• Key Questions (KQ) - focus on why certain modeling is needed to answer clinical questions
• Data (utilize data from nonclinical to all phases in clinic from adult and older children)
• Data quality due to efficacy endpoints variations (pain perception and analgesic response)
• Assumptions setting, testing/evaluation to increase confident, especially on extrapolation and simulation study using existing PK, PD data based on assumption
• Modeling approach (tailor based on the KQ, data and assumptions)
• Accumulation of knowledge to ↑ prob. of success of new trial design to collect data or replace study
• Accelerate development with real-time quantitative assessment of emerging data
• Utilize data from similar class of MoA in various pediatric population
• Impact: Support dose finding and selection based on TI
• Support communication for sponsors and regulators decision making

Making use of data from existing PK/PD studies
Optimize future PK/PD studies (collect useful data)
Robust model based on data PK/PD studies
Extrapolate to efficacy
Empirical Approach vs. Mechanistic Approach for Simulation and Extrapolation?

Consideration:
- Objective/ Key questions?
- Robustness of prior knowledge e.g. animal models, adult models etc.
- Assumption setting and evaluation!
- Amount and quality of data (sample and size)
- Describe? Extrapolation? Extend?
- Clinical trial simulation?

Usage: FTIH, pediatric, DDI and Renal and Hepatic impairment (where appropriate), formulation development
PK-PD data, modeling in acute and chronic pain

Pharmacokinetic-pharmacodynamic modeling in acute and chronic pain: an overview of the recent literature


Christian Marin*, ERI Ortmann, Adital Yasser, Leon Amin and Albert Schuh

*Corresponding author

In acute and chronic pain, the objective of pharmacokinetic-pharmacodynamic (PK-PD) modeling is to develop and apply mathematical models to describe and predict the time course of the active principle from multiple measurement data with PK-PD models (1, 2). Anticipating popular PK-PD modeling on newer macromolecular matrix effects, apart from the estimation of macromolecular PK and matrix variables, the quantification of various effects as within-and between-subject variability, effect compartment models and mechanism-based blood dilution models that incorporate drug-protein and activation-intensity and activation-specificity and application PK-PD models of pain treatment. Mechanistic approaches enable the quantification of the interacting factors. The effect of sensitivity to drug concentration, the effect compartment model is the simplest way to understand the complexity of specific proteins or enzymes functionally, but also mimics and its active metabolite in glucuronidase, especially with respect to the several of inhibited side effects, more importantly the diminishing, increasing depression. This approach in chronic studies, the application of intrinsic modes. However, do not necessarily need to study PK, the PK-PD models allow the estimation of the concentrations and the improvement of the interaction they may play an important role in the characterization of the effects in acute and chronic pain.

TABLE 1. PK-PD data, modeling in acute and chronic pain

PK-PD data, modeling in acute and chronic pain: an overview of the recent literature

Pharmacokinetic Models of Morphine and its Metabolites in Neonates:
Systematic Comparisons of Models from the Literature, and Development of a New Meta-Model


Population Pharmacokinetics of Intravenous Paracetamol (Acetaminophen) in Preterm and Term Neonates: Model Development and External Evaluation

Sarah F. Cook, Jessica K. Roberts, Sarina Samios-Zafarghandy, Chris Stockmann, Amber D. King, Nina Deutsch, Elaine F. Williams, Karli Allegaert, Diana G. Williams, Catherine M. T. Shrews, and John N. van den Anker.
Challenge of mathematic model development

• Even we have data, there are challenges of the complexity of the mathematical model e.g. diclofenac, if we don’t consider the use of PBPK but with simpler compartmental model/s
  
  • A non-steroidal anti-inflammatory drug (NSAID)
  • Reduce pain and inflammatory
  • Sodium salt
  • Linear PK in adult (25mg - 100mg)
  • Commonly used “off label” for acute pain in children (0.5-2.5mg/kg)
  • License for pediatric oral formulation is not available
  • PK model: new oral dose, 1mg/kg in pediatric patient
  • (aged 1-12)
  • Adult rich data (30 healthy volunteers) - 50mg
  • 70 pediatric patients – minor surgery – pre-op dose
  • Similar AUC
  • Pediatric patient won’t higher dose

Standing, J. F. et al, BJCP 2008
Cheung, Standing, Aarons, presentation 2008 PAGE
Diclofenac dual absorption first pass model

