Farmacokinetiek bij kinderen

Najaarssymposium V&VN
Jeroen Bosch ziekenhuis, November 1, 2018

Catherijne A.J. Knibbe

Leiden /Amsterdam Center for Drug Research

ZIEKENHUIS ST ANTONIUS

Erasmus MC Universitair Medisch Centrum Rotterdam

Clinical Drug Research

- **Phase I: human volunteers**
- **Phase II: small group of strictly selected patients**
- **Phase III: larger group of strictly selected patients**

  Restrictions on: (approved by US FDA)

  - **Renal function**
  - **Hepatic function**
  - **Age**
  - **Body weight etc**

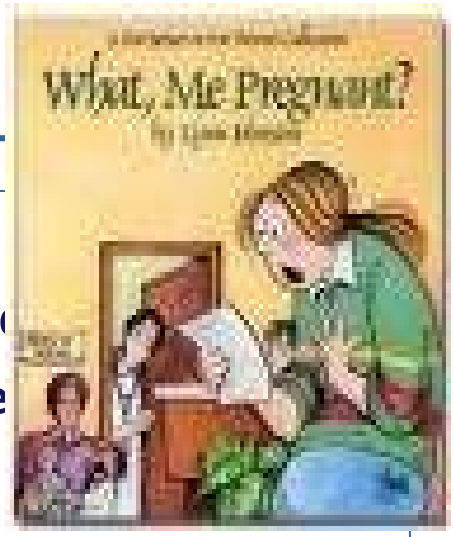
cal Drug Research

uman volunteers

mall group of strictly selecte

arger group of strictly selecte

Restrictions on: (approved by US



Drug use in children

Children: 36 - 90% of medicines used have never actually been studied in children!

1930 – diethylene glycol poisoning

1938 – sulfanilamide

1948 – chloramphenicol - gray baby syndrome

1960 – thalidomide

2004 – SSRIs

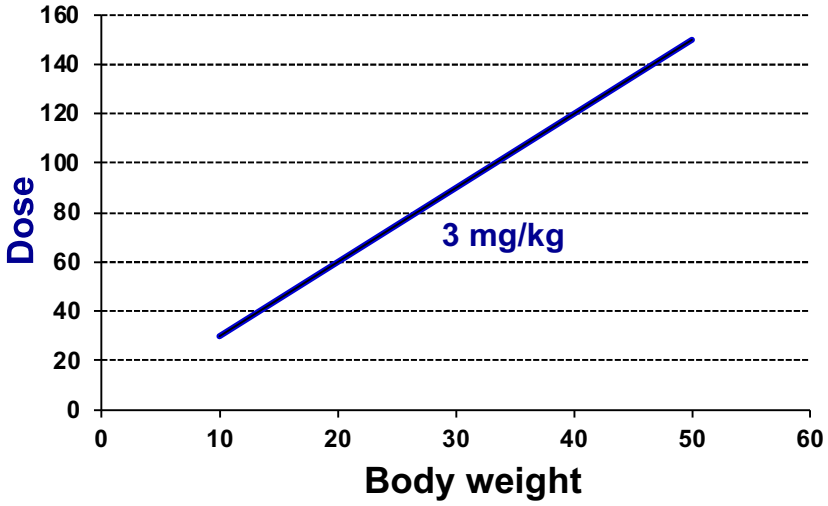
Cuzzolin et al. Expert Opin. Drug Saf.(2006)

Drug use in children

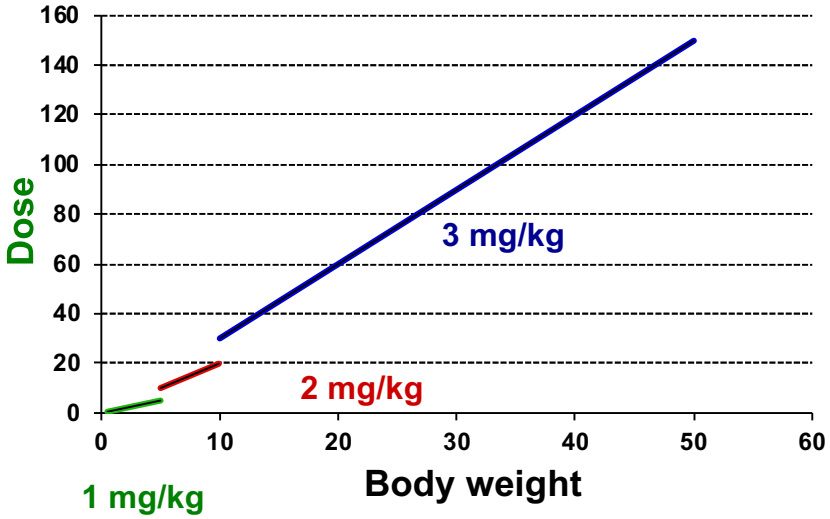
With or without evidence:…

In practice/in clinical trials drugs in children are mainly dosed in mg/kg

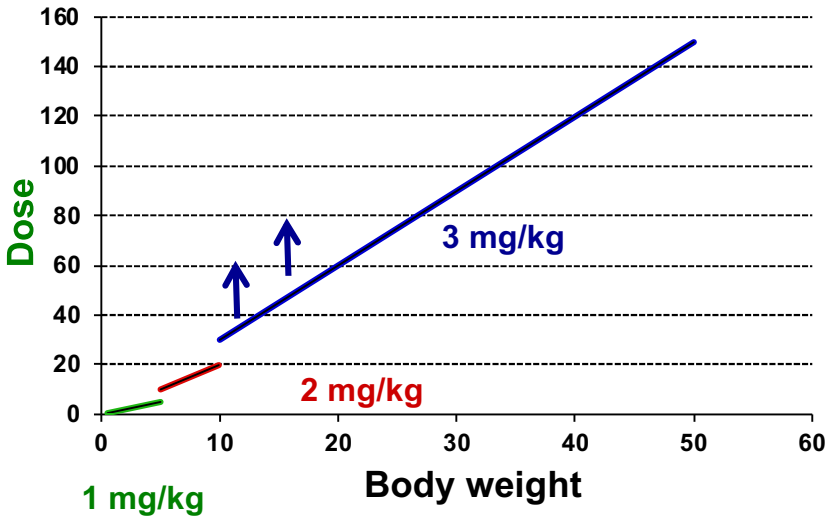
mg/kg dosing in children?



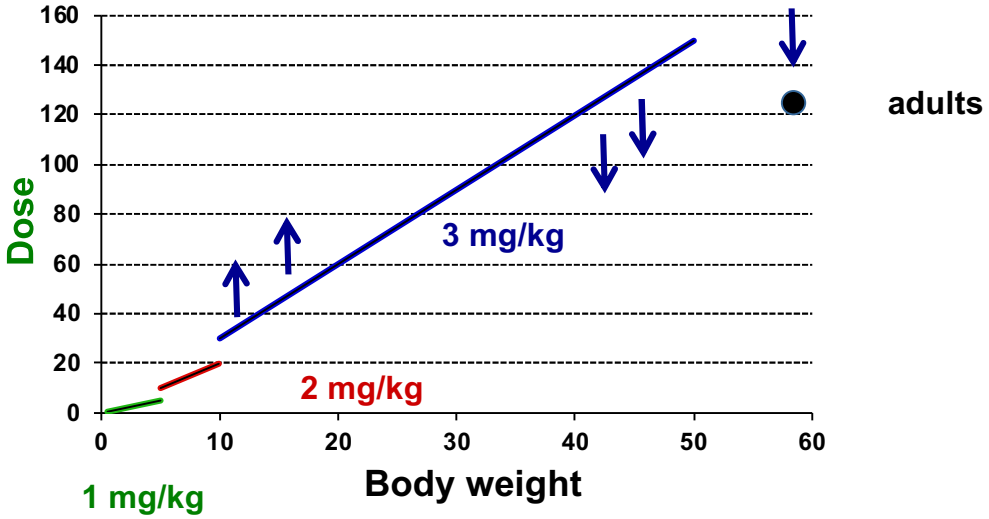
mg/kg dosing in children?



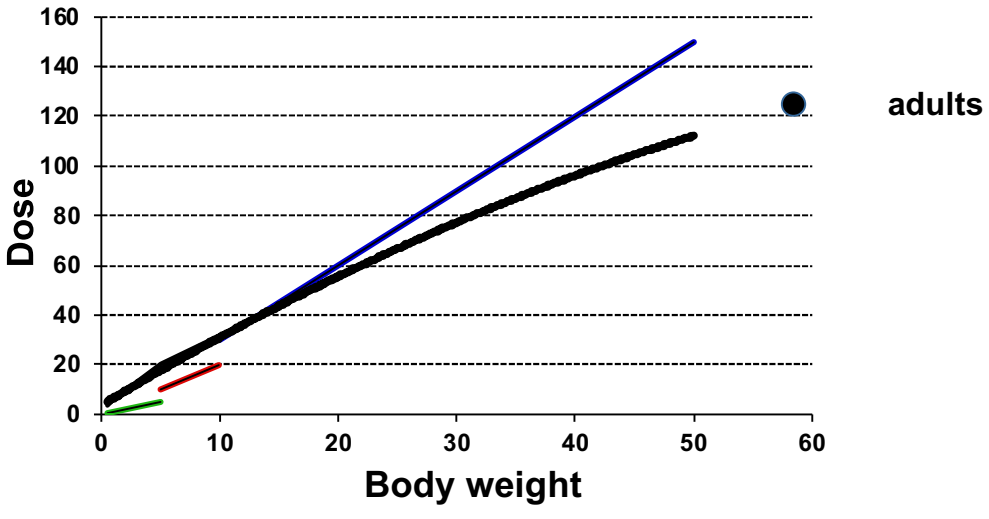
mg/kg dosing in children?



mg/kg dosing in children?

