Target Controlled Infusions for Kids 2010

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Overview

- Down scaling from adults?!
- Propofol: Manual control versus TCI
- Pharmacodynamics of Propofol
- What parameter set?
- What target?
- Conclusion

Down scaling from adults?

Up scaling rat → kids → adults?

The concept: Allometric scaling

$$P_i = a * P_{Std} * BW^b$$

$$V_i = V_{Std} * \left({BW_i}/{BW_{Std}} \right)^{1}$$

$$Cl_i = Cl_{Std} * \left({BW_i}/{BW_{Std}} \right)^{3/4}$$

$$t_{1/2\,i} = t_{1/2\,Std} * \left({BW_i}/{BW_{Std}} \right)^{1/4}$$

Often used definition: BW_{Std} = 70 kg

Up scaling Propofol Kinetics from adult rats to adult humans

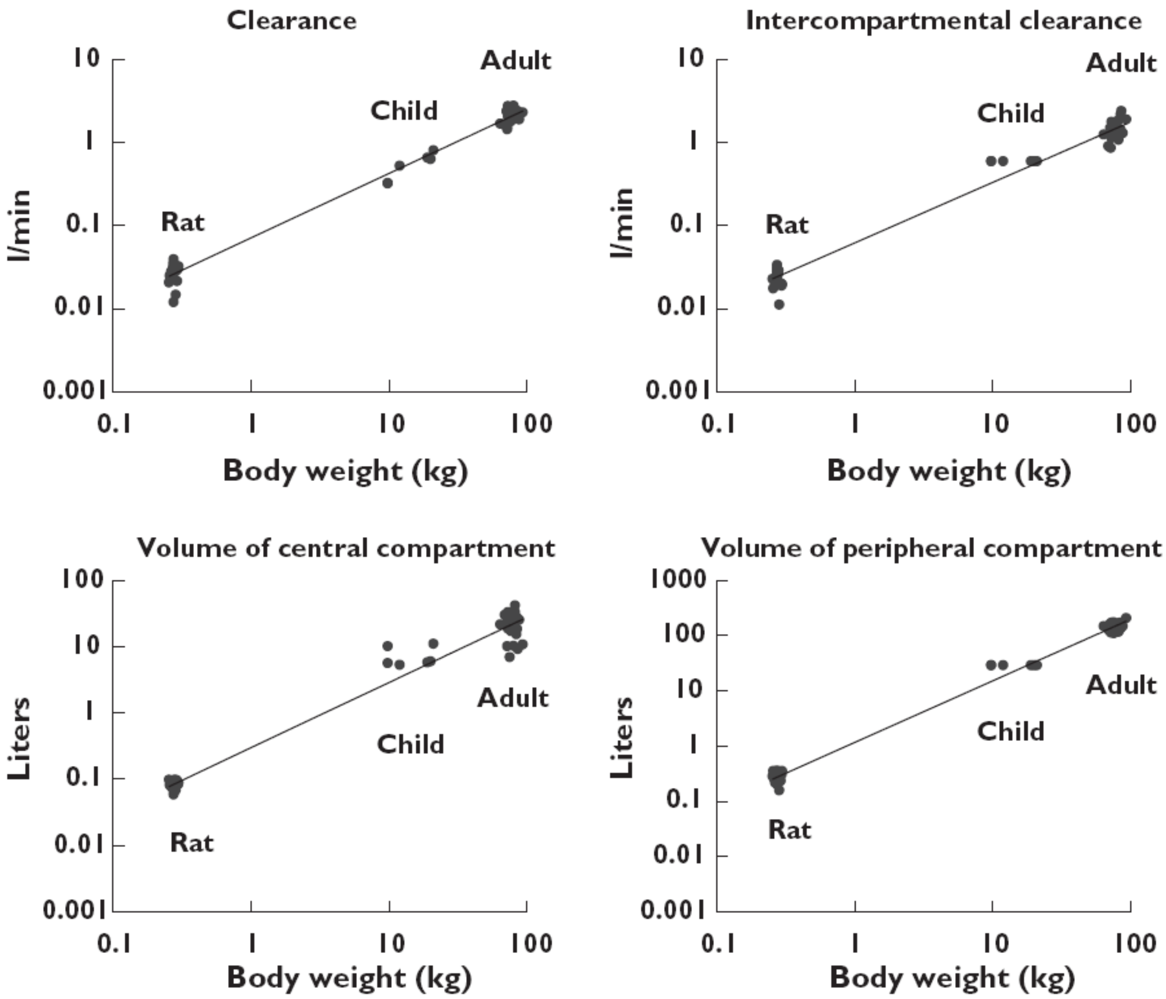
Knibbe et al. : Br J Clin Pharm 2005

Data analysis of 4 independent studies

	Rat	Children	Adults	Crit. ill adults
N	24	6	24	20
Age	adult	1-5y	37-73y	52-79y
Weight	250-300g	10-21kg	64-93kg	70-96kg
Liver	normal	normal	normal	normal
Heart	normal	post cardiac surgery	CABG	failure
Indication	exp.	Sedation PICU	Sedation ICU	Sedation IC
Dose:	30 mg/kg	2-3mg/kg/h (6h)	1mg/kg/h (5h)	1-4mg/kg/h (4-5d)
Blood samples:	19	7	24	16-20

Up scaling Propofol Kinetics : Results

Knibbe et al. : Br J Clin Pharm 2005



Parameter	Constant a	Exponent b	r^2
CL	0.071	0.78	0.9898
Q	0.062	0.73	0.9832
V_1	0.30	0.98	0.9774
V_2	1.2	1.1	0.9944

Up scaling Propofol Kinetics : Results

Knibbe et al. : Br J Clin Pharm 2005

Pharmacokinetic parameter	Observed in the rat (250 g) Value (SE)	%CV	Scaled for humans (70 kg) Value	Observed in intensive care patients [13] Value (SE)	%CV
CL (l min^{-1})	0.0261 (0.00205)	34%	1.63	2.1 (0.066)	17%
V_1 (l)	0.0811 (0.00544)	15%	20.6	20.5 (2.4)	47%
Q (l min^{-1})	0.0227 (0.00325)	26%	1.45	1.4 (0.11)	27%
V_2 (l)	0.291 (0.0067)	23%	71.9	150 (17.5)	25%
Intra-individual variability (%CV)	19.9%			36.5%	

Extension of the model: Maturation and organ function:

$$P = P_{\text{std}} \cdot F_{\text{size}} \cdot \text{MF} \cdot \text{OF}$$

P = parameter

P_{std} = parameter in a stardard adult (70 kg)

F_{size} = $(\text{weight}/70)^{0.75}$

MF = maturation factor

OF = organ function factor

Maturation model

$$\text{MF} = \frac{\text{PMA}^{\text{Hill}}}{\text{TM}_{50}^{\text{Hill}} + \text{PMA}^{\text{Hill}}}$$

