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?

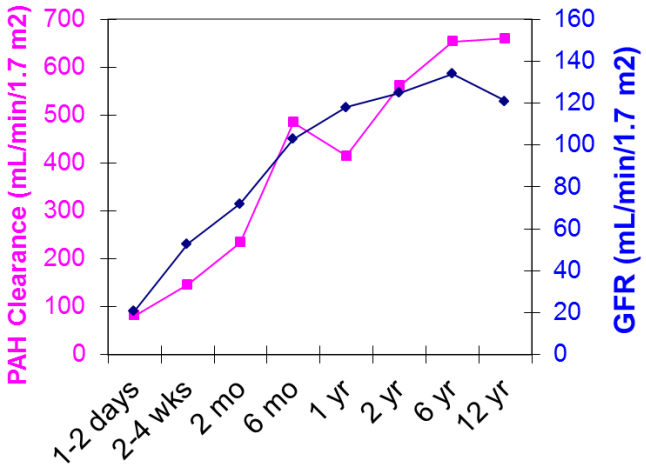
Neil Parrott - 5 May 2014

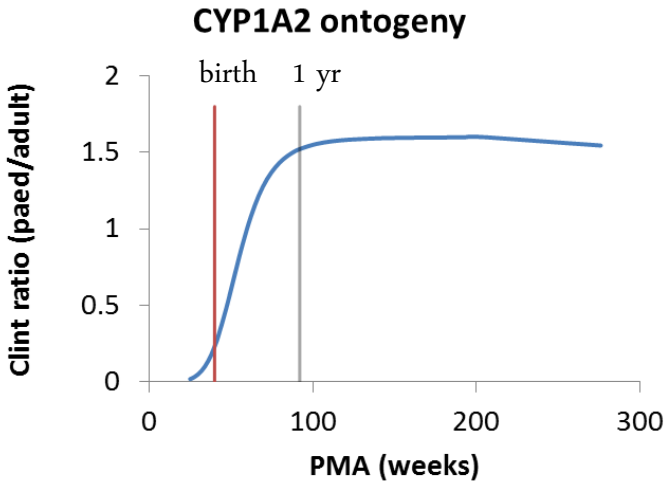
Physiologically based pharmacokinetic model use at Roche

- 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





Kearns N Engl J Med. 2003

Salem, Johnson, et al. Clin Pharmacokinet. 2014

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?