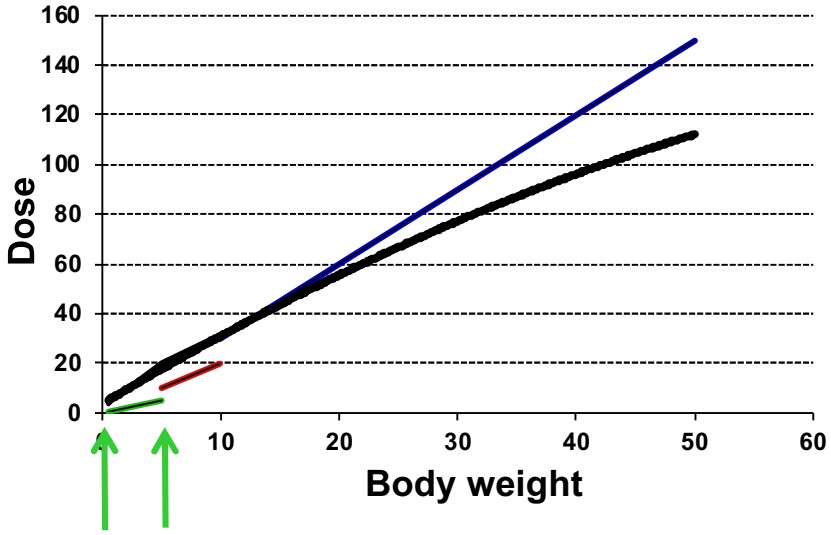


mg/kg dosing in children?



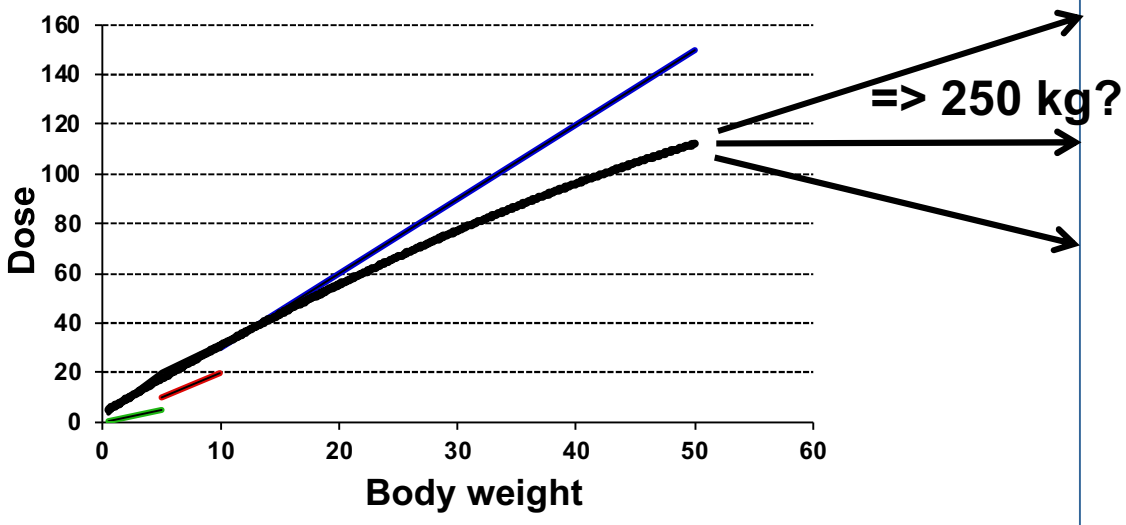
mg/kg dosing in children?

What about the heterogeneous group of neonates?

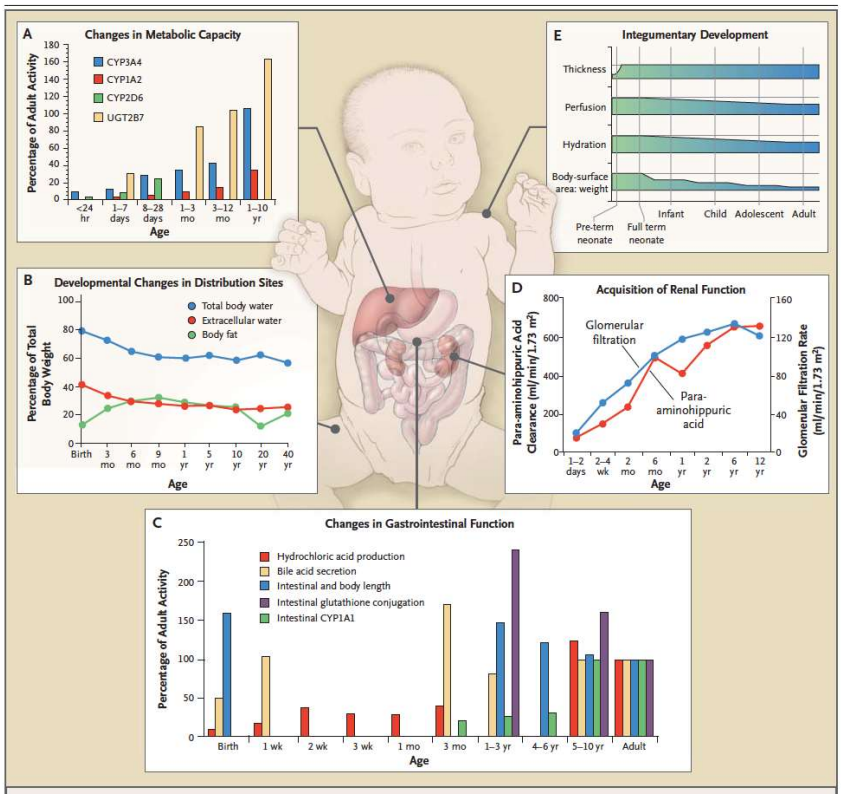


mg/kg dosing in children?

What about morbidly obese patients?



Paediatric Drug Dosing – How it Should Be



Kearns G, et al. NEJM 2003

Paediatric Drug Dosing – How it Should Be

Individualized dosing based on differences in

dose – effect relationship

Pharmacokinetics ***Pharmacodynamics***

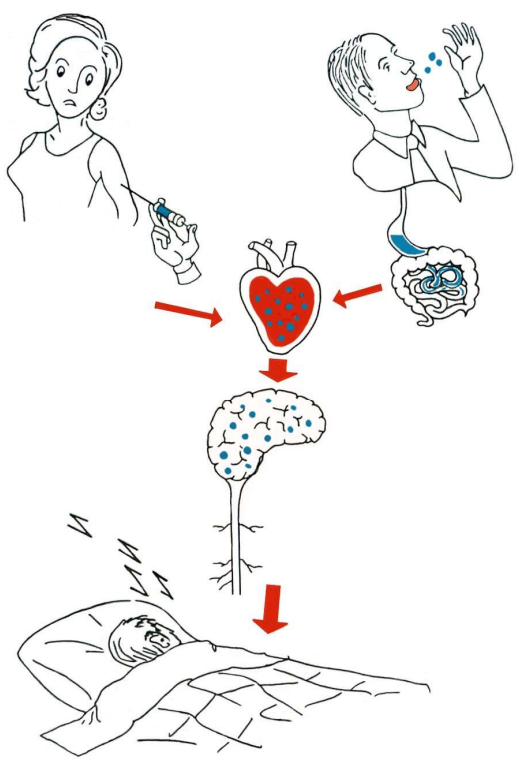
Drug Dose → **Drug Concentration** → **Drug Effect**

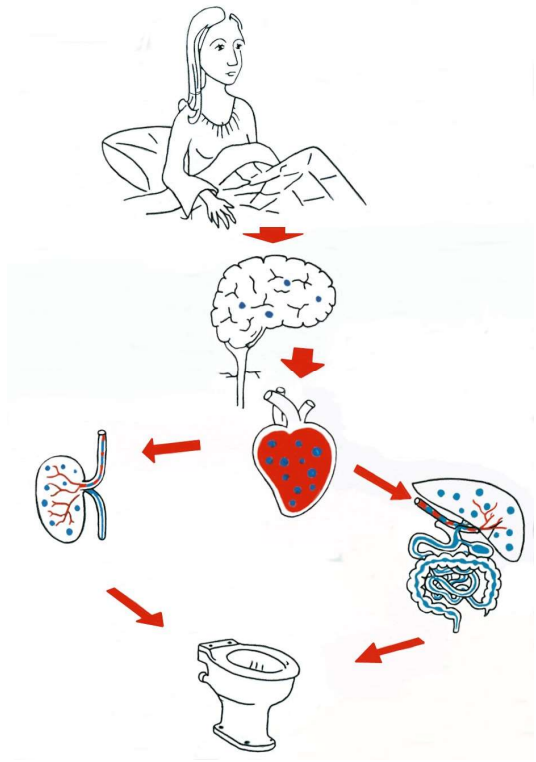
Admiraal R et al., Arch Dis Child (2014)

de Cock R et al., Eur J Clin pharmacol (2011)