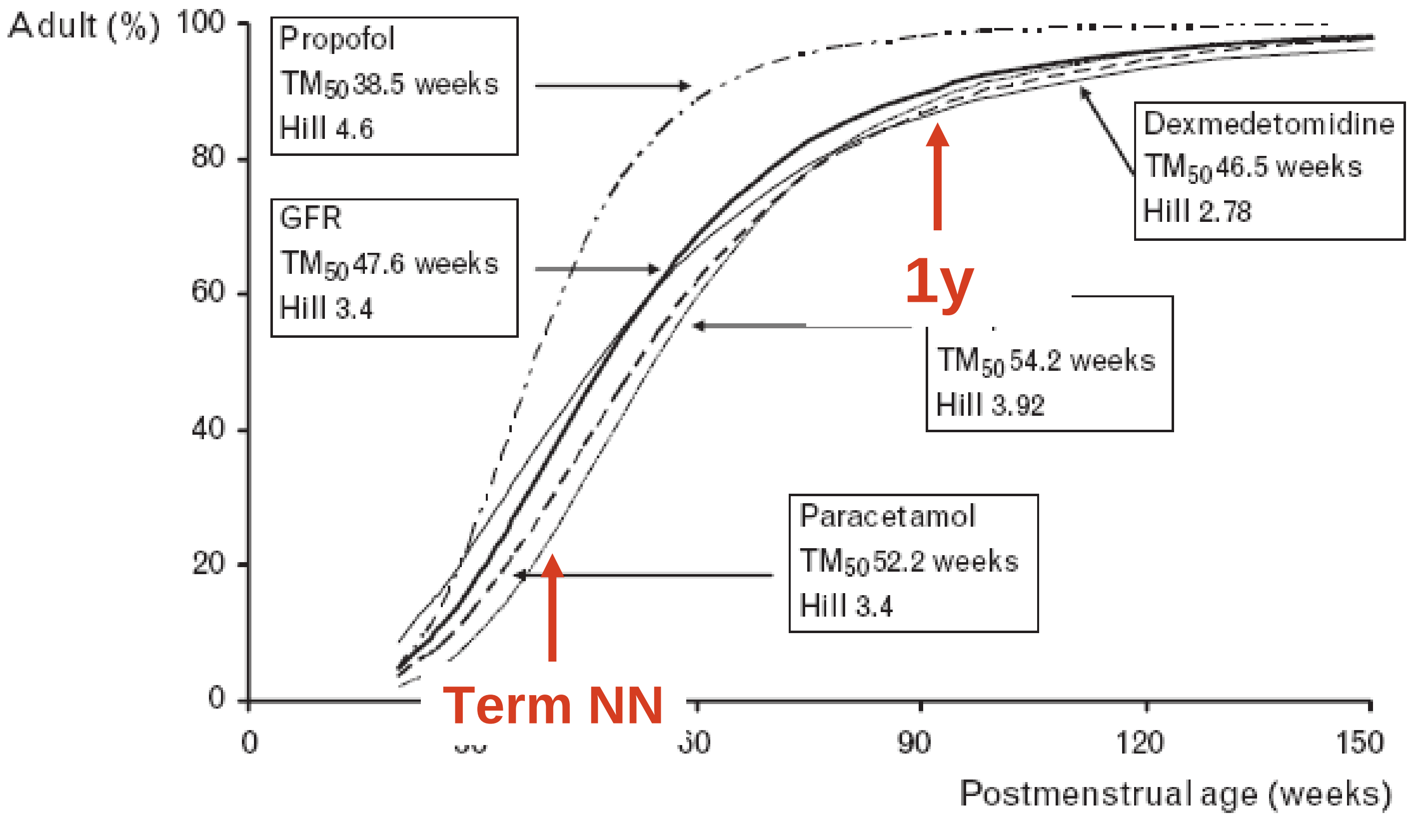
PMA = postmenstrual age

TM50 = time of half maximal maturation

Hill = Hill coefficient

Sumpter et al. Current Opinion in Anaesthesiology 2009,22:469–475

Maturation of clearances in neonates: E_{max} model



Propofol faster than GFR due to faster maturation of hepatic CYP 450

Sumpter et al. Current Opinion in Anaesthesiology 2009,22:469–475

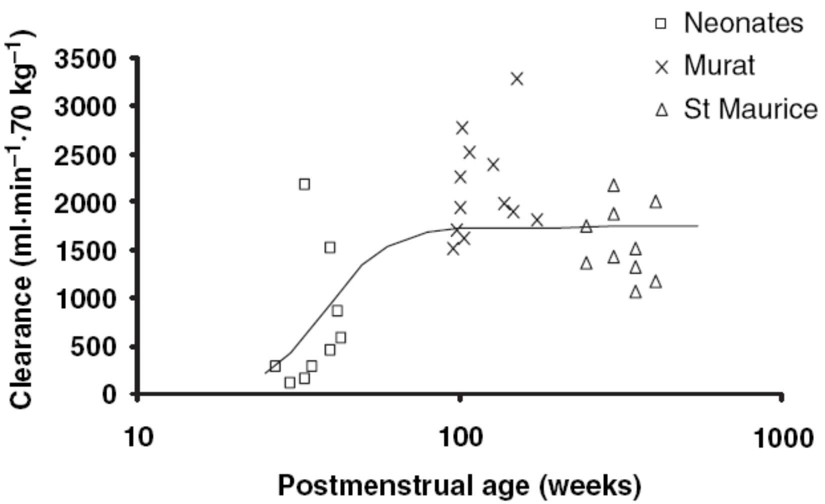
Variation of propofol Pk at different ages

Larger variation of Vc, Vss and Clearance in neonates!

	Present report	*Murat et al.*[10]	*Saint-Maurice et al.*[11]
Number of patients	9	12	10
Age (range)	4–25 days	1–3 years	4–7 years
Weight (kg, range)	0.9–3.8	8.7–18.9	17–24
Propofol dose ($mg{\cdot}kg^{-1}$, bolus)	3	3	2.5
Pharmacokinetic model	2-stage, open 3 compartment	2-stage, open 3 compartment	2-stage, open 3 compartment
V_c ($l{\cdot}kg^{-1}$)	0.34 (0.08–1.03)	0.95 (0.5–1.29)	0.59 (0.32–1.51)
V_{ss} ($l{\cdot}kg^{-1}$)	3.7 (1.33–7.96)	8.17 (4.35–12.08)	10.55 (5.8–15.6)
V_{ss} ($l\cdot70\ kg^{-1}$)	258 (93–555)	581 (304–845)	738 (406–1092)
Clearance ($ml{\cdot}min^{-1}{\cdot}kg^{-1}$)	13.6 (3.7–78)	43 (35–74)	28.2 (21.5–44.4)
Clearance ($ml{\cdot}min^{-1}{\cdot}70\ kg^{-1}$)	442 (97–2184)	1957 (1519–3284)	1479 (1064–2181)
	89-236%	**41-46%**	**37-100%**

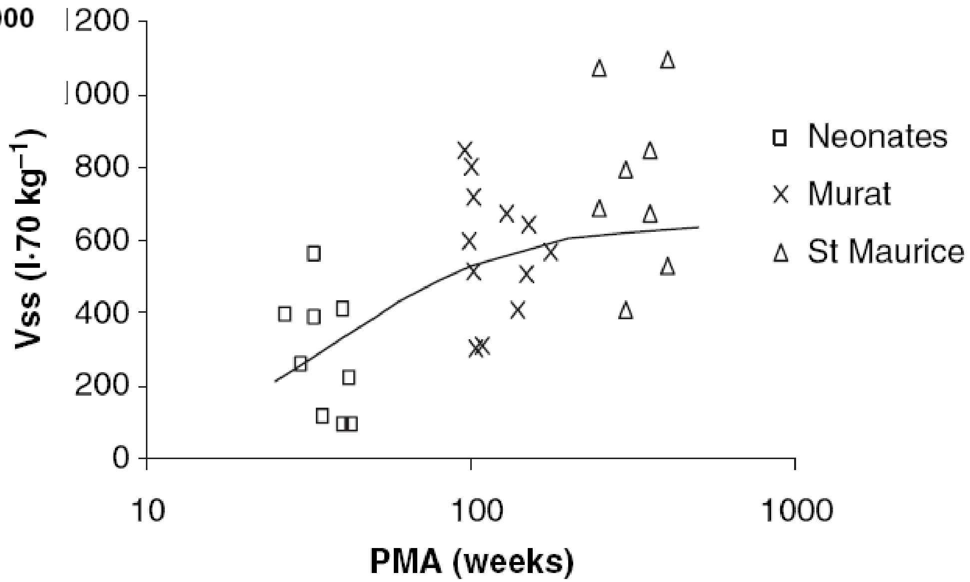
Allegaert et al. Pediatric Anesthesia 2007 17: 1028–1034

Maturation of Propofol V_D and Clearance (steady state)



Maturational pharmacokinetics of single intravenous bolus of propofol:

Allegaert et al. Pediatric Anesthesia 2007 17: 1028–1034



Application of weight based scaling by Schüttler et al. 2000

PROPOFOL data from 9 studies (6 adult, 3 pediatric):

Age 2 – 89y

Propofol application: bolus or infusion

Blood samples: arterial (3) or venous (6)

Covariates: **weight**, age, type of blood sample, type of application

Model Parameter	Value	% CV
Cl_1	$\theta_1 \cdot (BW/70)^{\theta_7}$ if age ≤ 60 $\theta_1 \cdot (BW/70)^{\theta_7} - (age - 60) \cdot \theta_{10}$ if age > 60	37.4
Cl_2	$\theta_3 \cdot (BW/70)^{\theta_8} \cdot (1 + ven \cdot \theta_{14}) \cdot (1 + bol \cdot \theta_{16})$	51.9
Cl_3	$\theta_5 \cdot (BW/70)^{\theta_{11}} \cdot (1 + bol \cdot \theta_{18})$	50.9
V_1	$\theta_2 \cdot (BW/70)^{\theta_{12}} \cdot (age/30)^{\theta_{13}} \cdot (1 + bol \cdot \theta_{15})$	40.0
V_2	$\theta_4 \cdot (BW/70)^{\theta_9} \cdot (1 + bol \cdot \theta_{17})$	54.8
V_3	θ_6	46.9

Allometric scaling will more and more be used and allow to define a universal Pk parameter set for children and adults

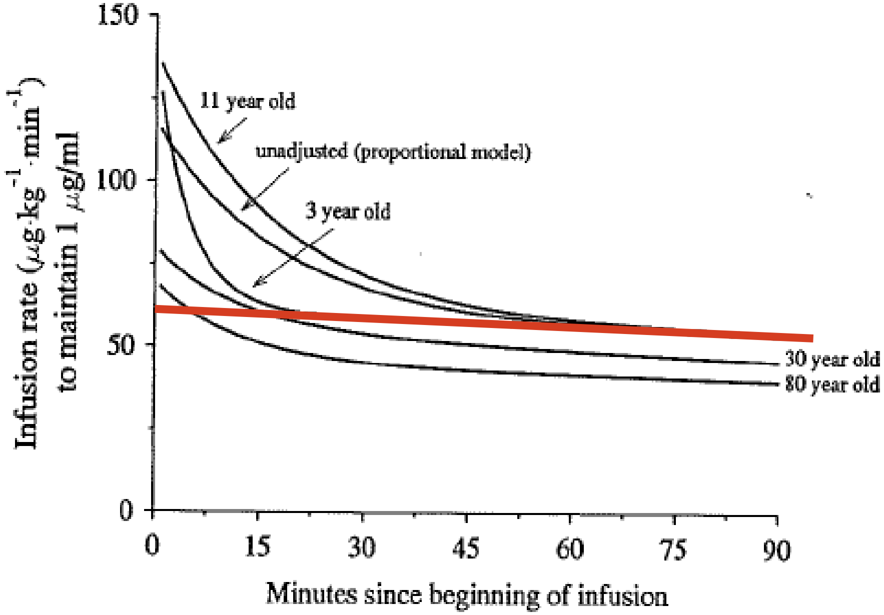
Open TCI initiative: Define an optimal parameter set to make life easier for clinicians

Modelling work is under way!

Propofol Infusions:

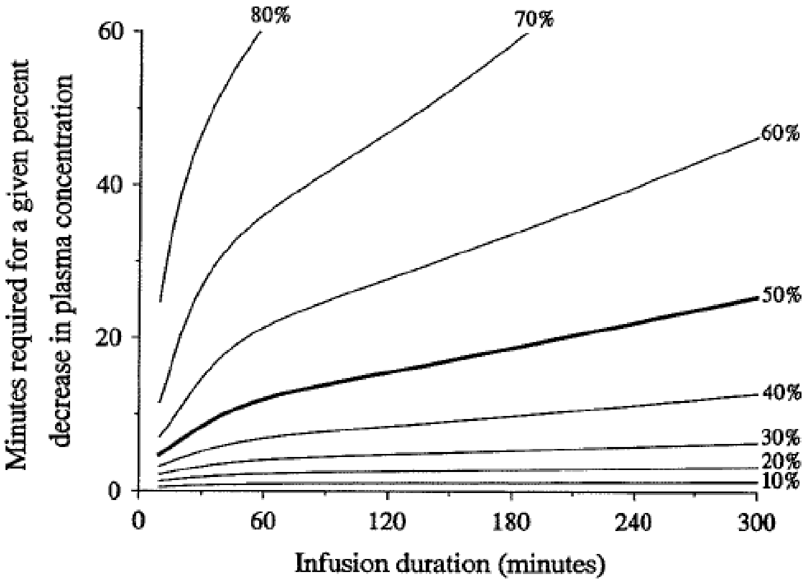
Manual control or TCI?
What Parameters?

Why TCI?



Rate adjustement during the first 45-60 minutes is complex

→ with TCI steady state faster achieved



Context sensitivity of decrement time

Several manual infusion schemes

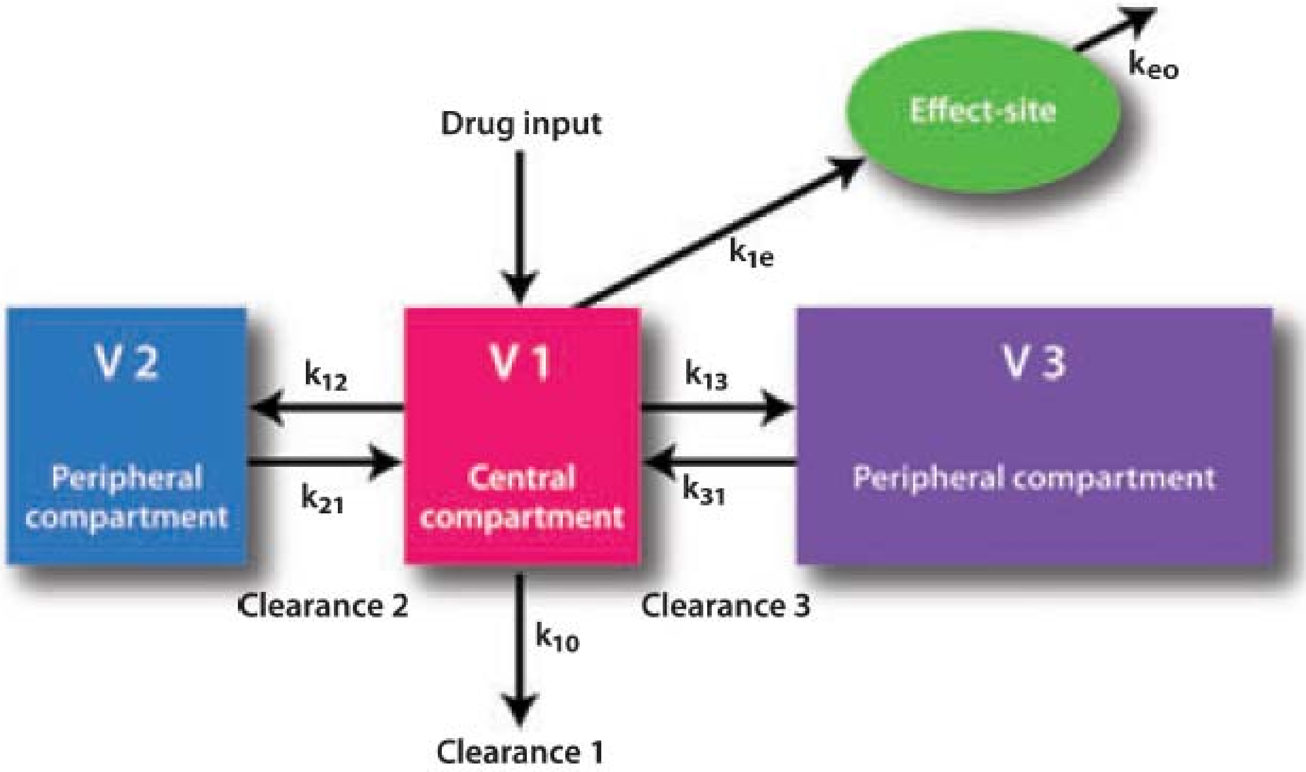
(Examples: estimated Cp 3 mcg/ml)