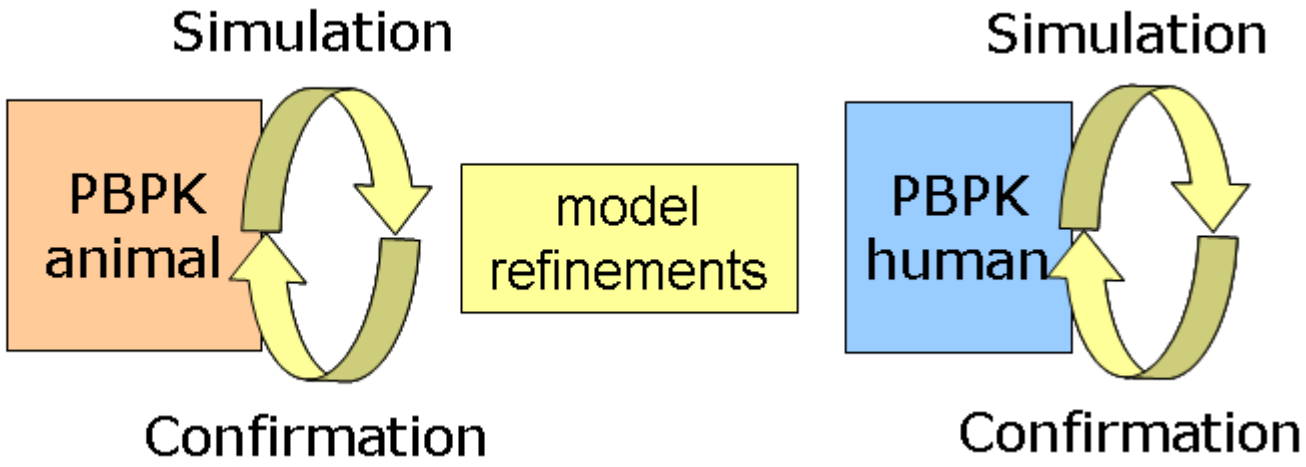
Building the bridge with M&S

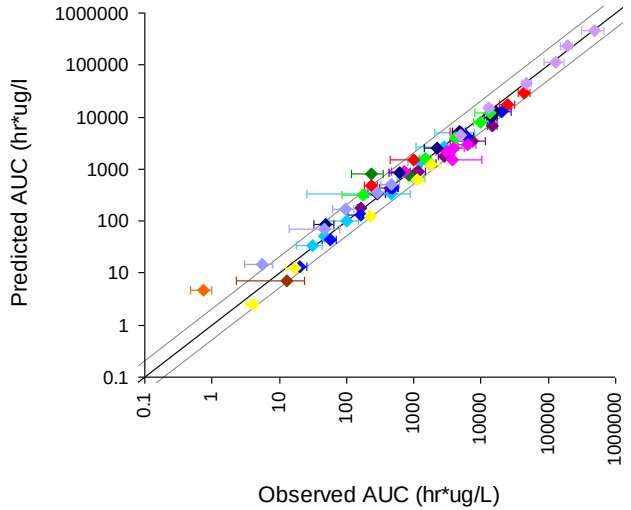
- Oral to IV
- Adult to juvenile
- Animal to human