Knibbe C et al, Expert Opin Drug Metab Toxicol (2011)

Lotgevallen van geneesmiddelen





Absorptie

Hogere pH bij pasgeborenen (preterm vs term)

Zuur-gevoelig: opname ↑ bij neonaat:

penicilline, erythromycine

Zwakke organische zuren: opname ↓

Fenobarbital, fenytoine

Vertraagde maag/darm passage bij pasgeborenen

Immature darmmucosa & transporters

First-pass metabolisme ↓

=> Snelheid van orale absorptie ↓ en tijd tot Cmax ↑

Absorptie

Biobeschikbaarheid kan verhoogd of verlaagd zijn: zuurgraad, maagpassage, transporters, first pass

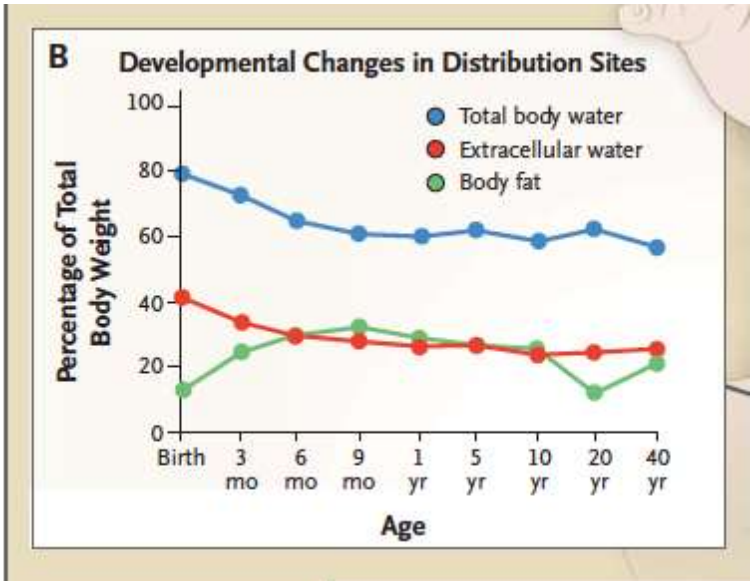
Rectale absorptie: incompleet, wisselend, verlies via feces

Absorptie via de huid: toegenomen huidoppervlak & permeabiliteit

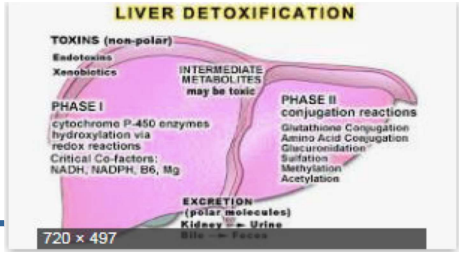
Distributie

Lichaams-samenstelling

Eigenschappen van het geneesmiddel: Lipofiel/hydrofiel, eiwitbinding etc



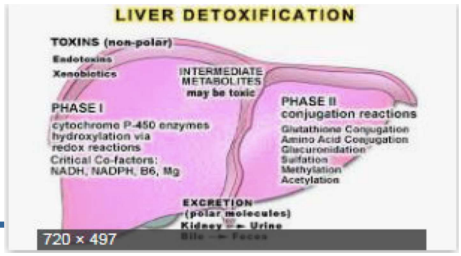
Metabolisatie



Metabolisme via enzymen Fase I en II:

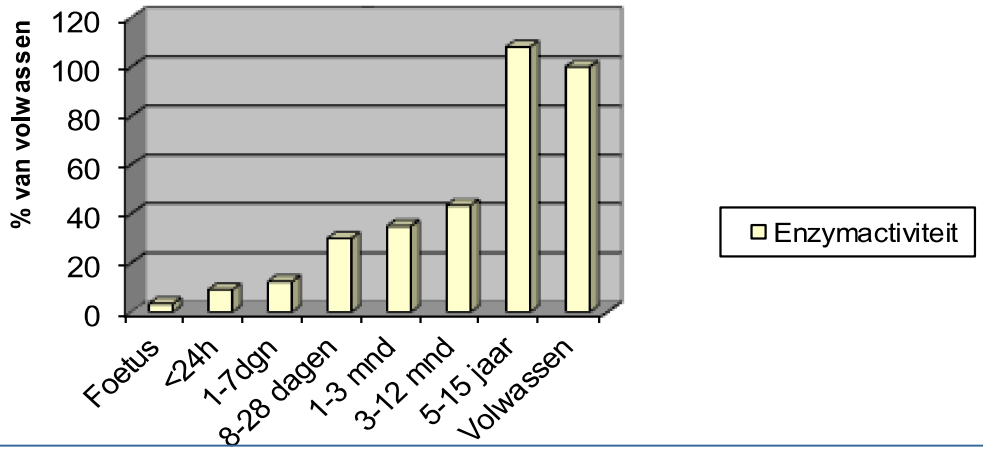
Toename vanaf 3e trimester tot 1-2 jaar (CYP1A, 2C9, 2C19, 2D6, 2E1, 3A4, UGT's)

Metabolisatie



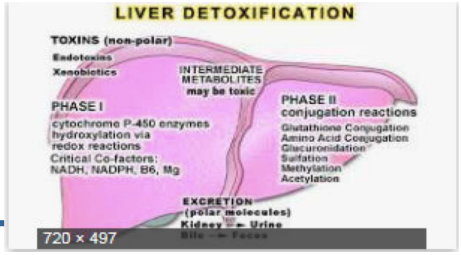
Metabolisme via enzymen Fase I en II:

Toename vanaf 3e trimester tot 1-2 jaar (CYP1A, 2C9, 2C19, 2D6, 2E1, 3A4, UGT's)



Alcorn et al, Clin Pharmacokinet 2002

Metabolisatie



Metabolisme via enzymen Fase I en II:

Toename vanaf 3e trimester tot 1-2 jaar (CYP1A, 2C9, 2C19, 2D6, 2E1, 3A4, UGT's)

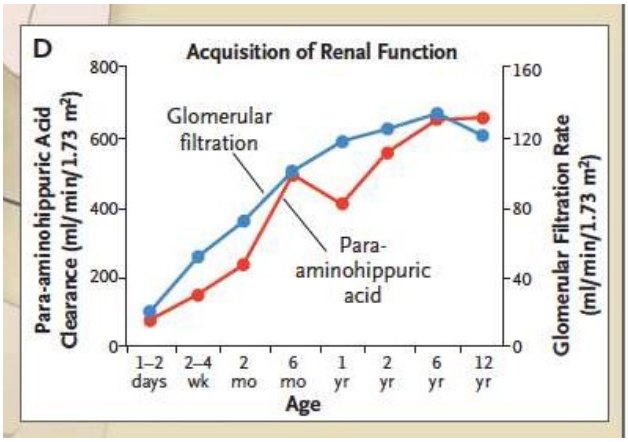
Foetale expressie daarna afname (CYP3A7)

Foetaal constant, daarna toename (CYP3A5, TPMT)

Excretie

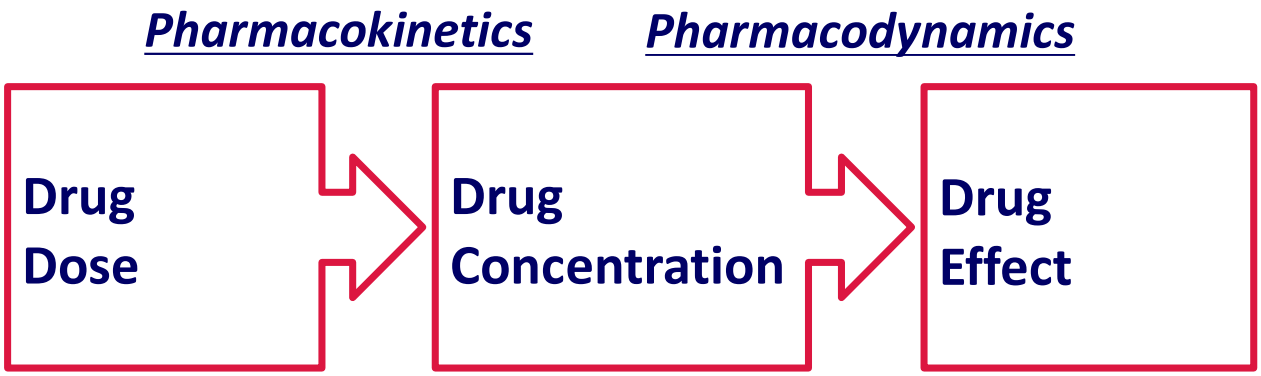
Eliminatie via de nier

- GFR (snelle maturatie)
- Tubulaire processen (maturatie trager dan GFR)