Complex

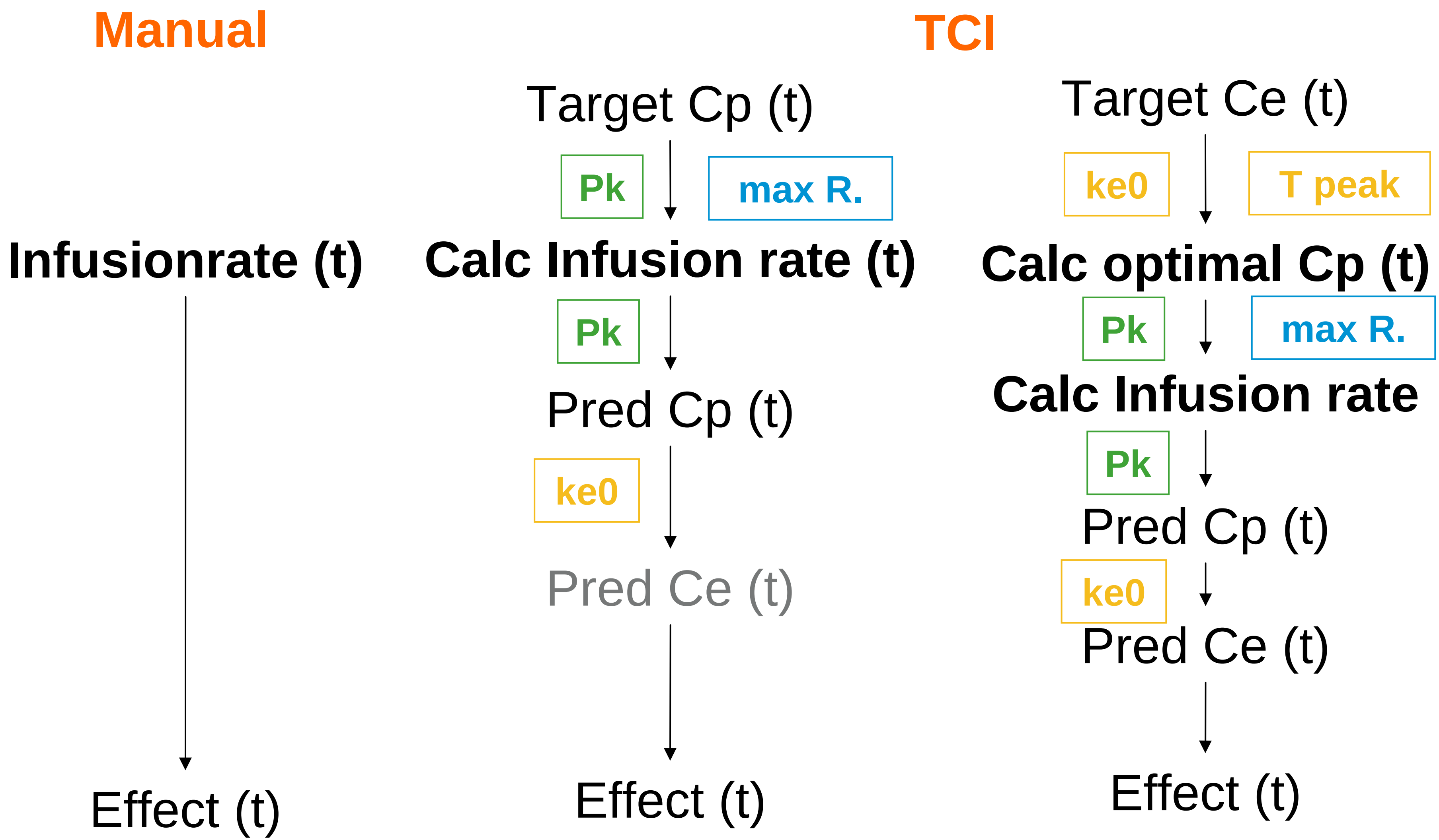
Risk of errors !

- **Roberts (Anaesthesia 1988) modified from “10-8-6”:**
  - Bolus: **1** mg/kg
  - Maintenance (mg/kg/h):**13** (for 10 min.) → **10** (10 min.) → **9** (thereafter)
- **Paedfusor Pk derived:**
  - Bolus:-
  - Maintenance (mg/kg/h):**19** (for 15 min.) →**15** (15 min.) → **12** (30 min.)
- **MacFarlan (Ped Anaesth 1999, derived from Kataria):**
  - Bolus **2.5** mg/kg
  - Maintenance (mg/kg/h):**15** (for 15 min.) →**13** (15 min.) **11** → (30 min.) → **10** (60 min.) → **9** (up to 4 h)

Three compartment model



Manual control versus TCI



Pk parameter sets for infants and children

	age	bolus/infusion	covariates	N
ShangGuan 2006	4m-9y	3mg/kg	w	35
Paedfusor 2003/05	1-15y	TCI*	w, age	29
Schüttler 2000	2-88y	b/i	various	270
Kataria 1994	2-11y	b/i	w, age	53
Marsh 1991	1-10y	TCI	w	30
St. Maurice 1989	4-7y	2.5 mg/kg	w	10

*validation of a previously unpublished parameter set

Bolus- or infusion data

Child: 5 y, 20 kg	Schüttler (Bolus, Ven)	Schüttler (Infusion, Ven)
V1	20.1*	7.7
V2	35.6	20.6
V3	103.9	103.9
Cl1	0.563	0.562
Cl2	1.875	0.620
Cl3	0.240	0.462

* Higher loading dose!

Comparison Paedfusor – Kataria Model

	'Paedfusor'	Kataria
V_1	0.458 × weight **(1-12y)***	0.41 × weight
V_2	0.95 × weight	0.78 × weight + 3.1 × age
V_3	5.82 × weight	6.9 × weight
k_{10}	$0.1527 \times \text{weight}^{-0.3}$	0.085
k_{12}	0.114	0.188
k_{21}	0.055	0.102
k_{13}	0.0419	0.063
k_{31}	0.0033	0.0038
k_{e0}	0.26 **from adults**	n/a

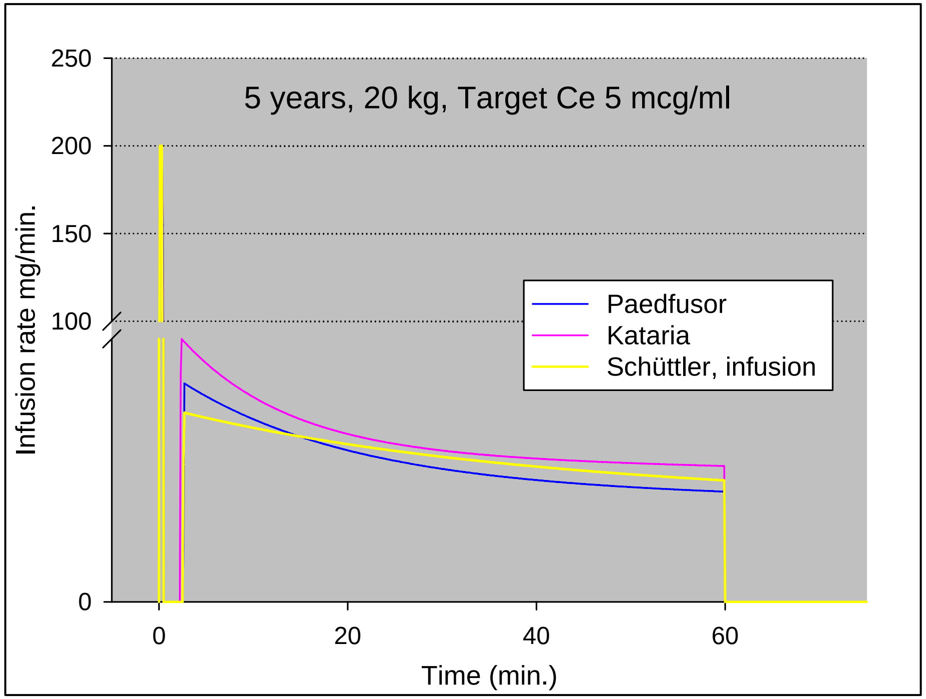
>12 y, non-linear decreased with age:

13y: 0.400xweight, 14y: 0.342xweight, 15y: 284xweight, 16y:229xweight

Pk parameters
→ loading doses and infusion rates

Simulation 5y, 20 kg, child, target Ce 5 mcg/ml, 60‘

	Paedfusor	Kataria	Schüttler
V1 (L)	**9.2**	**7.6**	**7.7**
V2 (L)	19	14.3	20.6
V3 (L)	116.4	122	104
Cl1 (L/Min.)	**0.57**	**0.74**	**0.563**
Cl2 (L/Min.)	1.045	1.26	0.621
Cl3 (L/Min.)	0.384	0.5	0.462



	Paedfusor	Kataria	Schüttler infusion
Bolus (mg/kg)	3.6	3.4	3
Totel dose (mg/kg)	20.7	23.3	20.8

What if individual Pk ≠ population Pk

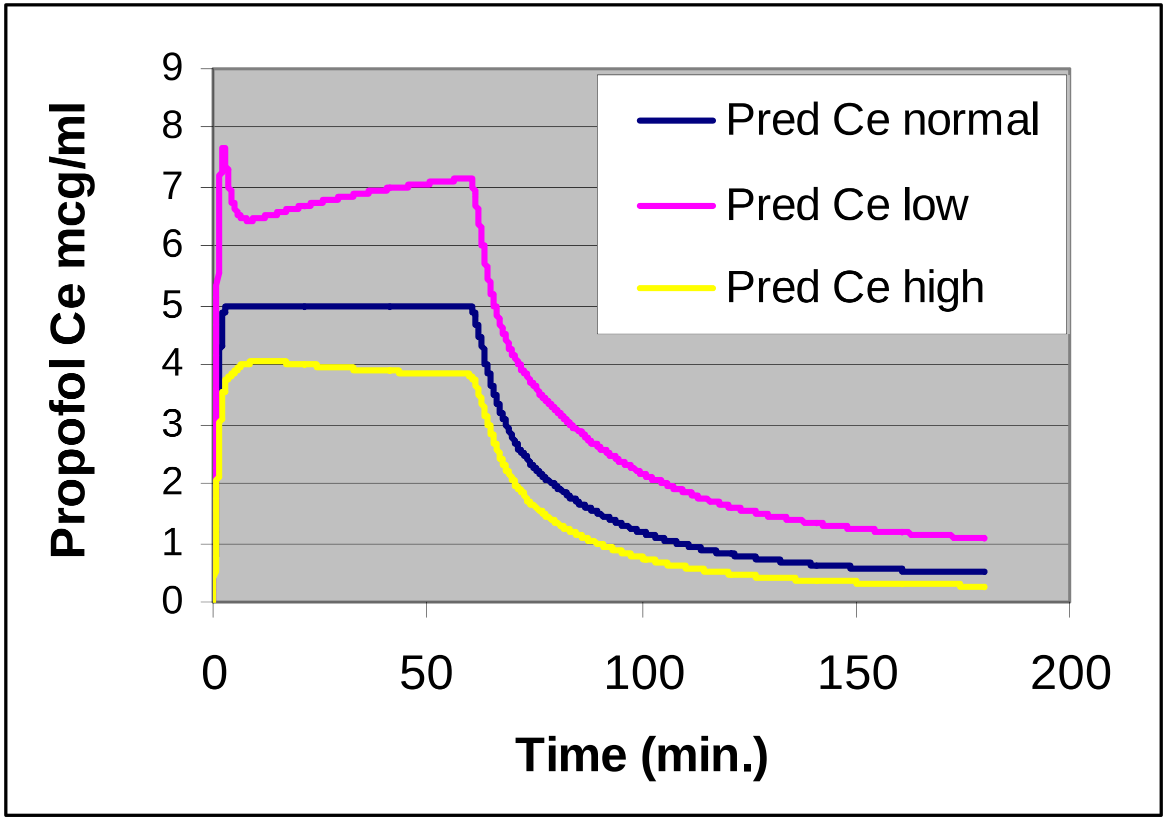
Simulation: 5y, 20 kg

V1 and Cl1

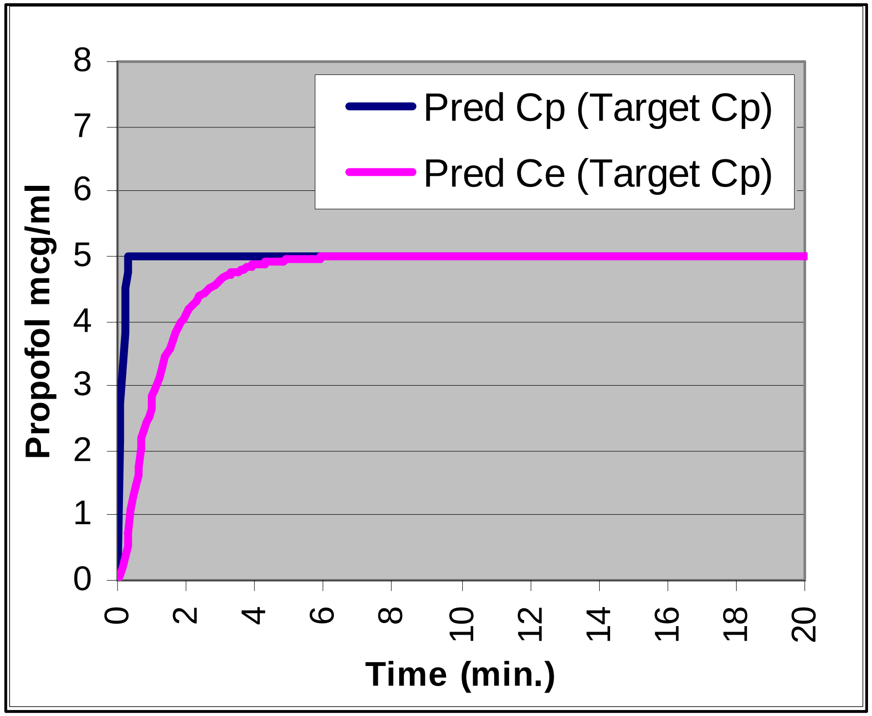
- 50%
- 100%
- 150%

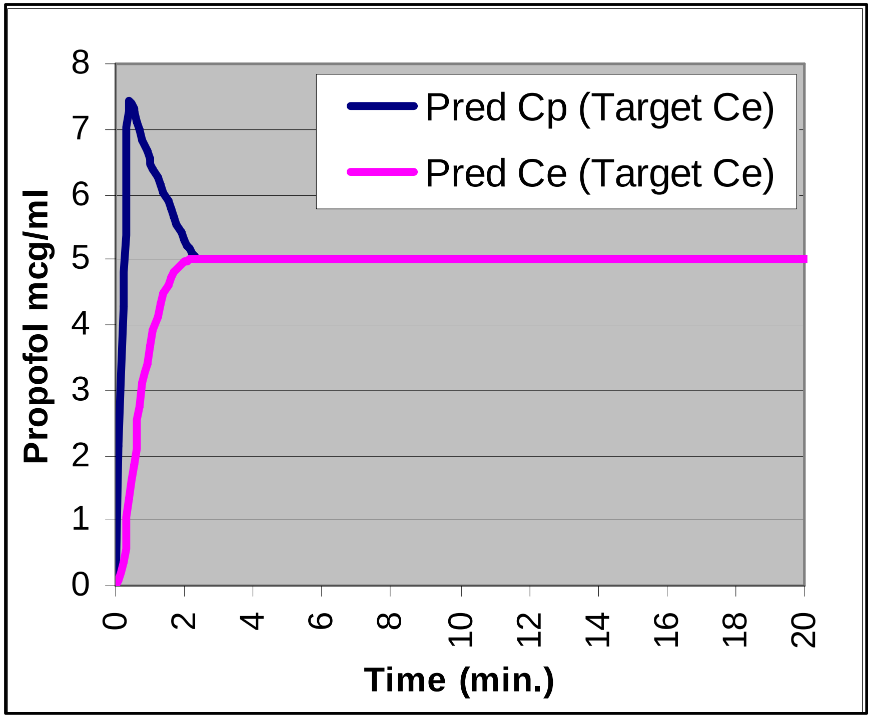
of population

Kataria parameters, ke0 0.41



Plasma or effect site target?





