# 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

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

$$V_i = V_{Std} * \left( BW_i / BW_{Std} \right)^1 \qquad Cl_i = Cl_{Std} * \left( BW_i / BW_{Std} \right)^{3/4}$$

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

**Often used definition: $BW_{Std}$ = 70 kg**

# Up scaling Propofol Kinetics from adult rats to adult humans

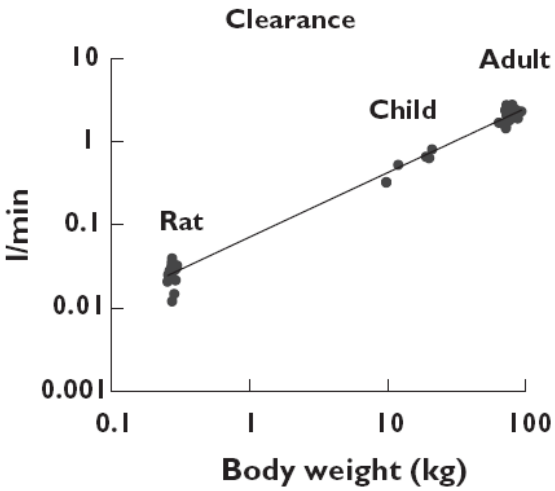
## Knibbe et al. : Br J Clin Pharm 2005

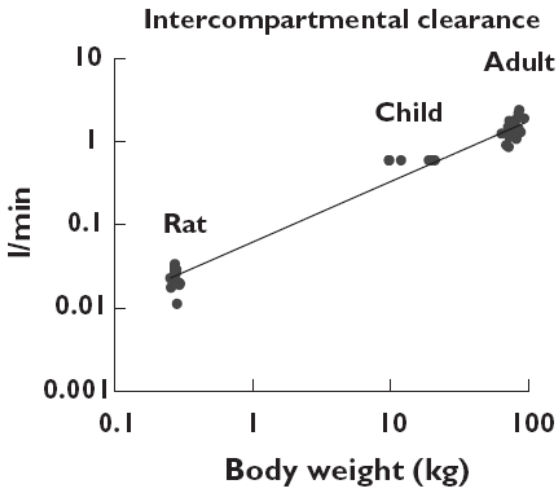
### Data analysis of 4 independent studies

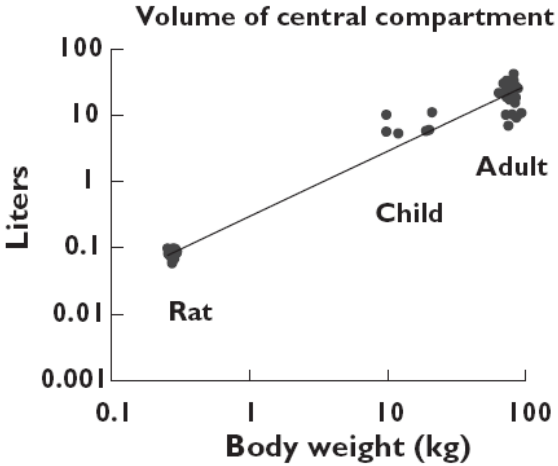
| | Rat | Children | Adults | Crit. ill adults |
|---|---|---|---|---|
| N | 24 | 6 | 24 | 20 |
| Age | adult | 1-5y | 37-73y | 52-79y |
| Weight | 250-300g | 10-21kg | 64-93kg | 70-96kg |
| Liver | normal | normal | normal | normal |
| Heart | normal | post cardiac surgery | CABG | failure |
| Indication | 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 |

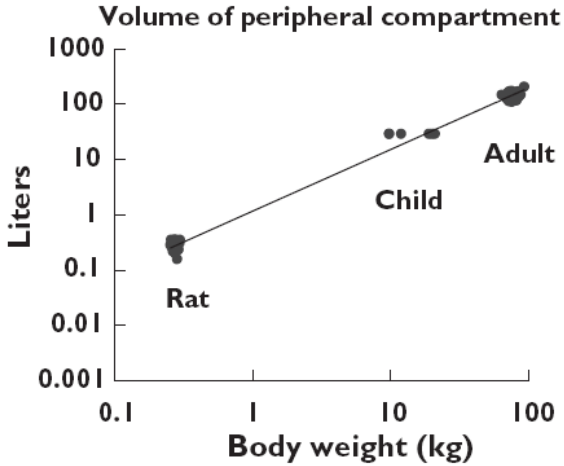
# Up scaling Propofol Kinetics : Results

