Practical Application of PBPK in Neonates and Infants, Including Case Studies

Presented at the conference: Innovative Approaches to Pediatric Drug Development and Pediatric Medical Countermeasures: A Role for Physiologically-Based PK?

Neil Parrott - 5 May 2014
Physiologically based pharmacokinetic model use at Roche

- PBPK modelling now applied routinely during small molecule development
- When PBPK sufficiently verified in adults, pediatric-PBPK is method of choice for PK prediction & dose setting in children
- Pediatric-PBPK is applied in many development projects Ph 2 to aid internal decisions as well as for PIP and PSP
- Allows us to leverage PK knowledge gained in adults and growing physiological knowledge on ontogeny of PK processes
Physiologically based pharmacokinetic models for neonates and infants

- Profound changes in PK processes in infants and neonates make PBPK particularly beneficial for this age group.
- However, sparse data and many gaps in our knowledge of this population, especially oral drug absorption including intestinal UGT’s & transporters.

Mooij, de Wildt et al Expert Opin. Drug Metab. Toxicol. 2012
Case Study: Oseltamivir use in infants

Background

- Approved for oral treatment of influenza and for prophylaxis in adults and children ≥1 year of age

- In the light of the pandemic, several Health Authorities (e.g. FDA, EMEA, Australia, Canada) issued compassionate use authorization in children <1 of age for oral and > 1 year of age for IV route

- In communications with EMA the agency indicated
  - For IV registration in the EU-label and IV compassionate use in children <1 year of age, additional pre-clinical data are needed

EMEA requested a repeated dose IV toxicology study in juvenile marmosets
Toxicity studies to support IV use in children <1 year

What was available?

Juvenile studies (n=8)
- Single oral dose in rats (PND 7, 14, 24 and 42)
- 14-day oral repeat dose in rats (PND 7-21 and 21-49)
- Single SC dose in rats (active metabolite; PND 7)

General toxicity studies i.v.
- 14-day rat and marmoset (pro-drug & active metabolite adult animals)
- Safety Pharmacology (IRWIN mouse and CV dog)

General toxicity studies oral
- Single and repeat-dose toxicity in rats (27 wk) and marmoset (39 wk)
- Special studies (incl. Safety Pharm.) in mice, rats, guinea pig, rabbit and dog
- Reproductive toxicity studies in rats and rabbits
- Carcinogenicity studies in mice, rats and transgenic mice

Clinical: Ongoing NIH trial in children <1 year (oral) and IV Compassionate Use in EU
Data to support IV use in children

What is missing?

• No pre-clinical juvenile studies by the intravenous route

What do we have to add?

EMEA request:

repeated dose IV toxicity in 3 day old marmosets

Hardly feasible ?

Ethically justified ?

An alternative?

Building the bridge with M&S

• Oral to IV
• Adult to juvenile
• Animal to human

SDPK IV in adult and newborn marmosets
PBPK is optimal method for species scaling of PK

Compare model to data to gain knowledge of mechanisms missing from model

Simulation

PBPK animal

PBPK human

model refinements

Confirmation

Observed AUC (hr*ug/L)

Predicted AUC (hr*ug/L)

PREDICTION ACCURACY ~ 75%, n=34
A strategy for pediatric-PBPK

1. Compound specific physicochemical and in vitro data
   - Adult Animal Model
   - Simulation
   - Refinement

2. Age dependencies in Enzyme/Transporters, Protein binding, Renal function, Distribution/Absorption
   - Adult Human Model
   - Simulation
   - Refinement

3. Compound specific physicochemical and in vitro data
   - Juvenile Animal Model
   - Simulation
   - Refinement

4. Age dependencies in Enzyme/Transporters, Protein binding, Renal function, Distribution/Absorption
   - Juvenile Human Model
   - Simulation
   - Refinement

Verify in Animal
Predict in Man
Physicochemical & in vitro properties

pro-drug

oseltamivir (Os)
- Log D = 0.36
- Base 7.7
- good permeability

active metabolite

oseltamivir carboxylate (OC)
- Log D = -2.25
- Base 8.2, Acid 3.6
- very low permeability