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



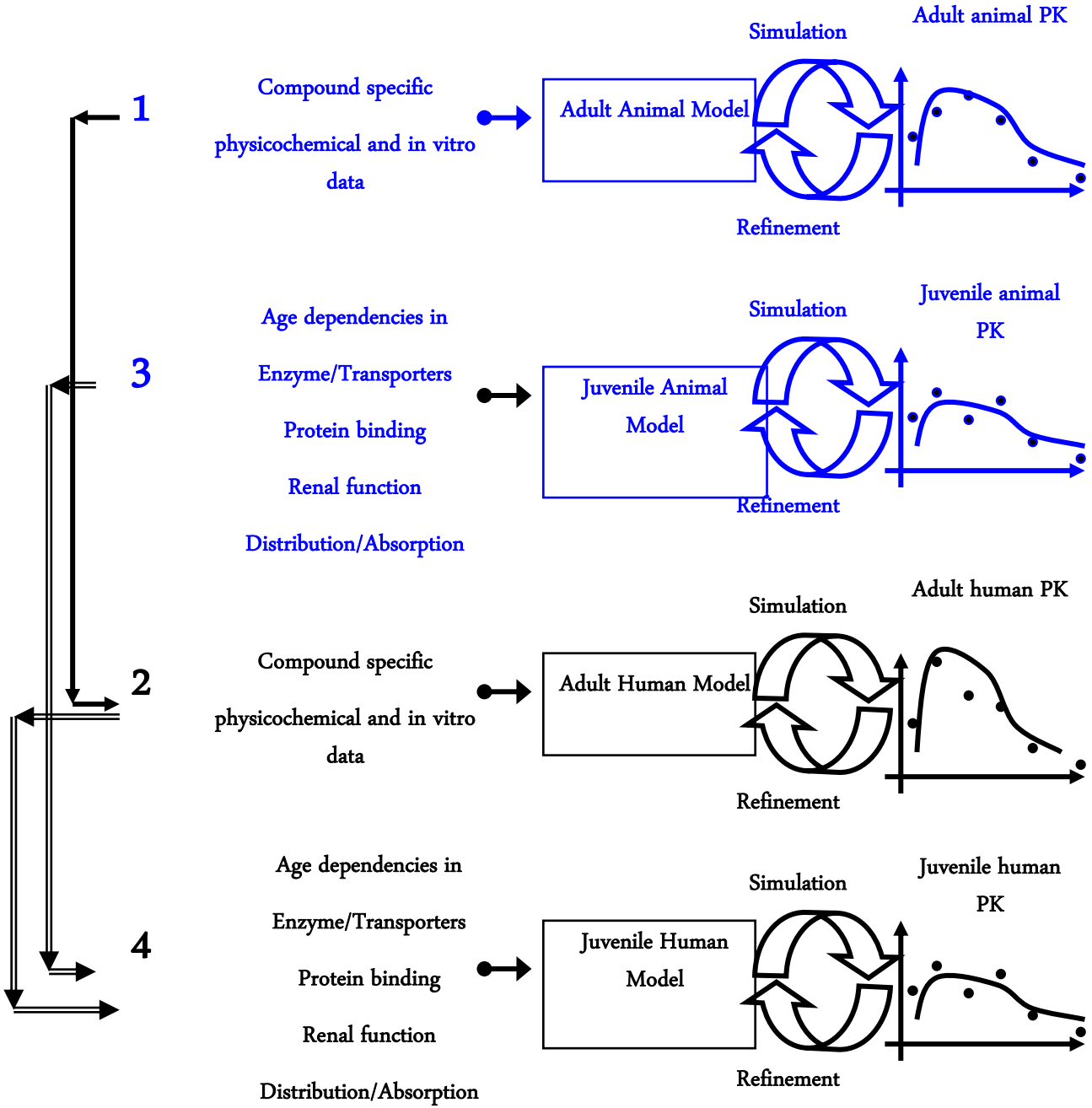


PREDICTION ACCURACY ~ 75%, n=34

A strategy for pediatric-PBPK

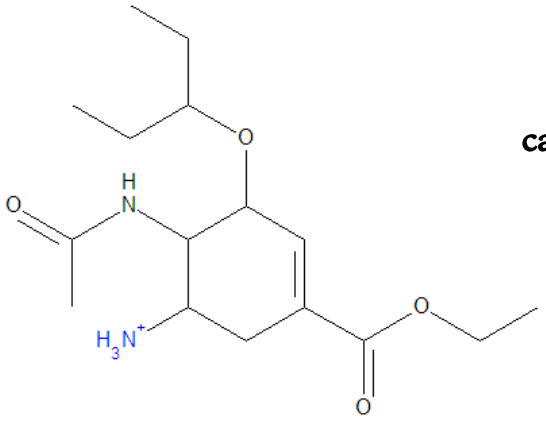
Verify in Animal

Predict in Man



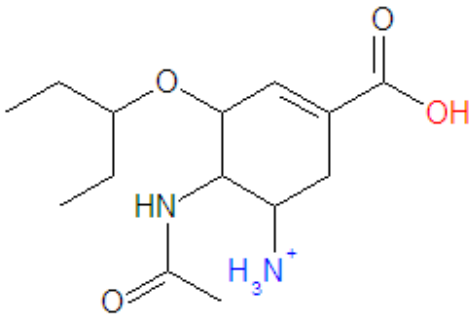
Physicochemical & in vitro properties

pro-drug



carboxylesterase

active metabolite



oseltamivir (Os)

Log D = 0.36

Base 7.7

good permeability

oseltamivir carboxylate (OC)