Paediatric Drug Dosing – How it Should Be

Individualized dosing based on differences in dose – effect relationship



Admiraal R et al., Arch Dis Child (2014)
de Cock R et al., Eur J Clin pharmacol (2011)
Knibbe C et al, Expert Opin Drug Metab Toxicol (2011)

Peadiatric projects (2007- to date)

- Morphine glucuronidation and u-opioid analgesia vs paracetamol (ErasmusMC)
- Midazolam CYP3A and GABA-A sedation (ErasmusMC)
- Propofol liver blood flow and multiple PD endpoints (ErasmusMC)
- Busulfan chemoablation and immunosuppression and ATG dosing (UMCU)
- Aminoglycoside/glycopeptide renal function (KU Leuven)

And many others

Approach

Population PK-PD models

Approach

Population PK-PD models

Individualized dosing guidelines for *specific* drugs

Approach

Population PK-PD models

DOSE → Drug Concentration → Efficacy / Safety

Individualized dosing

guidelines for *specific* drugs

'Systems approach'

Biological system

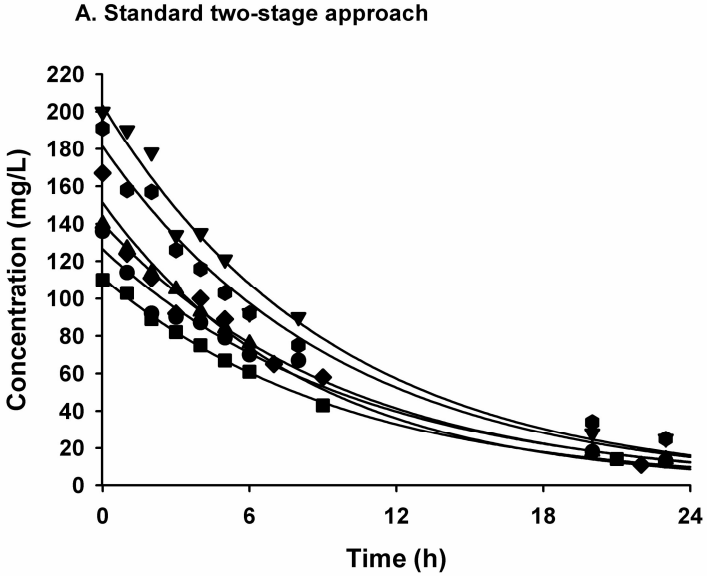
specific information

For predictions of other drugs that are metabolised through the same pathway

Traditional approach

Standard two stage approach

PK and/or PD parameters are individually estimated in each participating patient



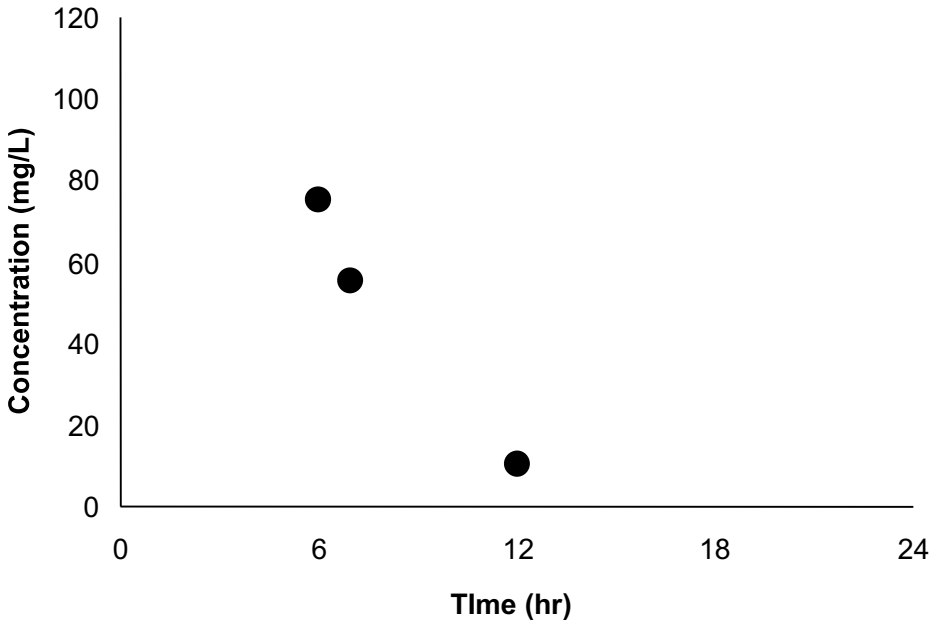
De Cock R et al., Eur J Clin Pharmacol 2010

What are characteristics of pediatric trials?

- Additional legislation
- Small numbers of patients
- Reduced possibilities for vena puncture
- Low volume/small number of blood samples
- Varying drug formulations
- Low percentage of informed consent
- Different PD endpoints (validation?)

De Cock R et al., Eur J Clin Pharmacol 2010

e.g. AUC estimation in children?



De Cock R et al., Eur J Clin Pharmacol 2010

Pediatric Research Issues

Unbalanced vs balanced designs:

7 observations for subject A

1 observation for subject B

Sparse vs. serial data:

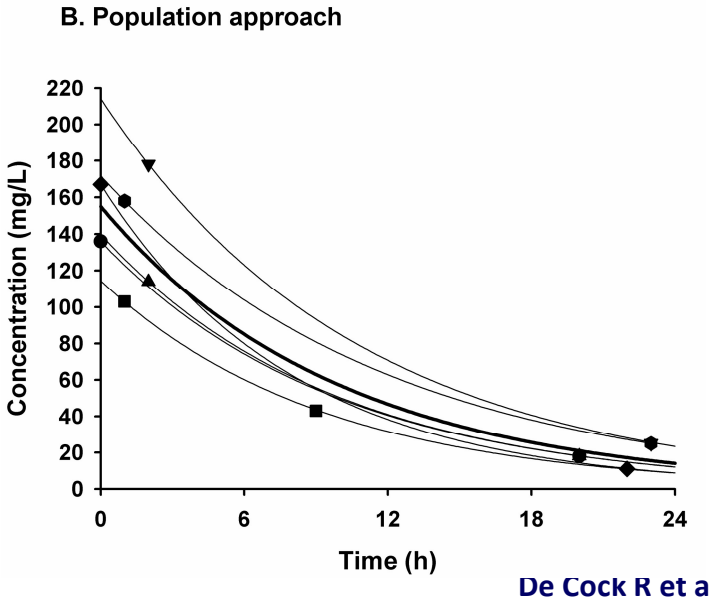
2 measurements per subject

De Cock R et al., Eur J Clin Pharmacol 2010

Population approach

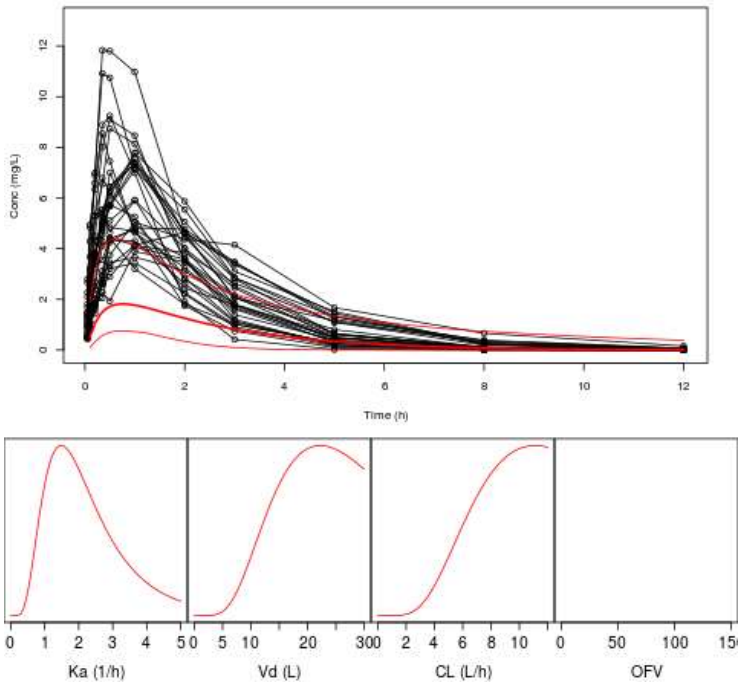
Simultaneous analysis of all available data:

PK and/or PD parameters are simultaneously estimated taking into account differences between patients