Mathematical structural identifiability

- A major metabolite 4’-hydroxydiclofenac
- (CYP2C9)
- $\text{CL}_{4\text{OH}}$, a useful *in vivo* marker of CYP2C9
- expression
- Previous *in vitro*: CYP2C9 expression to be adult
- equivalent by age five months
- CYP2C9 ontogeny using the base model

- Proven that the delay mechanism occurring prior to the introduction of the absorption in the 2nd depot compartment in the model enhances the identifiability status of the model
- From an unidentifiable model to a globally identifiable model = which essential to predict unique and stable PK parameter and model to link with PD/efficacy
PBPK model applications in drug development Increased regulatory acceptance over the years

Grimstein et al. J Pharm Sci 2019

The focus should be to PD, but PK and exposure still essential for extrapolation and linking to PD especially < 2yr
Maturation impact to PK

Overview of Developmental Changes of ADME
Determining appropriate dosing regimes is complex owing to the physiological and anatomical changes that occur during childhood

- Drug-metabolising enzymes show age-dependent changes in activity
- Time of maturation is enzyme-specific
- Body composition depends on age – so does drug distribution: Low plasma protein concentrations and a higher body water composition
- Absorption can be affected by differences in gastric pH and stomach emptying time

Clinical Pharmacology & Therapeutics

Article
Predictive Performance of Physiologically Based Pharmacokinetic (PBPK) Modeling of Drugs Extensively Metabolized by Major Cytochrome P450s in Children
Wangda Zhou, Trevor N. Johnson, Khanh H. Buí, S. Y. Amy Cheung, Jianguo Li, Hongmei Xu, Nidal Al-Huniti, Diansong Zhou
First published: 13 October 2017 | https://doi.org/10.1002/cpt.905 | Citations: 25

CPT: Pharmacometrics & Systems Pharmacology

Original Article
Predictive Performance of Physiologically Based Pharmacokinetic and Population Pharmacokinetic Modeling of Renally Cleared Drugs in Children
W. Zhou, T.N. Johnson, H.Xu, S.YA Cheung, KH Buí, J.Li, N. Al-Huniti, D Zhou
Predictive Performance of PBPK Modeling of Drugs

- PBPK modeling is a useful tool for extrapolation of PK profiles in children with only adult clinical trial results and is exceptionally valuable to guide selection of doses in first-in-pediatric studies.

- A total of 67 clinical studies from 10 CYP metabolized drugs were available across all pediatric age groups (1 month to <18 years).

- Predictive performance of PBPK modeling approach was evaluated using 10 drugs extensively metabolized by major CYP enzymes, desloratadine, diclofenac, itraconazole, lansoprazole, montelukast, ondansetron, sufentanil, theophylline, and tramadol.

PBPK models can reasonably predict exposure in children 1 month and older for an array of predominantly CYP metabolized drugs. The default ontogeny functions within Simcyp should be applied for all CYP enzymes except for CYP2C8, where the function proposed by Upreti and Wahlstrom should be used.

OVERALL PREDICTIVITY of PBPK MODELS: Filled circles represent mean ratios of PBPK predicted clearance over observed clearance of all drugs (except esomeprazole, presented as filled triangles) in children 1 month to 18 years old. Blue dashed lines and red dotted lines represent the 1.5-fold and 2-fold error.
Example Morphine neonatal PKPD model (prior and meta-model)
Example Acetaminophen (Paracetamol) Model in preterm, neonates and infants

**Population Pharmacokinetics of Intravenous Paracetamol (Acetaminophen) in Preterm and Term Neonates: Model Development and External Evaluation**

Sarah F. Cook1, Jessica K. Robota2, Samira Samee-Zafarghandy3,4, Chris Stockmann2,5, Amber D. King5, Nina Deutsch2, Elaine F. Williams5, Karel Allegaert1,2,9, Diana G. Wilkins1,9, Catherine M. T. Sherwin2, and John N. van den Anker6,10,11,12