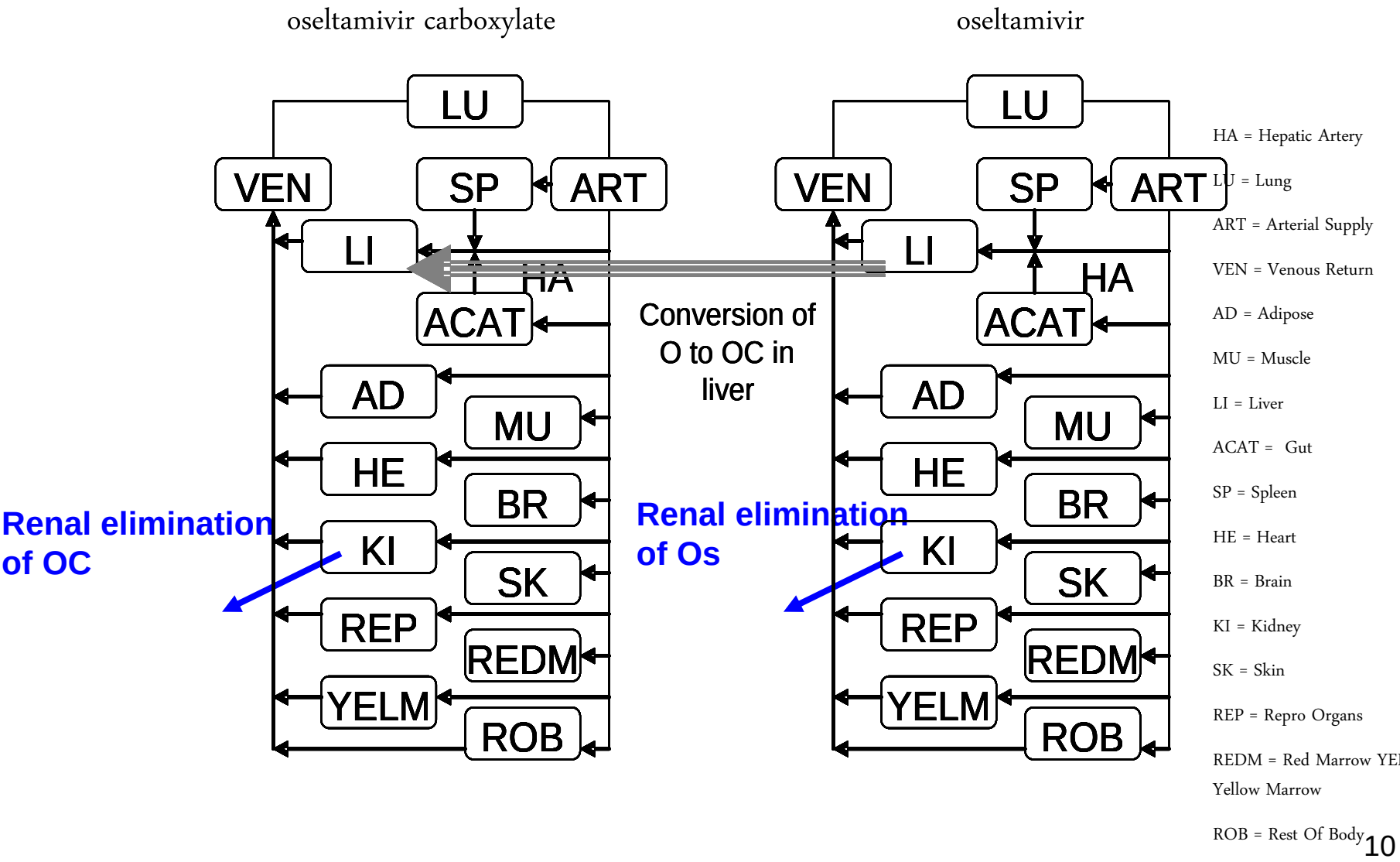
Log D = -2.25

Base 8.2, Acid 3.6

very low permeability

Conversion of pro-drug in liver in both monkey and human

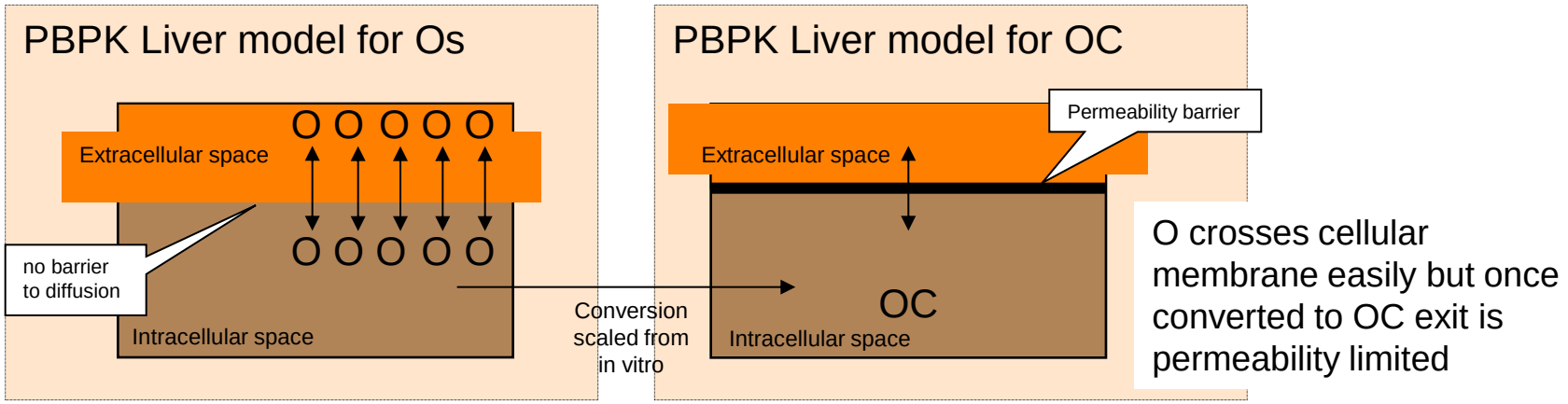
PBPK models for pro-drug and metabolite run in parallel