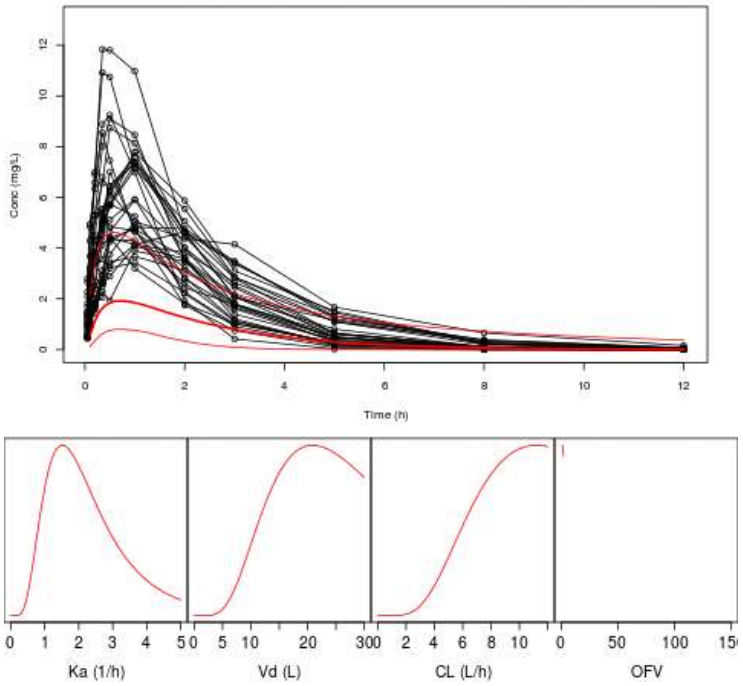
De Cock R et al., Eur J Clin Pharmacol 2010

Population approach



Courtesy to Pyry Valitalo

Population approach



Courtesy to Pyry Valitalo

Population PK-PD modelling

- Applicable to sparse and unbalanced data sets (neonates, children, critically ill patients etc)
- Co-variate analysis for identification of predictors of variability in PK and PD (genetics, body weight, age, interactions etc)
- Scientific basis for study/trial simulations, dose adjustment or labeling extensions in other populations (intra and interspecies extrapolations)

De Cock R et al., Eur J Clin Pharmacol 2010

Amikacin clearance in preterm and term neonates

De Cock R et al, Clin Pharmacokinet 2012

Targets for antibiotics

Aminoglycosides

- Area Under the Curve relates to efficacy
  - Peak concentration is used as proxy for AUC….
- Trough concentration relates to toxicity

Vancomycin

- Area Under the Curve relates to efficacy
  - Trough concentration is used as proxy for AUC….
- Toxicity related to (peak) concentrations above 40 mg/l?

De Cock R et al, Clin Pharmacokinet 2012, Janssen E et al., AAC 2015

Datasets to develop and validate a model to guide amikacin dosing in neonates

N=874 neonates

Amikacin internal validation datasets:

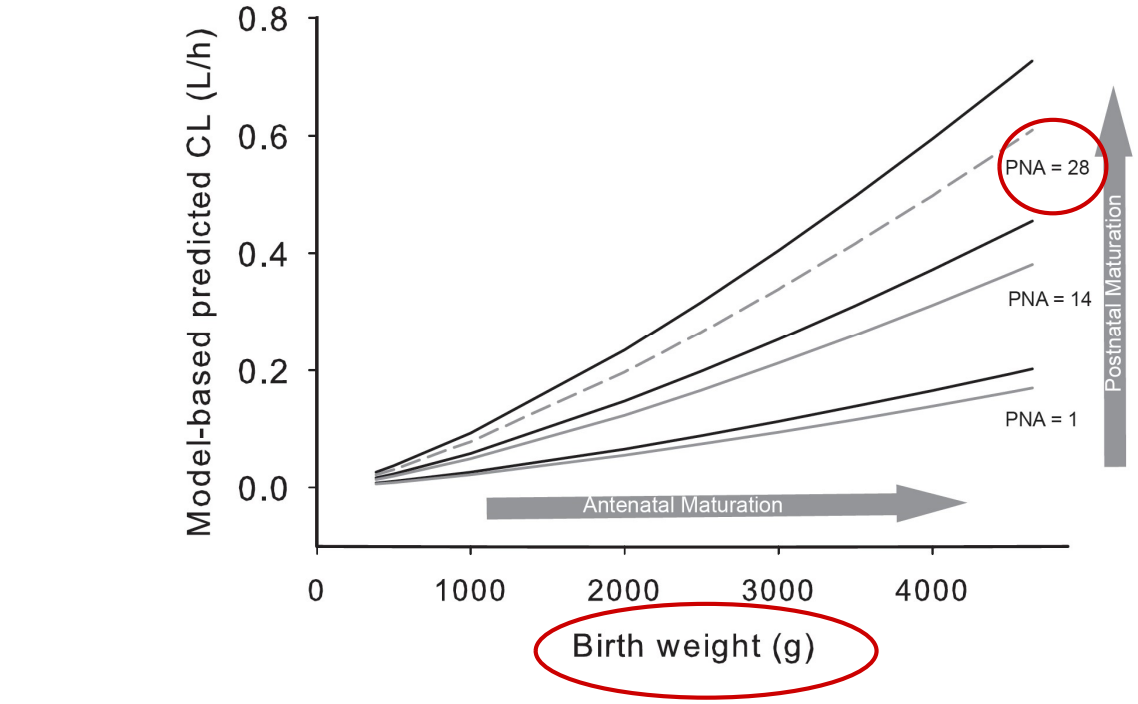
- 162 preterm neonates: GA 24-30 weeks, current weight 475-1910g, PNA 1-3 days[1]
- 712 (pre)term neonates: GA 24-43 weeks, current weight 385-4780g, PNA 1-30 days[2]

Amikacin external validation datasets:

- N=80 (pre)term neonates: GA 24-41 weeks, current weight 450-4430g, PNA 3-30 days[3]
- N=159 (pre) term neonates: GA 25-42 weeks, current weight 526-5420g, PNA 1-3 days[4]

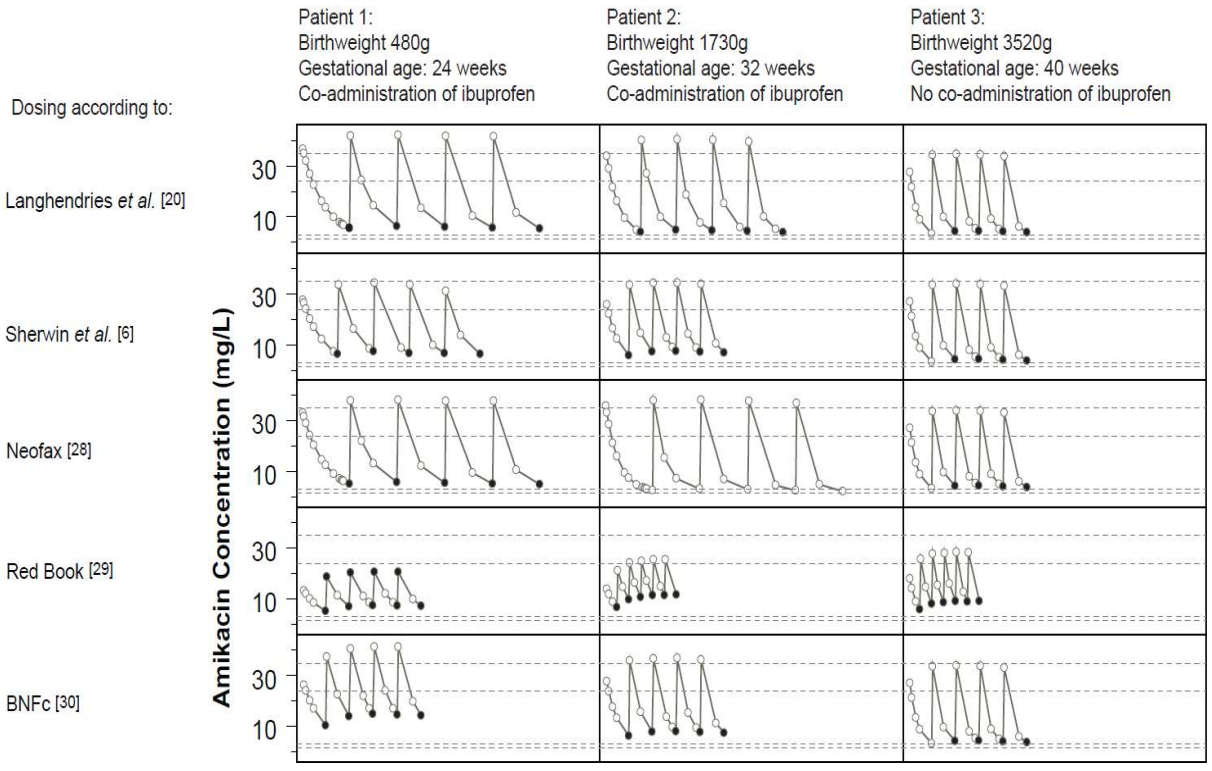
De Cock R et al, Clin Pharmacokinet 2012