Simulation, 5y, 20kg, Paedfusor, ke0 0.91

How reliable are the pd models (ke0)?

Ke0 estimated from A-line peak effect

(auditory evoked potential index)

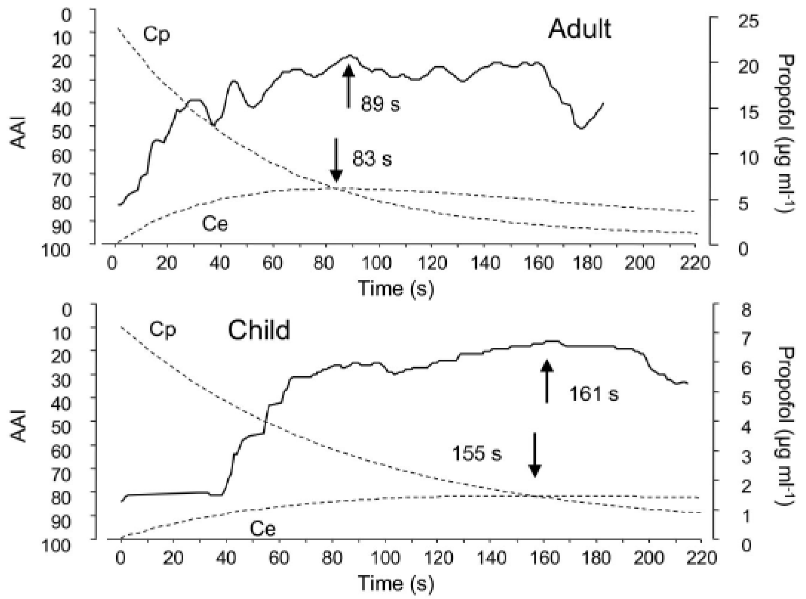
<u>Munoz, Anesthesiology 2004</u>

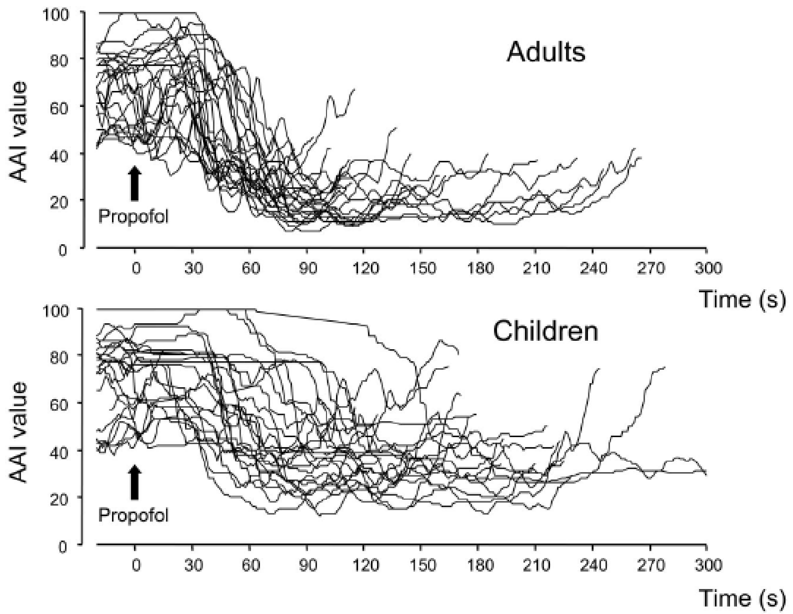
Kids 3-11 y, Adults 35-48, N=25 each

“sub-maximal bolus”

Pk: Paedfusor and Kataria

ke0 Kataria:	**0.41**
ke0 Paedfusor:	**0.91**
ke0 Schnider:	**0.56**
(ke0 original:	**0.453)**





Time to peak EEG effect: A-Line and BIS compared

Munoz, Anesthesiology 2009

Bolus 3 mg/kg

4-11 y, N=25

Tpeak true > Tpeak pred

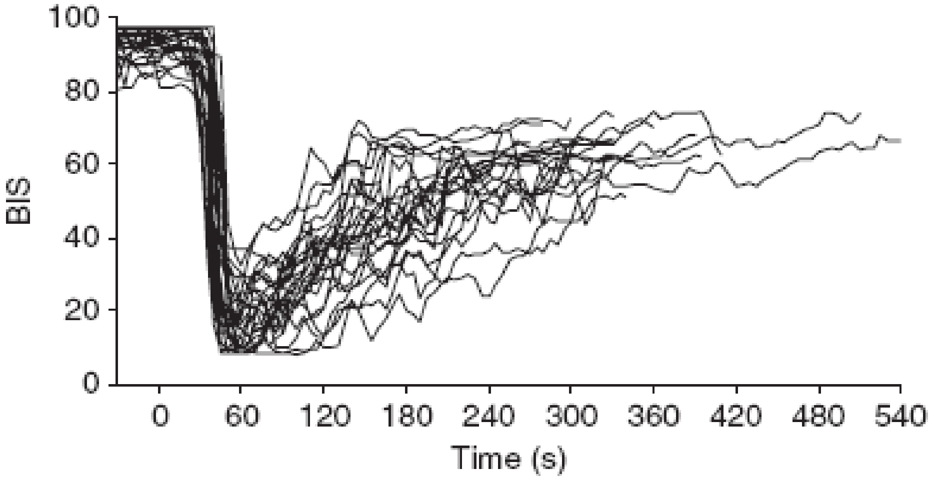
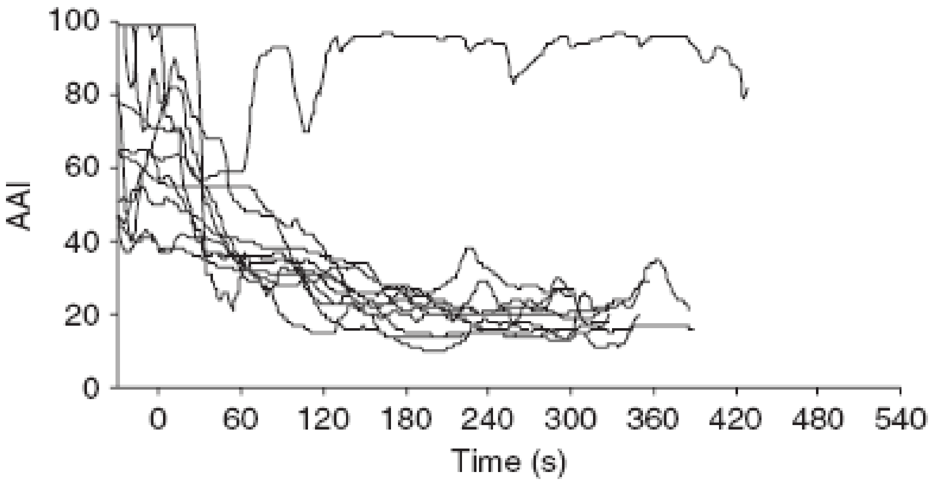


Table 2

Measurements of performance during the induction.