PBPK model refinement in the monkey

- Metabolism scaling from in vitro verified in monkey

- Liver disposition for poorly permeable OC verified in monkey

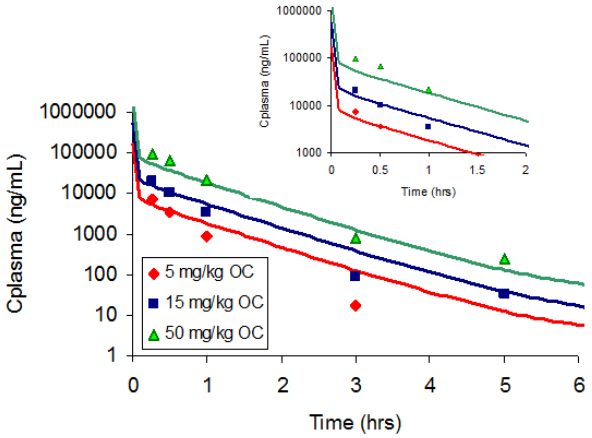


Model verification in the animal is an essential step in PBPK

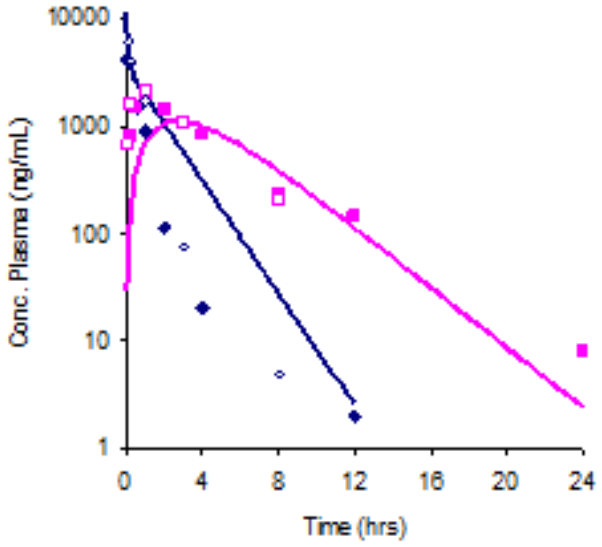
PBPK model refinement in the monkey

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

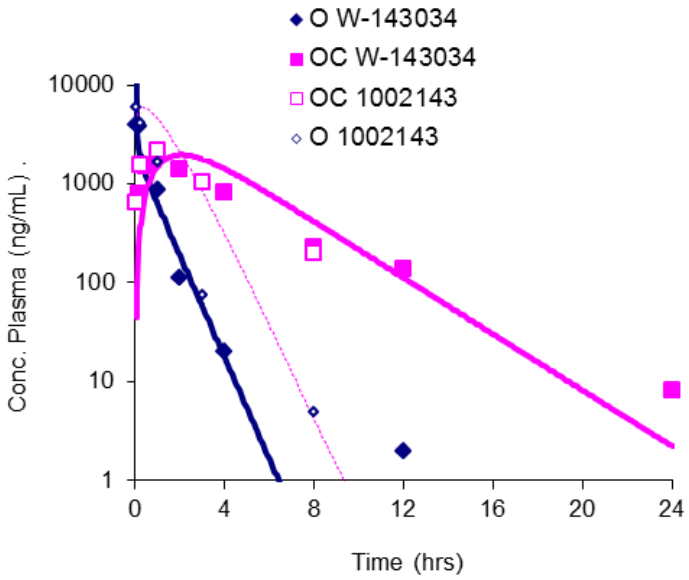
1.



2.