Three major covariates for amikacin clearance that can be used to guide dosing



De Cock R et al, Clin Pharmacokinet 2012

Model based simulations to illustrate exposure upon existing dosing guidelines



De Cock R et al, Clin Pharmacokinet 2012

Prospective evaluation of model-based dosing of amikacin dosing De Cock R et al, Clin Pharmacokinet 2012

	a. Original model-based dosing regimen (4)		b. Simplified model-based dosing regimen		c. Final proposed dosing regimen after prospective validation	
Current bodyweight (g)	PNA <14 days	PNA ≥14 days	PNA <14 days	PNA ≥14 days	PNA <14 days	PNA ≥14 days
0-800	16 mg/kg/48h (group 1)	20 mg/kg/42h (group 2)	16 mg/kg/48h	20 mg/kg/42h	16 mg/kg/48h	20 mg/kg/42h
800-1200	16 mg/kg/42h (group 3)	20 mg/kg/36h (group 4)	16 mg/kg/42h	20 mg/kg/36h	16 mg/kg/42h	20 mg/kg/36h
1200-2000	15 mg/kg/36h (group 5)	19 mg/kg/30h (group 6)	15 mg/kg/36h	***18 mg/kg/30h***	15 mg/kg/36h	18 mg/kg/30h
2000-2800	13 mg/kg/30h (group 7)	18 mg/kg/24h (group 8)	***15 mg/kg/30h***	18 mg/kg/24h	***15 mg/kg/36h***	18 mg/kg/24h
≥2800	12 mg/kg/24h (group 9)	17 mg/kg/20h (group 10)	***15 mg/kg/24h***	***18 mg/kg/20h***	***15 mg/kg/30h***	18 mg/kg/20h

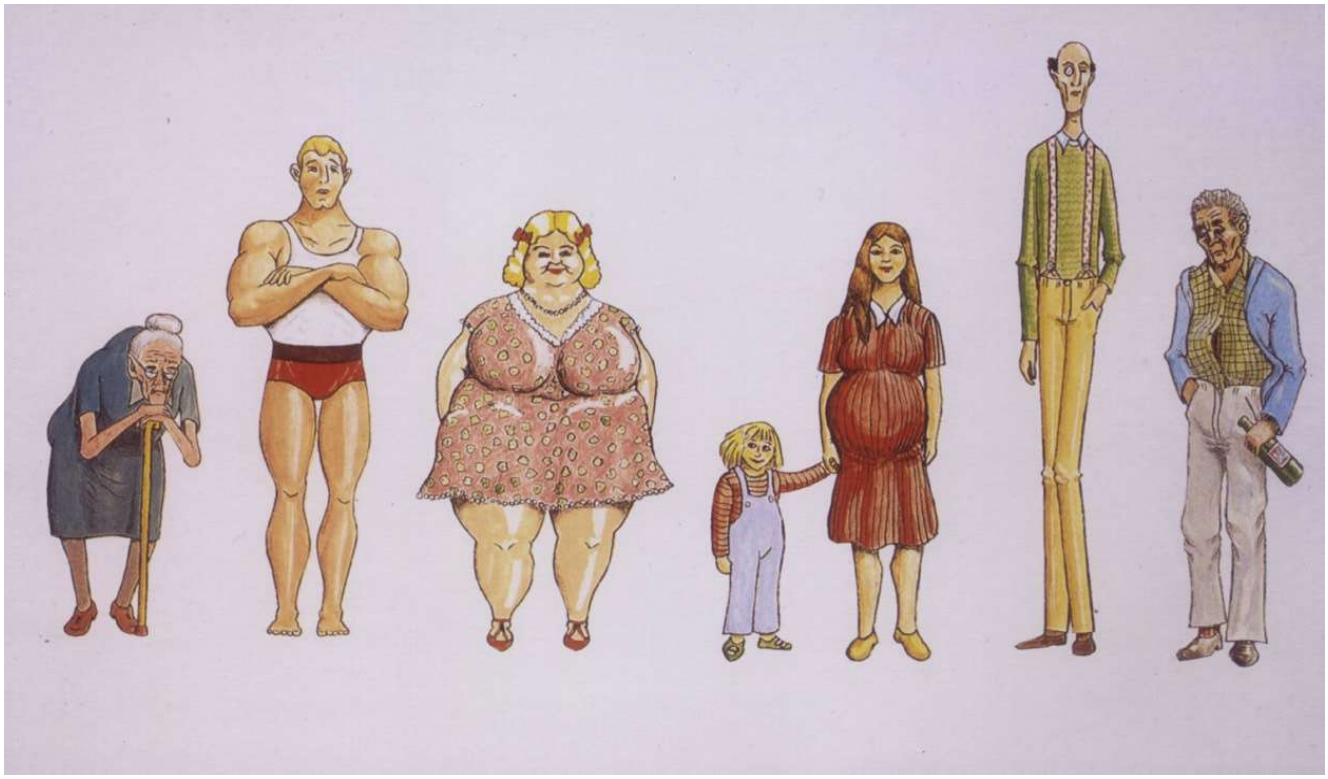
The dosing interval was prolonged 10 hours, when ibuprofen was co-administered or when asphyxia was diagnosed/considered by the treating physician. Duration of the intravenous infusion was 20 minutes, PNA = postnatal age.

Prospective evaluation of model-based dosing of amikacin dosing De Cock R et al, Clin Pharmacokinet 2012

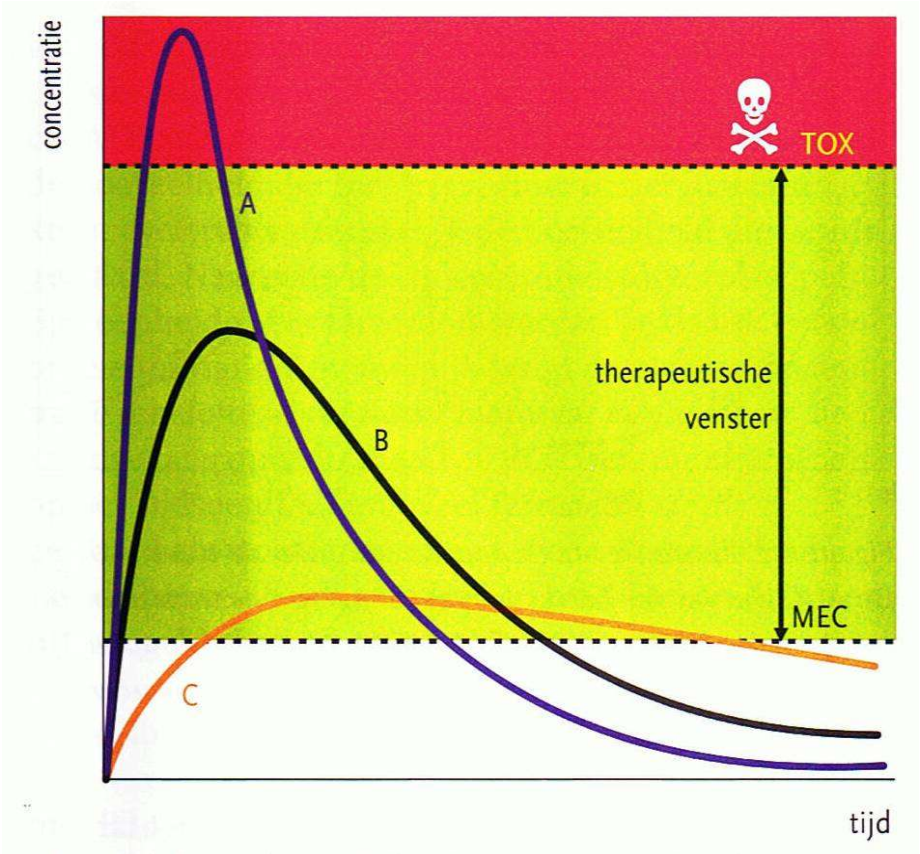
- N=579 neonates [median birth bodyweight 2285 (range 420-4850) g, postnatal age 2 (1-35 30) days, gestational age 34 (24-41) weeks]
- Early TDM:
  - peak > 24 mg/L: 90.5%
  - trough < 3 mg/L: 60.2% (93.4% ≤5 mg/L)
- Steady state
  - peak: almost all patients > 24 mg/L
  - trough: 78-100% and 45-96% < 3 mg/L