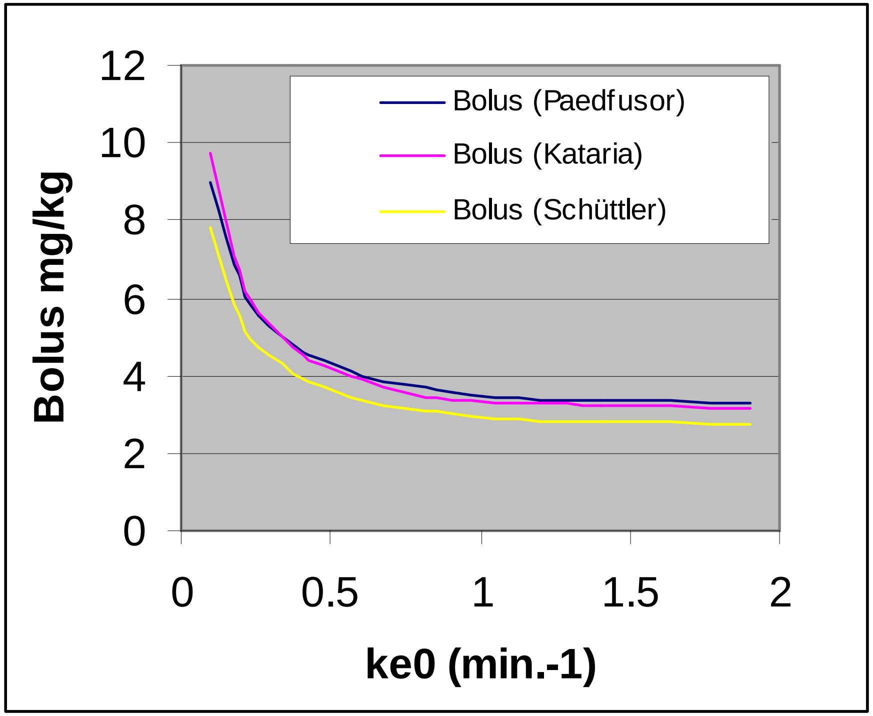
	Kataria ($n = 20$)	Paedfusor ($n = 20$)
MD t_{error} (s)*	−7.5 (−27.0–9.0)	−11.0 (−36.0–11.0)
MDA t_{error} (s)*	9.0 (0.0–27.0)	11.5 (0.0–36.0)
MDPE (%)*	9.4 (−11.4–33.8)	14.2 (−13.6–46.6)
MDAPE (%)*	11.2 (0.0–33.8)	14.6 (0.0–46.6)

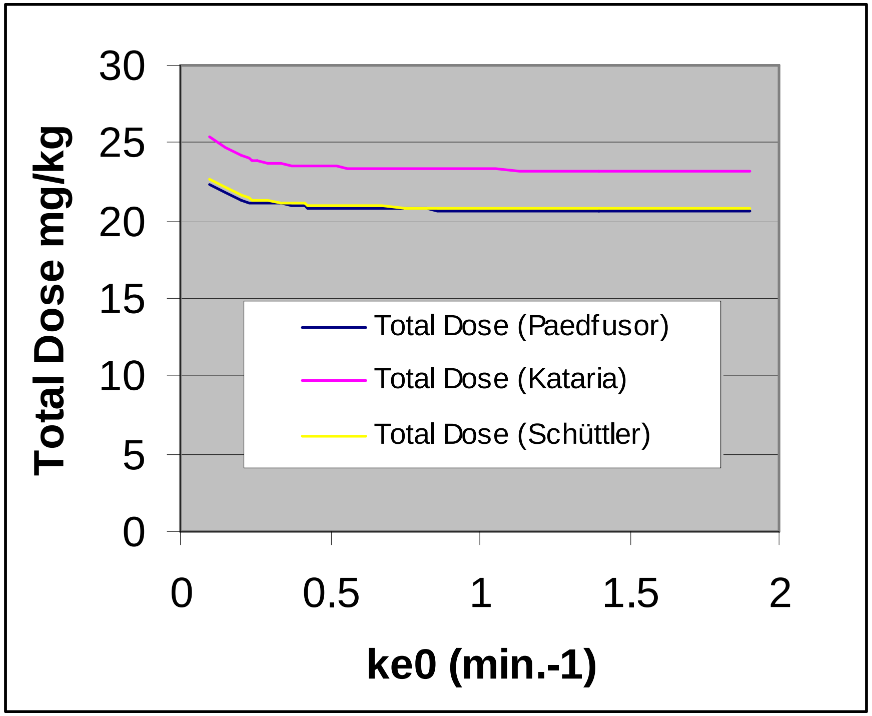
*Values are median (range).
MD,median; MDA; absolute median; MDPE, median prediction error; MDAPE, absolute median prediction error.



What is the impact of different ke0 on TCI Drug delivery?

Target Ce 5 mcg/ml, max. Rate 200 mg/min.





Conclusion: Selection of Parameter Set

- **Kataria:**
  - + Well validated
  - + Scientifically more adequate (source data published, model development reported)
  - + Preferred by Pk Pd modelling experts (Ped Anesth 2010)
  - – Limited to >15 kg and > 3y
  - 0 Lower bolus, higher maintenance rate

- **Paedfusor:**
  - + Well validated
  - + Works in infants ≥ 1y
  - – Source data and model development not published (“intermediate result” of the Schüttler Parameters, published only as a letter)
  - 0 higher bolus, lower maintenance rate

Summary pk pd parameters

- Loading doses:
  - Volume 1
  - ke0
- Maintenance infusion (t)
  - Clearance 1
- Kataria or Paedfusor set ?
  - Differences are below the inter-interindividual variation
  - Titrate to clinical effect

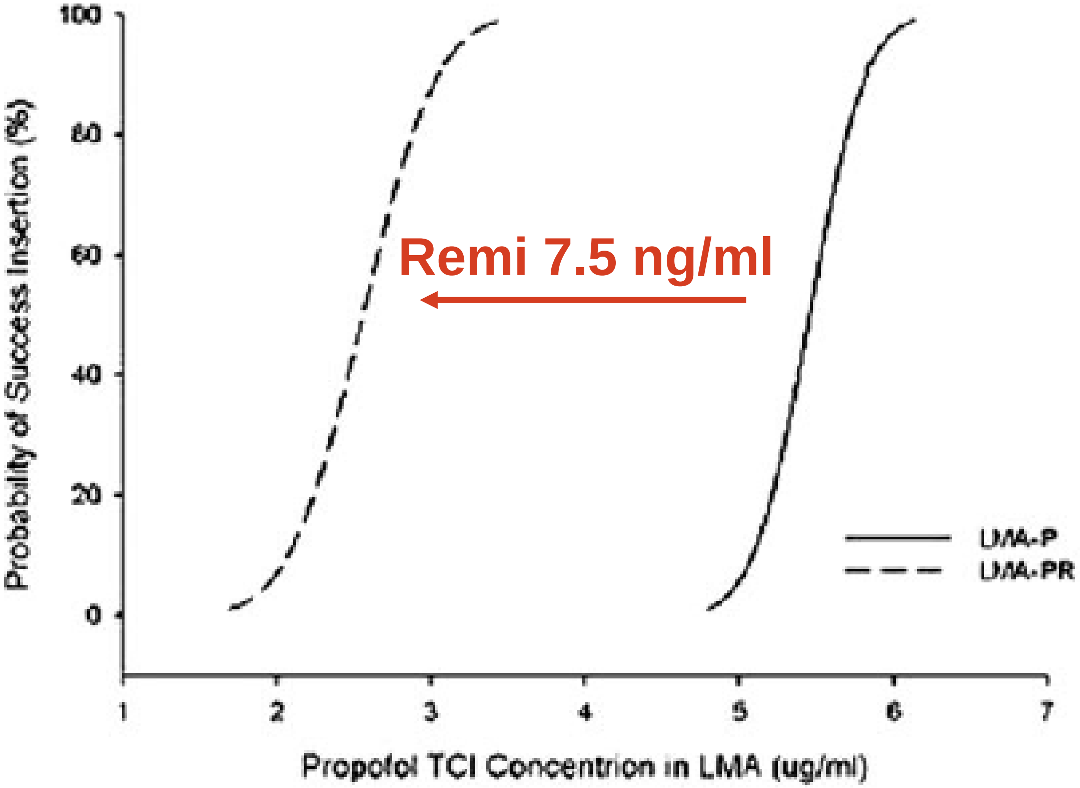
Propofol Pharmacodynamics:
What Concentrations are needed?