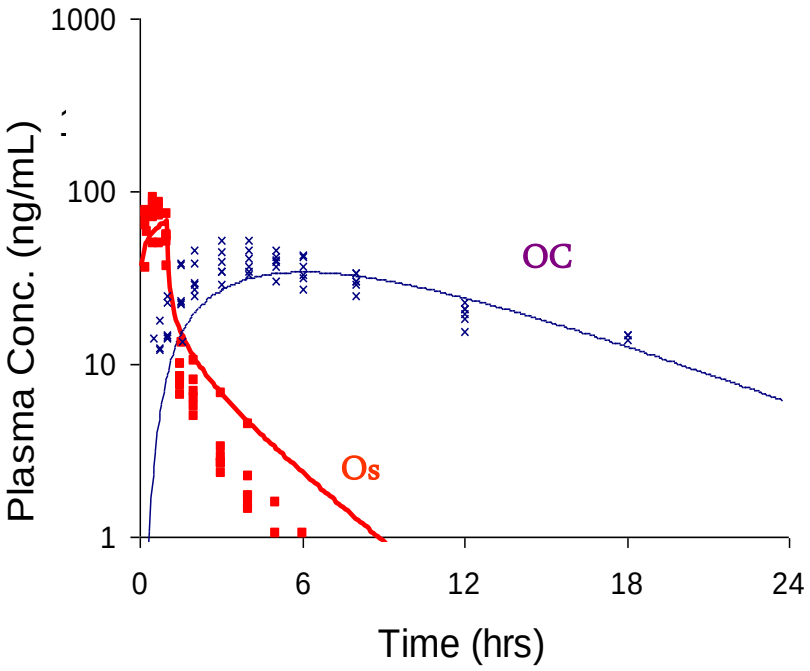
3 & 4



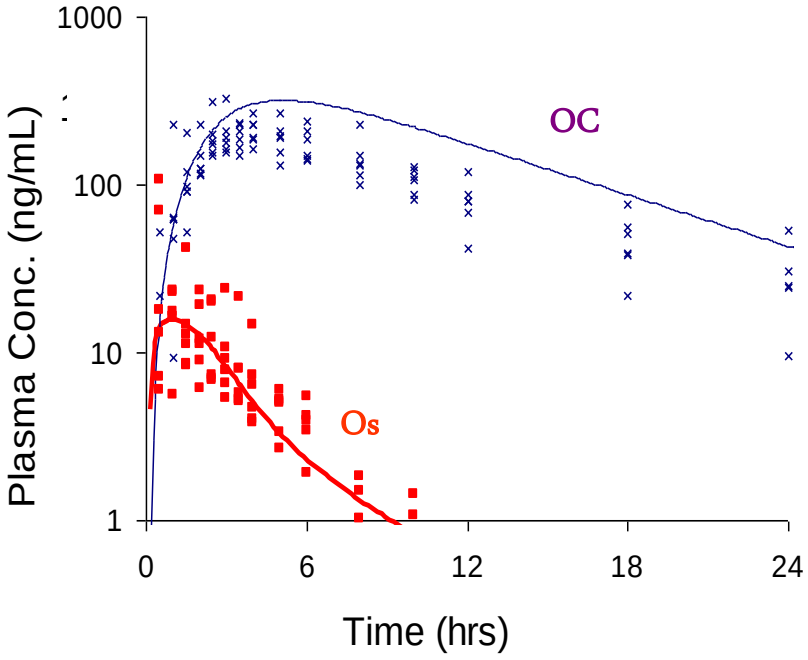
Model verification in the animal is an essential step in PBPK

Simulations in adult human

15 mg infused over 1 hour



100 mg oral dose



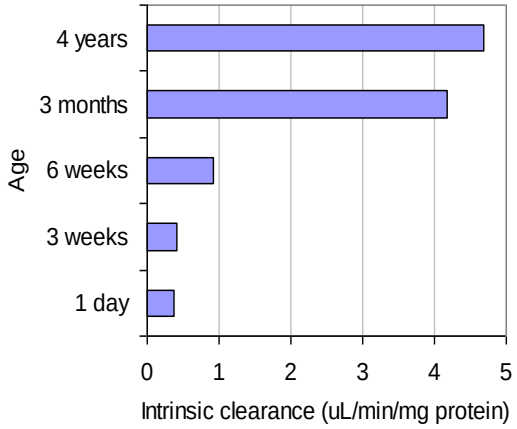
Good simulations in adult human using model refinements scaled from monkey