Smits A et al, submitted for publication

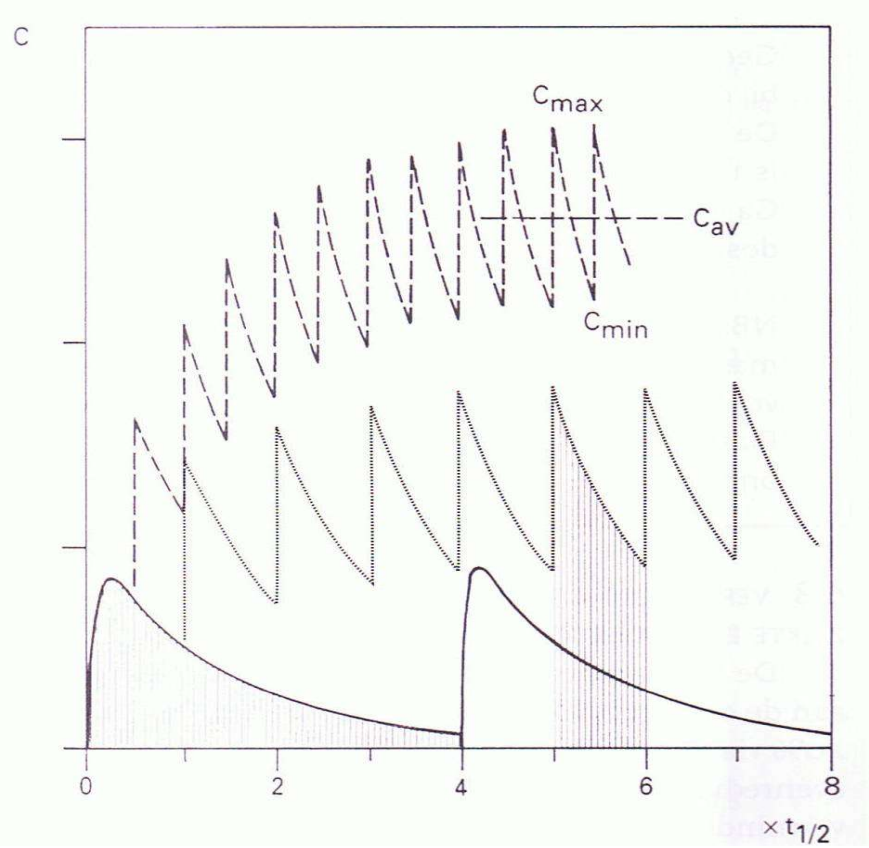
En dan nog even over farmacokinetiek voor de praktijk…



Farmacokinetiek (enkelvoudige toediening)



Farmacokinetiek (meervoudige toediening)



To summarize

Population PK-PD models

'Systems approach'

DOSE → Drug Concentration → Efficacy / Safety → **Biological system**

specific information

Individualized dosing

guidelines for *specific* drugs

For predictions of other drugs that are metabolised through the same pathway

Research group

- LACDR/Leiden

  Elke Krekels, Coen van Hasselt, Pyry Valitalo, Jantine Brussee, Elisa Calvier, Bas Goulooze, Sinziana Cristea, Ibrahim Ince, Maurice Wang, Roosmarijn de Cock, Meindert Danhof, Piet Hein van der Graaf, Thomas Hankemeier

- Rotterdam, Erasmus MC Sophia

  Sinno Simons, John van den Anker, Matthijs de Hoog, Ron van Schaik, Nienke Vet, Paola Mian, Monique van Dijk, Dick Tibboel, Irwin Reiss

- KU Leuven

  Anne Smits, Karel Allegaert

- Radboud Nijmegen

  Roger Bruggemann, Roeland Wasmann, Robert Flint, David Burger, Saskia de Wildt

- Utrecht Medical Centre

  Rick Admiraal,Toine Egberts, Jaap Jan Boelens, Lieke Sanders

- St. Antonius, Nieuwegein

  Cornelis Smit, Margreke Brill, Anne van Rongen, Sjoerd de Hoogd, Jeroen Diepstraten, Simone van Kralingen, Rifka Peeters, Eric van Dongen, Bert v Ramshorst, Marja van der Vorst, Marloes van der Aa, Rene Wiezer, Erik Hazebroek, Mathieu Tjoeng

- Cincinnati Childrens Hospital

  Sander Vinks

- University of Utah

  Catherine Sherwin

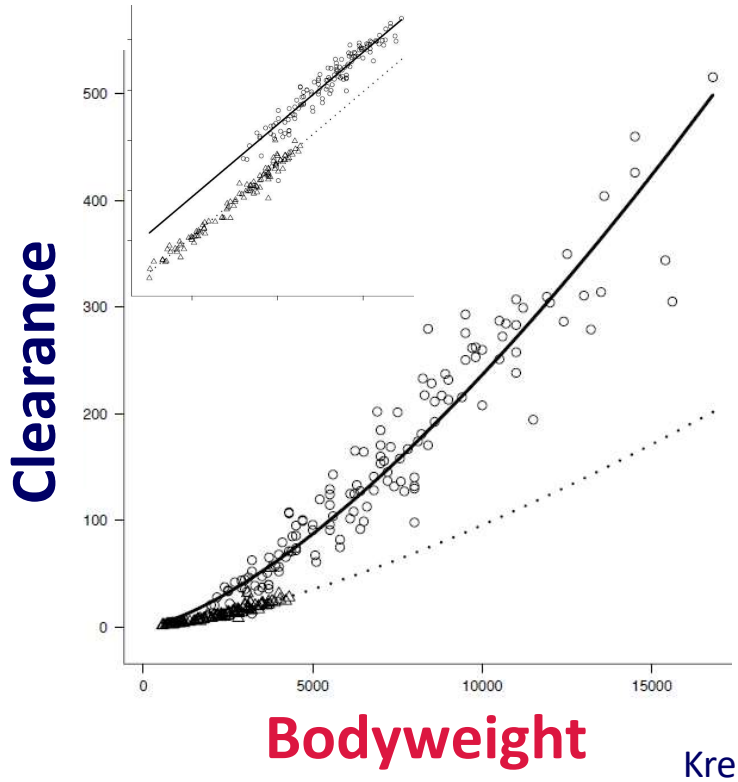
- University of Manchester

  Amin Rostami, Adam Darwich, Leon Aarons

....

BACKUP SLIDES

Morphine Pharmacokinetics



$CL = CL_p * BW^{1.44}$

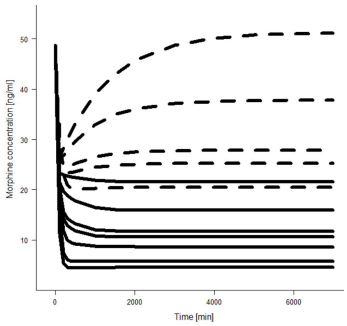
If PNA < 10 days
'CL_p' 50% reduced

Krekels et al. *Clin. Pharmacokinet.*(2011)
Knibbe et al. *Clin. Pharmacokinet.*(2009)

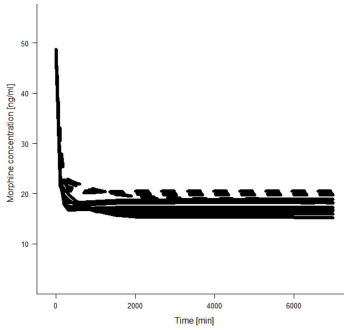
Model-Derived Morphine Dosing

Clearance determines steady state concentrations

Traditional dosing:
10 µg/kg/h



Proposed dosing:
5 µg/kg$^{1.5}$/h
or
2.5 µg/kg$^{1.5}$/h



	PNA < 10 days *2.5 µg/kg$^{1.5}$/h*	*PNA > 10 days* *5 µg/kg$^{1.5}$/h*
Bodyweight (kg)	Infusion rate µg/kg/h	Infusion rate µg/kg/h
1.5 – 2	3.1	6.1
2 – 2.5	3.5	7.1
2.5 – 3	4.0	7.9
3 – 3.5	4.3	8.7
3.5 – 4	4.7	9.4
4 – 4.5	5.0	10.0
4.5 – 5	5.3	10.6
5 – 5.5	5.6	11.2
5.5 – 6	.	11.7
6 – 6.5	.	12.3
6.5 – 7	.	12.8
7 – 7.5	.	13.2
7.5 – 8	.	13.7
8 – 8.5	.	14.1
8.5 – 9	.	14.6
9 – 9.5	.	15.0
9.5 – 10	.	15.4
10 – 10.5	.	15.8

Knibbe et al. *Int.J.Pharm.*(2011)

Prospective morphine PK-PD study

Prospectively evaluate model-derived morphine dosing regimen:

1. **Analgesic efficacy** (total morphine rescue dose & average actual morphine infusion rate)

1. **Morphine and metabolite concentrations**

Krekels EH et al. *Clin Pharmacokinet.* (2014)

Effect of Intravenous Paracetamol on Postoperative Morphine Requirements in Neonates and Infants Undergoing Major Noncardiac Surgery

A Randomized Controlled Trial

Ilse Ceelie, MD, PhD
Saskia N. de Wildt, MD, PhD
Monique van Dijk, MSc, PhD
Margreeth M. J. van den Berg, MD
Gerbrich E. van den Bosch, MD
Hugo J. Duivenvoorden, PhD
Tom G. de Leeuw, MD
Ron Mathôt, PharmD, PhD
Catherijne A. J. Knibbe, PharmD, PhD
Dick Tibboel, MD, PhD

Importance Continuous morphine infusion as standard postoperative analgesic therapy in young infants is associated with unwanted adverse effects such as respiratory depression.

Objective To determine whether intravenous paracetamol (acetaminophen) would significantly (>30%) reduce morphine requirements in neonates and infants after major surgery.

Design, Setting, and Patients Single-center, randomized, double-blind study conducted in a level 3 pediatric intensive care unit in Rotterdam, the Netherlands. Patients were 71 neonates or infants younger than 1 year undergoing major thoracic (noncardiac) or abdominal surgery between March 2008 and July 2010, with follow-up of 48 hours.