Study information for the model-building and external evaluation datasets

<table>
<thead>
<tr>
<th>Study 1, model-building dataset</th>
<th>Study 2, external evaluation dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
<td><strong>Study</strong></td>
</tr>
<tr>
<td>Phase IIIB, multiple dose study of intravenous paracetamol</td>
<td>Phase IIIB, multiple dose study of intravenous paracetamol</td>
</tr>
<tr>
<td>Volunteers (18 mg/kg)</td>
<td>179 neonates (30 mg/kg)</td>
</tr>
<tr>
<td>Sampling site</td>
<td>Arterial</td>
</tr>
<tr>
<td>Analytical method</td>
<td>HPLC, UV</td>
</tr>
<tr>
<td>Units</td>
<td>mg/kg or mg/l</td>
</tr>
<tr>
<td>Samples</td>
<td>260</td>
</tr>
<tr>
<td>Tyre blood baker (mg/l)</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Primary solubility for intravenous administration (%)</td>
<td>74 (15)</td>
</tr>
<tr>
<td>Parenteral analgesia</td>
<td>19 (34)</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>15 (34)</td>
</tr>
<tr>
<td>Thoracic surgery</td>
<td>11 (25)</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Medical condition</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Adult population</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Parenteral analgesia</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Parenteral antibiotics</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Intravenous pain</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Fever</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Gestational and birth data (%</td>
<td>18 (33)</td>
</tr>
<tr>
<td>Duration of therapy (24 h/ 48 h)</td>
<td>16 (27)</td>
</tr>
<tr>
<td>Preterm (&lt;17 weeks GGA)</td>
<td>17 (29)</td>
</tr>
<tr>
<td>Follow-up (37-42 weeks GGA)</td>
<td>16 (27)</td>
</tr>
<tr>
<td>Current body weight (kg)/ gestational age subgroup</td>
<td>9.9 (6.1-1.4)</td>
</tr>
<tr>
<td>Intravenous therapy (50 mg/kg</td>
<td>9.9 (6.1-1.4)</td>
</tr>
<tr>
<td>Parenteral analgesia</td>
<td>229 (161-348)</td>
</tr>
<tr>
<td>Thoracic surgery</td>
<td>321 (160-530)</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>17 (27)</td>
</tr>
<tr>
<td>Intravenous pain</td>
<td>6 (10.9)</td>
</tr>
<tr>
<td>Fever</td>
<td>11 (19.2)</td>
</tr>
</tbody>
</table>

**Randomized Population Pharmacokinetic Analysis and Safety of Intravenous Acetaminophen for Acute Postoperative Pain in Neonates and Infants**

Gregory B. Hammer, MD1, Lynne G. Maxwell, MD2, Brad M. Taicher, DO, MBA2, Mihaela Visanu, MD3, David S. Cooper, MD, MPH4, Peter Szmuk, MD5, Teng Hong Peng, PhD5, Nathalie H. Gosselin, PhD5, Jia Lu, PhD5, and Krishna Devarakonda, PhD, FCP6

<table>
<thead>
<tr>
<th>Intraoperative Atefrin groups</th>
<th>Control groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td>Number of subjects randomized to</td>
<td>66</td>
</tr>
<tr>
<td>Neonates</td>
<td>15</td>
</tr>
<tr>
<td>Younger infants</td>
<td>17</td>
</tr>
<tr>
<td>Intermediate-age infants</td>
<td>18</td>
</tr>
<tr>
<td>Older infants</td>
<td>18</td>
</tr>
<tr>
<td>Number of subjects completed (%</td>
<td>52 (78.8)</td>
</tr>
<tr>
<td>Neonates</td>
<td>13 (69.7)</td>
</tr>
<tr>
<td>Younger infants</td>
<td>16 (60)</td>
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<tr>
<td>Intermediate-age infants</td>
<td>13 (60.9)</td>
</tr>
<tr>
<td>Older infants</td>
<td>12 (60.9)</td>
</tr>
</tbody>
</table>

Figure 4. The relationship between clearance and postmenstrual age: a sigmoidal pattern with a clearance plateau of 18.9 L/h per 70 kg observed in neonates, infants, children, and adolescents.
**Systems model**

- Systems view of the complexity and connectivity of clinical pain. A systems understanding of pain relies on a mechanistic understanding of its underlying processes. Data types which can provide information on this understanding include patient-reported outcomes, psychological assessments, neuroimaging and molecular markers, of which examples are shown.

- Integration of data from different populations within a translational quantitative systems pharmacology (QSP) model to support personalized treatment and drug development.

CNS, central nervous system.

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Towards personalized treatment of pain using a quantitative systems pharmacology approach

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