Integration of age dependencies

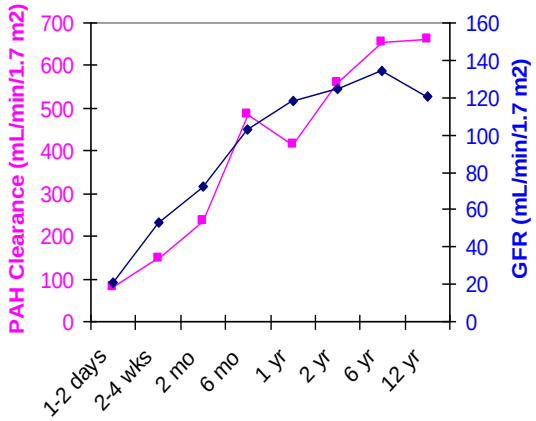
Roche

Development of body and organ size with age

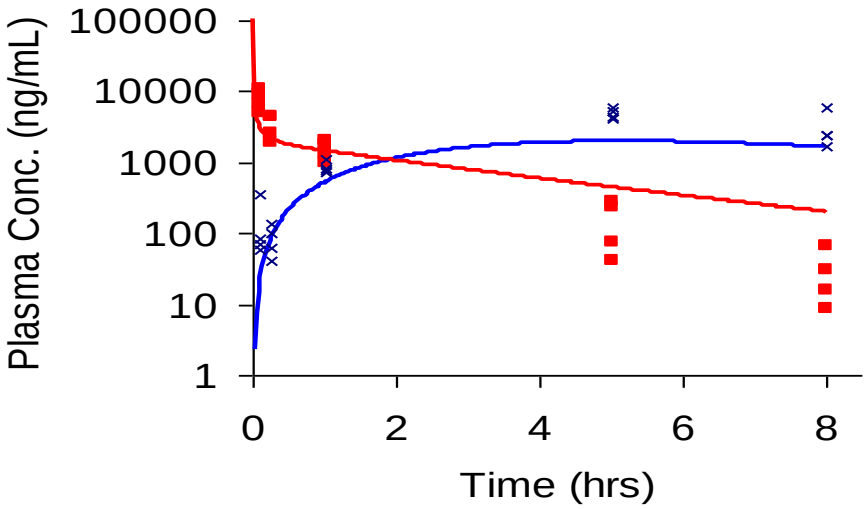
Development of metabolism with age



Maturation of renal function

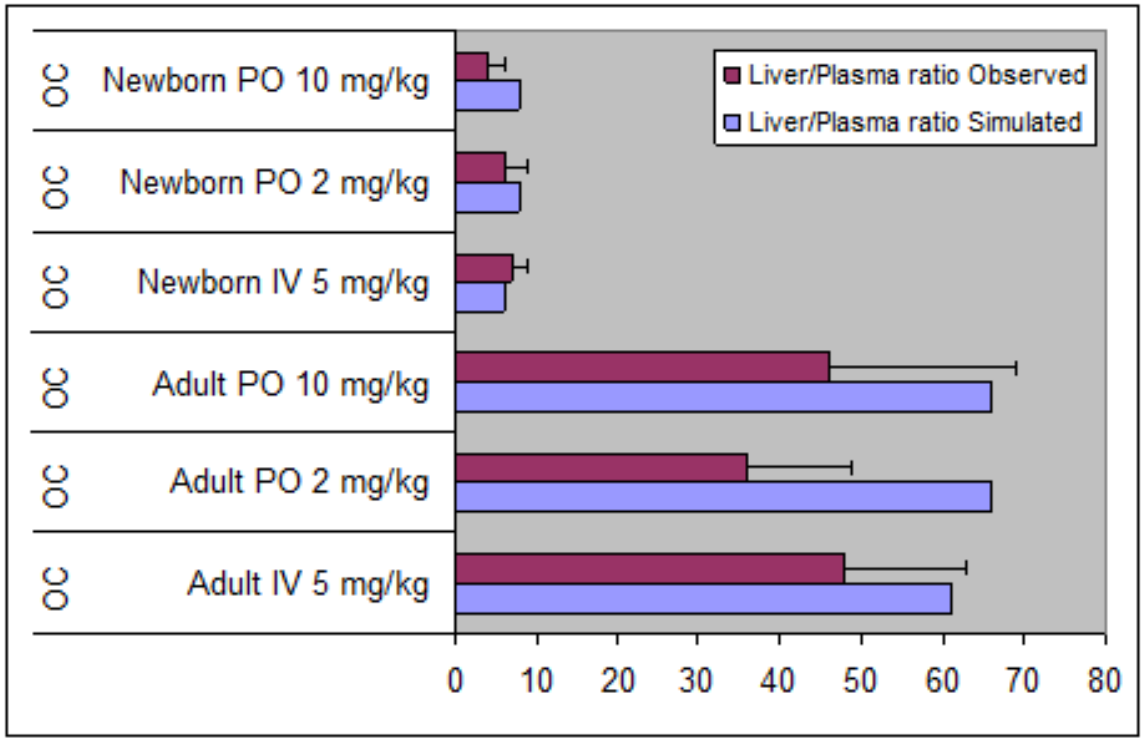


Simulation/Verification in newborn marmoset



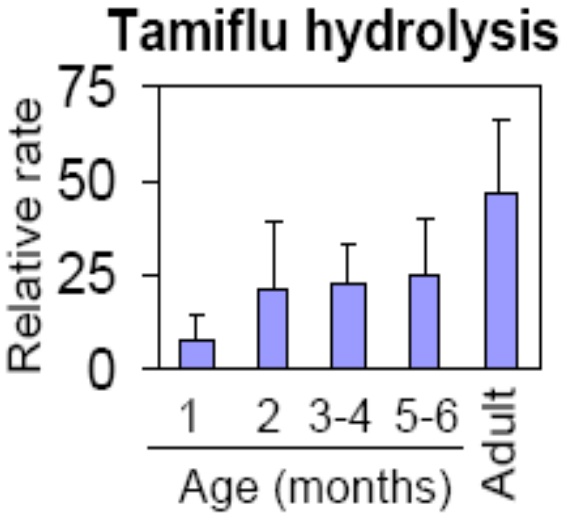
Simulated tissue concentration verification

Terminal liver concentrations of Os and OC provided further verification of the hepatic disposition model



Liver/plasma ratio difference with age is driven by balance of metabolism and release from liver