Interventions All patients received a loading dose of morphine 30 minutes before the end of surgery, followed by continuous morphine or intermittent intravenous paracetamol up to 48 hours postsurgery. Infants in both study groups received morphine (boluses and/or continuous infusion) as rescue medication on the guidance of the validated pain assessment instruments.

Main Outcome Measures Primary outcome was cumulative morphine dose (study and rescue dose). Secondary outcomes were pain scores and morphine-related adverse effects.

Results The cumulative median morphine dose in the first 48 hours postoperatively was 121 (interquartile range, 99-264) μg/kg in the paracetamol group (n=33) and 357 (interquartile range, 220-605) μg/kg in the morphine group (n=38), $P < .001$, with a between-group difference that was 66% (95% CI, 34%-109%) lower in the paracetamol group. Pain scores and adverse effects were not significantly different between groups.

Conclusion and Relevance Among infants undergoing major surgery, postoperative use of intermittent intravenous paracetamol compared with continuous morphine resulted in a lower cumulative morphine dose over 48 hours.

Trial Registration trialregister.nl Identifier: NTR1438

JAMA. 2013;309(2):149-154 www.jama.com

THE TREATMENT OF PAIN IN young children has improved after the publications by Anand et al[1,2] in 1987 that made clear that neonates have well-developed nociceptive pathways and therefore are capable of experiencing pain. Because untreated pain is both an unwanted experience and ultimately may lead to adverse consequences,[3-6] opioids were introduced and have been used ever since.[7] Opioid therapy, however, is associated with adverse effects, in particular respiratory depression.[8] Researchers, therefore, are in search of

(2013)

Results – Analgesic efficacy

PNA <10 days – 2.5 µg/kg$^{1.5}$/h

5 (=27.8%) need of rescue

0 (0 – 539) µg/kg total rescue dose

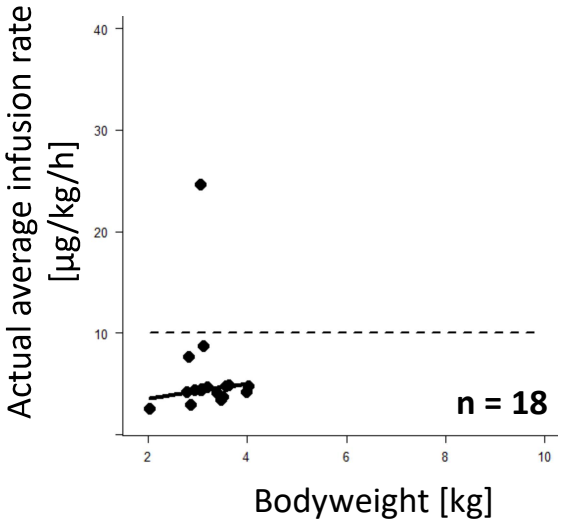
4.4 (3.6 – 5.0) µg/kg/h average rate

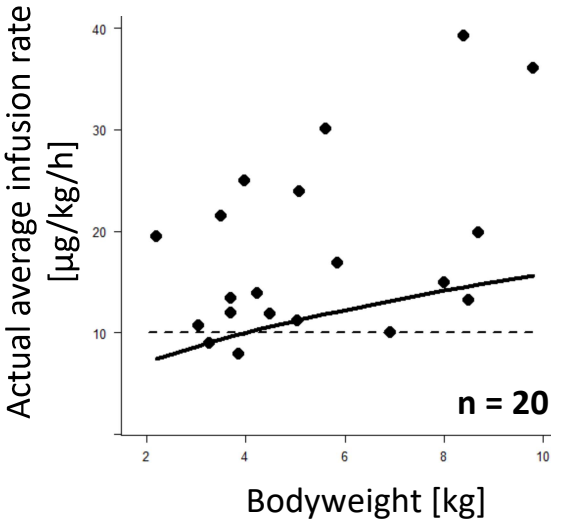
PNA >10 days – 5 µg/kg$^{1.5}$/h

18 (=90.0%) need of rescue

193 (0 – 1183) µg/kg total rescue dose

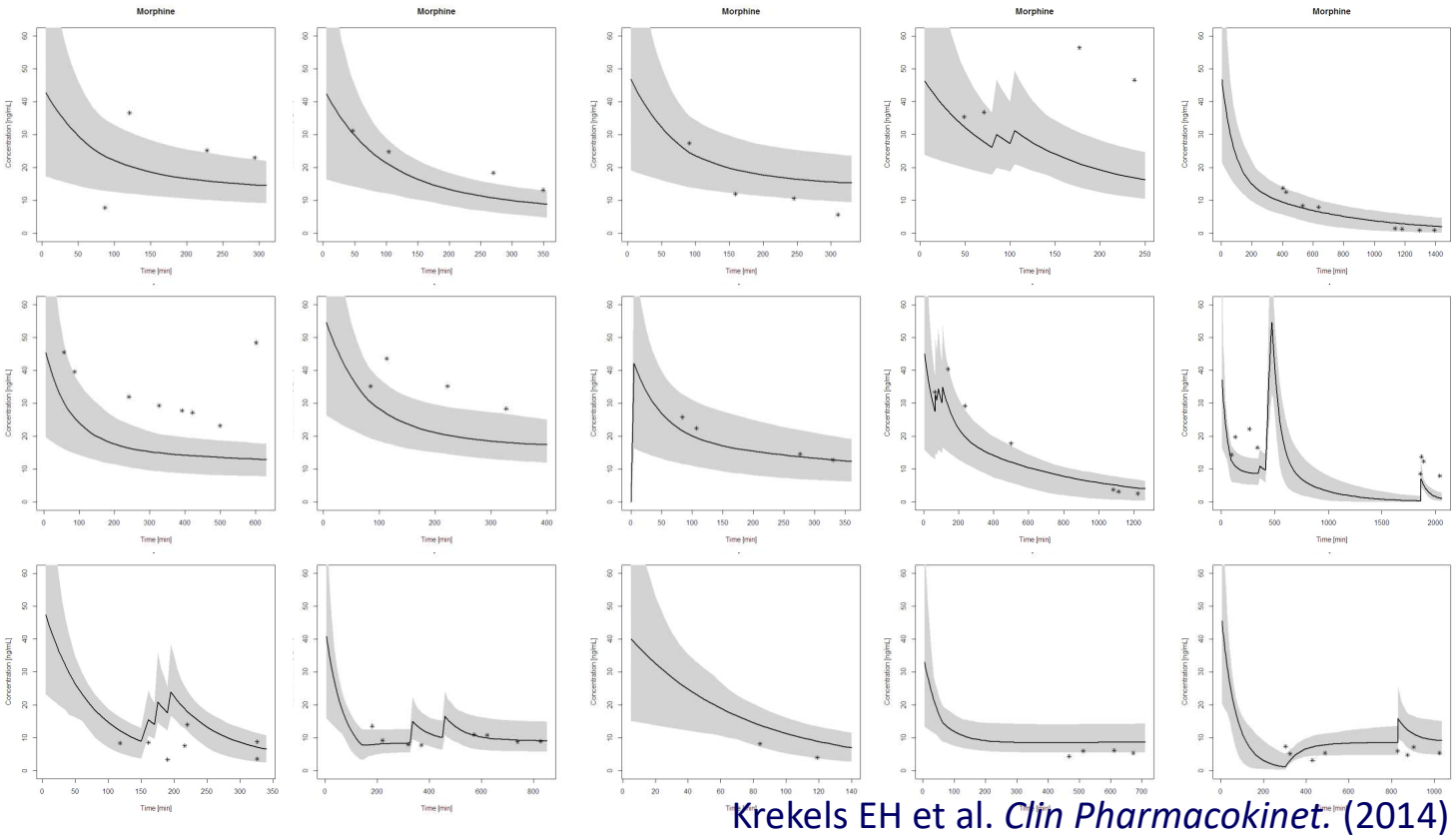
14.4 (7.4 – 15.7) µg/kg/h average rate





Krekels EH et al. *Clin Pharmacokinet.* (2014)

Results – Morphine concentrations



Krekels EH et al. *Clin Pharmacokinet.* (2014)

Covariate relation to other drugs

	PNA < 10 days *2.5 μg/kg$^{1.5}$/h*	*PNA > 10 days* *5 μg/kg$^{1.5}$/h*
Bodyweight (kg)	Infusion rate μg/kg/h	Infusion rate μg/kg/h
1.5 – 2	3.1	6.1
2 – 2.5	3.5	7.1
2.5 – 3	4.0	7.9
3 – 3.5	4.3	8.7
3.5 – 4	4.7	9.4
4 – 4.5	5.0	10.0
4.5 – 5	5.3	10.6
5 – 5.5	5.6	11.2
5.5 – 6	.	11.7
6 – 6.5	.	12.3
6.5 – 7	.	12.8
7 – 7.5	.	13.2
7.5 – 8	.	13.7
8 – 8.5	.	14.1
8.5 – 9	.	14.6
9 – 9.5	.	15.0
9.5 – 10	.	15.4
10 – 10.5	.	15.8

Zidovudine dosing?

Morphine->Zidovudine

- Model predicted CL similar to reference model
- Model predicted concentrations similar to reference model

Krekels et al, CPT PSP 2012