## 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:

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

P = parameter

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

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

MF = maturation factor

OF = organ function factor

## Maturation model

$$MF = \frac{PMA^{Hill}}{TM_{50}^{Hill} + PMA^{Hill}}$$

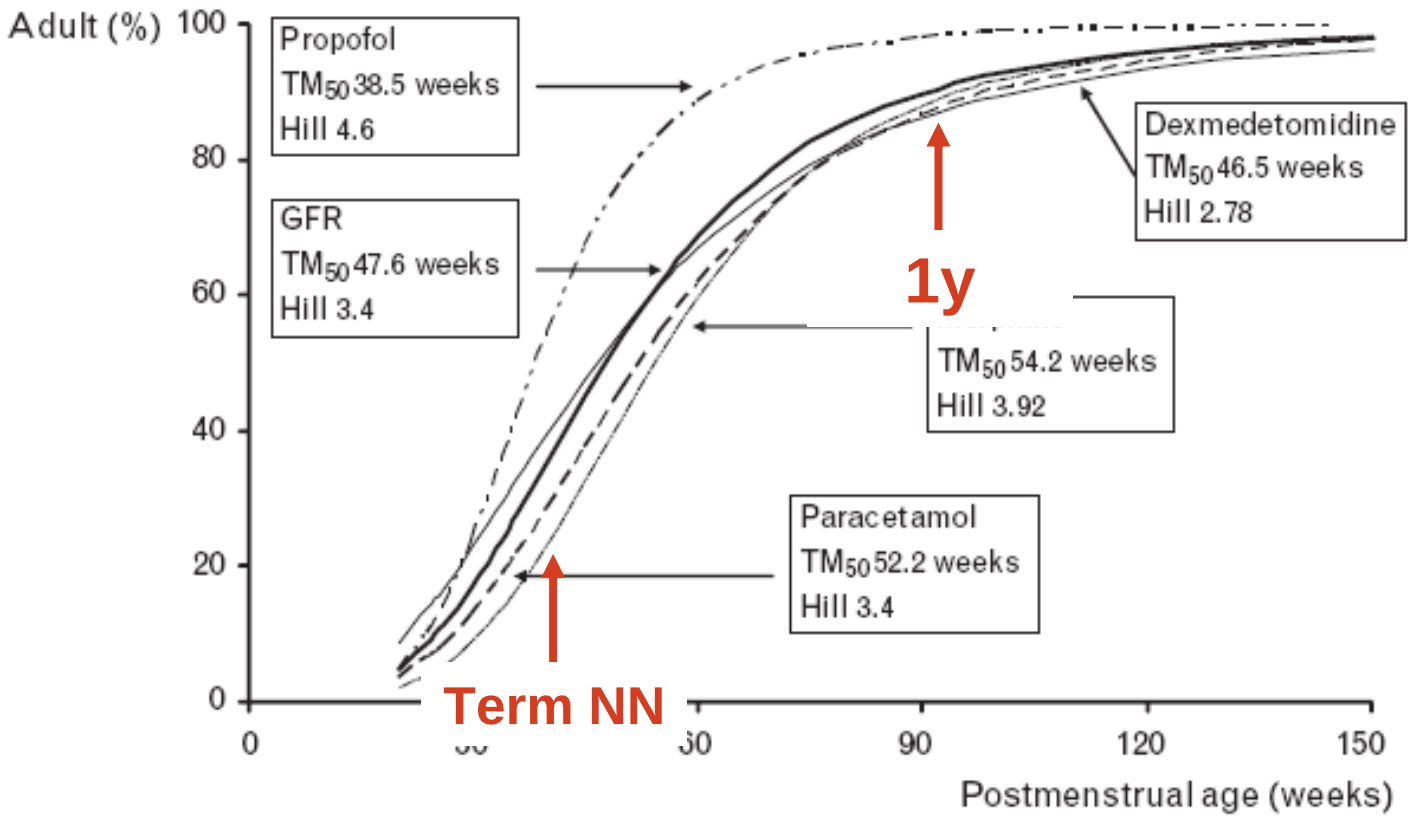
PMA = postmenstrual age

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

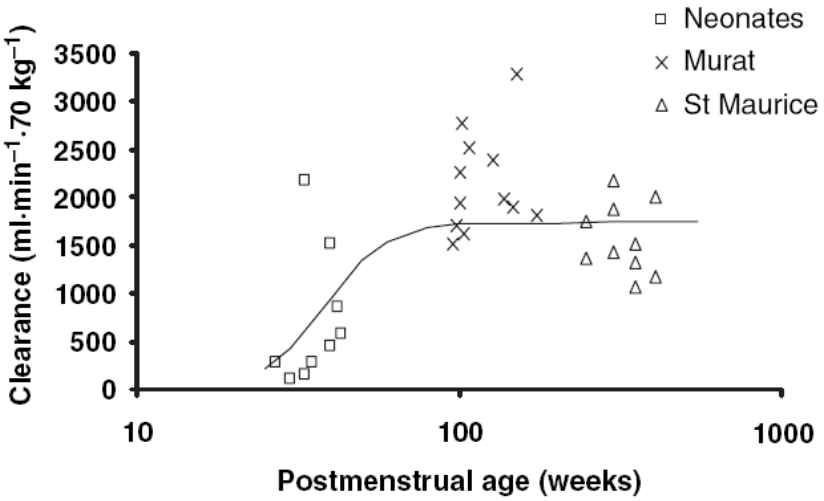