Development of esterases in human



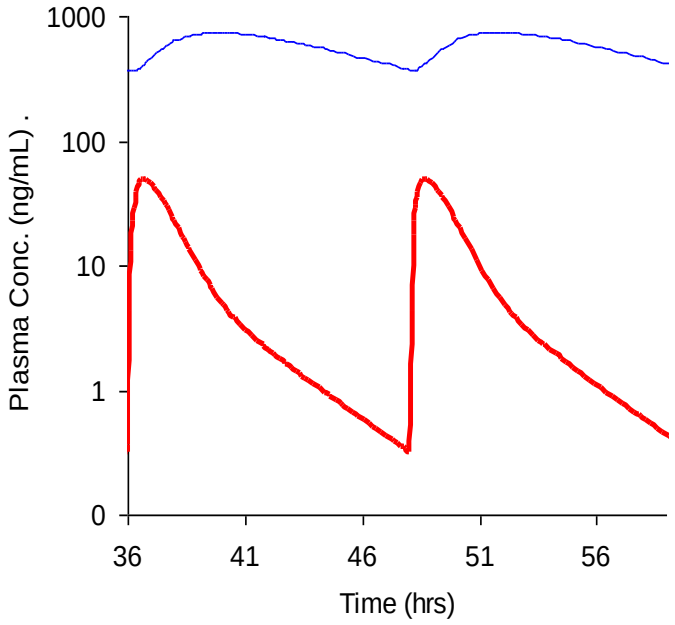
Tamiflu cleavage is approx. 10-fold reduced in human newborns – similar to marmosets

Yang, D. et al, Human carboxylesterases HCE1 and HCE2: Ontogenic expression, inter-individual variability and differential hydrolysis of oseltamivir, aspirin, deltamethrin and permethrin. Biochemical pharmacology, 2009. 7(7): p. 238 – 247.

Shi, D., et al. Surged expression of carboxylesterase-1 (CES1) during the neonatal stage and significance in the activation of the anti-influenza pro-drug oseltamivir. J Infect Dis. 2011 Apr 1;203(7):937-42

Simulation of oral dosing in infants

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



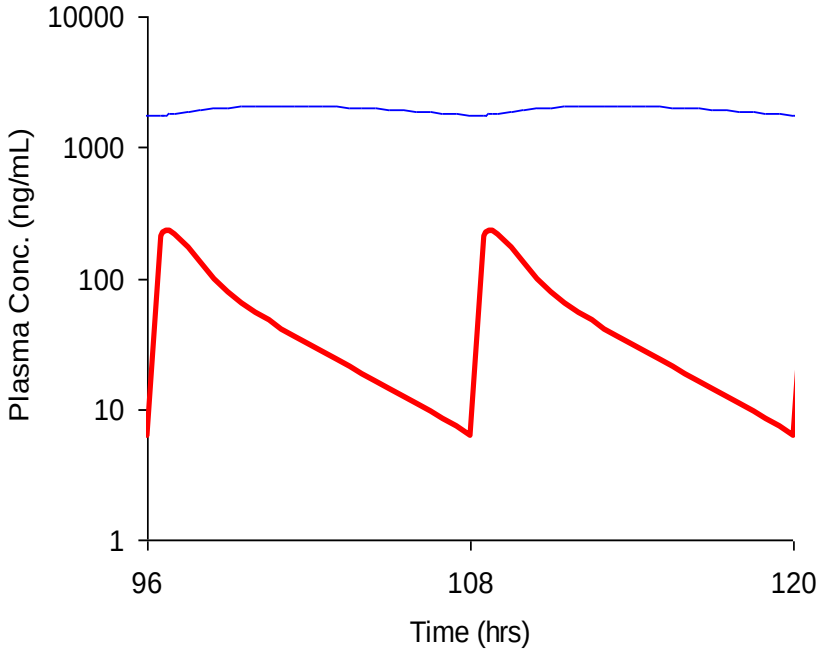
	AUC12 for OC
	(ng.hr/mL)
Reported	4326 +/- 1878
Simulated	5700

The simulated steady state AUC is within the reported range

Acosta, Edward P., P. Jester, P. Gal, J. Wimmer, J. Wade, Richard J. Whitley, and David W. Kimberlin, Oseltamivir Dosing for Influenza Infection in Premature Neonates. The Journal of Infectious Diseases, 2010. 202(4): p. 563-566.

Simulation of oral dosing in newborns

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



	AUC12 for OC (ng.hr/mL)
Reported	9250
Simulated	23000

The simulated steady state AUC approx 2x the reported value

Acosta, Edward P., P. Jester, P. Gal, J. Wimmer, J. Wade, Richard J. Whitley, and David W. Kimberlin, Oseltamivir Dosing for Influenza Infection in Premature Neonates. The Journal of Infectious Diseases, 2010. 202(4): p. 563-566.

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

Acknowledgements

Clin Pharmacokinet 2011; 50 (9): 613-623
0312-5963/11/0009-0613/$49.95/0

Development of a Physiologically Based Model for Oseltamivir and Simulation of Pharmacokinetics in Neonates and Infants

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