Propol C_{50} (mcg/ml)

	1-5y	6-12y	12-16y	adults
LOC	2.25(0.48)[1]	1.78(0.41)[1]	1.37(0,44)[1]	2.9(0.8)[2]
	2-7y			
ROC	1.5(1.0-1.9)[3]			2.6(0.6)[4]
Spont Breathing	1.7(1.5-1.7)[3]			
	3-11y			
BIS 50	3.6(3.4-3.9)[5]			3.8(2.9-4.8)[5]
	4-10y			
OGD	3.7(0.4)[6]			
	2-12y			
LMA	5.5(0.2)[7]			4.3(0.6)[10] / 3.3(0.2)[10]
	7.8(6.5-9.2)[9]			8.7(7.7-9.8)[12]

[1] Münte 2009, [2] Bouillon 2004, [3] Park 2007, [4] Chortkoff 1995, [5] Munoz 2005,
[6] Dover 2004, [7] Park 2007, [8] Münte 2009, [10] Kodaka 2004 [11] Higuchi 2002

Pd Interaction Propofol – Reminfentanil (LMA), Park A&A2007



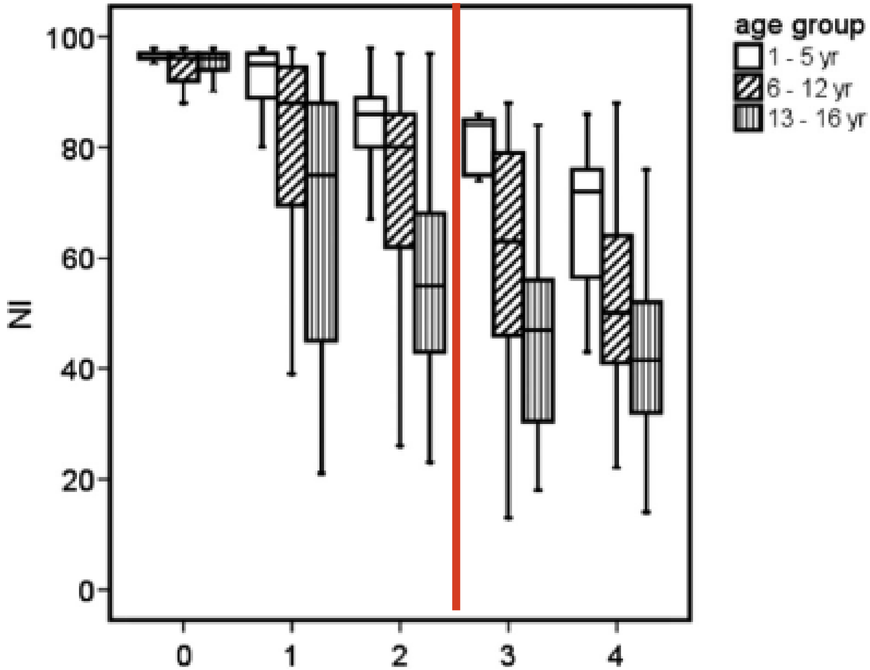
Loss of consciousness (Münte et al, A&A 2009)

Mean (SD) Cp loss of conciousness (LOC)

Prop TCI, Kataria (>15kg) otherwise 20 mg/kg/h until LOC

1-16 y, N=61

EEG Effect: Narcotrend Index (0-100)



University of Michigan Sedation Scale (UMSS).

Mean(sd)	1-5y	6-12y	12-16y
Narcotrend at LOC	77(19)	71(18)	59(16)
Prop Cp at LOC mcg/ml	2.25(0.48)	1.78(0.41)	1.37(0,44)

BIS does not discriminate propofol 4 and 6 mcg/ml

<u>**Tirel et al. BJA 2008**</u>

Pseudo steady state

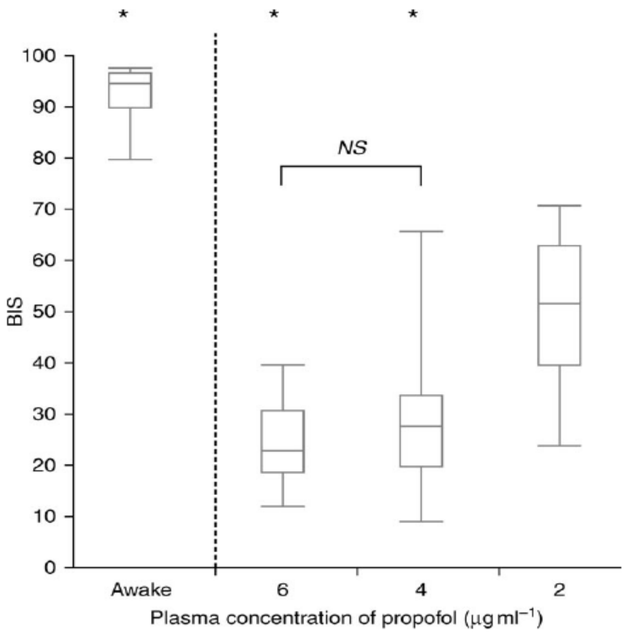
Kids 3-15 y, N=50, Kataria

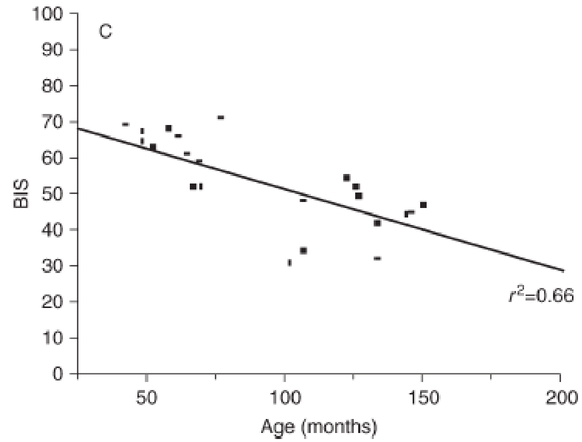
Remifentanil 1 mcg/kg followed by 0.2 mcg/kg/min.

Propofol TCI:

Induction: target Cp 7mcg/ml

then 6 – 4 -2 mcg/ml for 6 min. each.





At 2 mcg/ml correlation with age!

Propofol Pk and Pd in kids: Summary

- Allometric scaling according to mass (weight) above 1-2 y
- Maturation of Pk to consider in kids below 1-2y
- Increased Pk variation in infants and neonates
- Larger variation of Pk in children compared to adults
- EEG effect
  - is age dependent
  - dad discrimination
    - between awake and asleep
    - Between different propofol concentrations
  - below 5y: more uncertainty

Conclusion: TCI probably better than manual control

- **TCI**
  - \+ No calculation, no complex rate adjustment
  - \+ faster steady state
  - \+ weight and age variation incorporated
  - \+ target concentrations determined
  - \- Interindividual variation of Pk and Pd → under- or overdosing (as in adults)

  → **Titration to effect**
- **Selection of parameter set: probably not so important**
  - Use only one – avoid confusion among staff members and trainees
- **General problem of TIVA in children:**
  - EEG parameters of limited value
  - ke0 estimation difficult


Thank you!