Conversion of pro-drug in liver in both monkey and human
PBPK models for pro-drug and metabolite run in parallel

oseltamivir carboxylate

oseltamivir

Conversion of O to OC in liver

Renal elimination of OC

Renal elimination of Os

HA = Hepatic Artery
LU = Lung
ART = Arterial Supply
VEN = Venous Return
AD = Adipose
MU = Muscle
LI = Liver
ACAT = Gut
SP = Spleen
HE = Heart
BR = Brain
KI = Kidney
SK = Skin
REP = Repro Organs
REDM = Red Marrow
YELM = Yellow Marrow
ROB = Rest Of Body
PBPK model refinement in the monkey

- Metabolism scaling from in vitro verified in monkey

- Liver disposition for poorly permeable OC verified in monkey

Model verification in the animal is an essential step in PBPK
PBPK model refinement in the monkey

1. Model verification for OC dosed IV refinement of renal CL
2. Addition of conversion of Os->OC & simulation
3. Refinement of Os->OC conversion
4. Refinement of OC release from liver

Model verification in the animal is an essential step in PBPK
Simulations in adult human

15 mg infused over 1 hour

100 mg oral dose

Good simulations in adult human using model refinements scaled from monkey
Integration of age dependencies

Development of body and organ size with age

Maturation of renal function

Development of metabolism with age

Simulation/Verification in newborn marmoset
Simulated tissue concentration verification

Terminal liver concentrations of Os and OC provided further verification of the hepatic disposition model.
Development of esterases in human


Tamiflu cleavage is approx. 10-fold reduced in human newborns – similar to marmosets
Simulation of oral dosing in infants

A dose of 3 mg/kg b.i.d. given to infants of < 2 years

<table>
<thead>
<tr>
<th></th>
<th>AUC12 for OC (ng.hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported</td>
<td>4326 +/- 1878</td>
</tr>
<tr>
<td>Simulated</td>
<td>5700</td>
</tr>
</tbody>
</table>

The simulated steady state AUC is within the reported range

**Simulation of oral dosing in newborns**

A dose of 1.73 mg/kg b.i.d. given to premature neonates

<table>
<thead>
<tr>
<th>AUC12 for OC (ng.hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported</td>
</tr>
<tr>
<td>Simulated</td>
</tr>
</tbody>
</table>

The simulated steady state AUC approx 2x the reported value

Conclusions

- PBPK model simulations were verified sequentially in adult marmoset, adult human and newborn marmosets.

- Simulations in human newborns were in line with the limited available clinical data.

- Slow IV infusion produces plasma profiles of OC close to those of oral dosing while levels of Os are approx. 3-fold increased.

In view of safety margins IV doses are not expected to have higher safety risk than the oral dose.
Impact

- The modeling and simulation work was documented in a comprehensive report including an overview of all available non-clinical and clinical safety data.

- The comprehensive report also stressed the technical feasibility & ethical concerns of a repeated dose toxicological study in newborn marmosets.

- The report was submitted to the EMEA rapporteur.

**EMA withdrew request for the IV tox. study and accepted existing data and M&S as sufficient to support IV use in infants < 1 year.**
Development of a Physiologically Based Model for Oseltamivir and Simulation of Pharmacokinetics in Neonates and Infants

Neil Parrott,1 Brian Davies,2 Gerhard Hoffmann,1 Annette Koerner,1 Thierry Lave,1 Eric Prinssen,3 Elizabeth Theogaraj4 and Thomas Singer1

1 Non-Clinical Safety, Pharmaceuticals Division, F. Hoffmann-La Roche Ltd., Basel, Switzerland
2 Clinical Pharmacology, Pharmaceuticals Division, F. Hoffmann-La Roche Ltd., Basel, Switzerland
3 Discovery Neuroscience, Pharmaceuticals Division, F. Hoffmann-La Roche Ltd., Basel, Switzerland
4 Drug Regulatory, Pharmaceuticals Division, F. Hoffmann-La Roche Ltd., Basel, Switzerland
Doing now what patients need next