# Variation of propofol Pk at different ages

## 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.70 $kg^{-1}$) | 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%** |

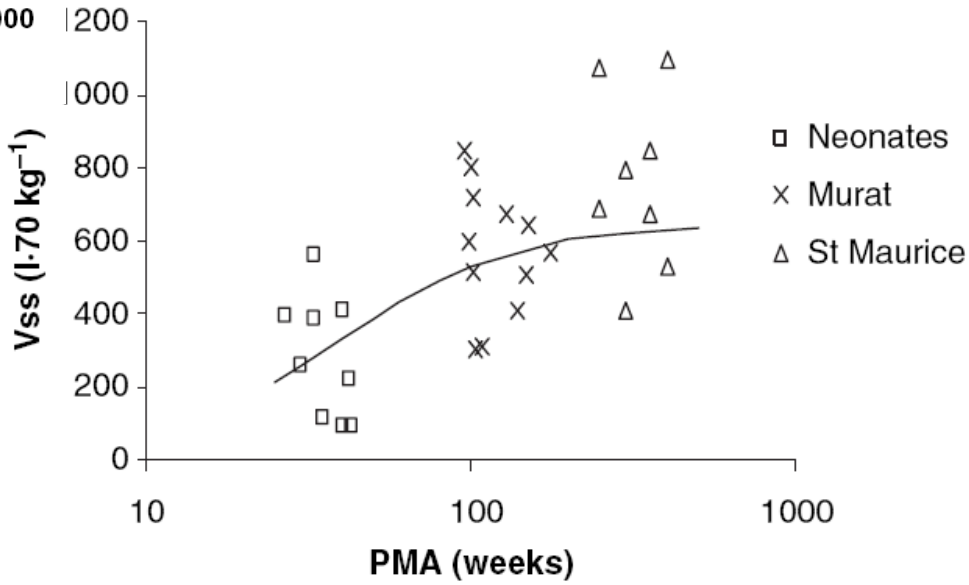
Allegaert et al. Pediatric Anesthesia 2007 17: 1028–1034

# 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 $\leq 60$<br>$\theta_1 \cdot (BW/70)^{\theta_7} - (age - 60) \cdot \theta_{10}$ 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 |
| $V_3$ | $\theta_6$ | 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

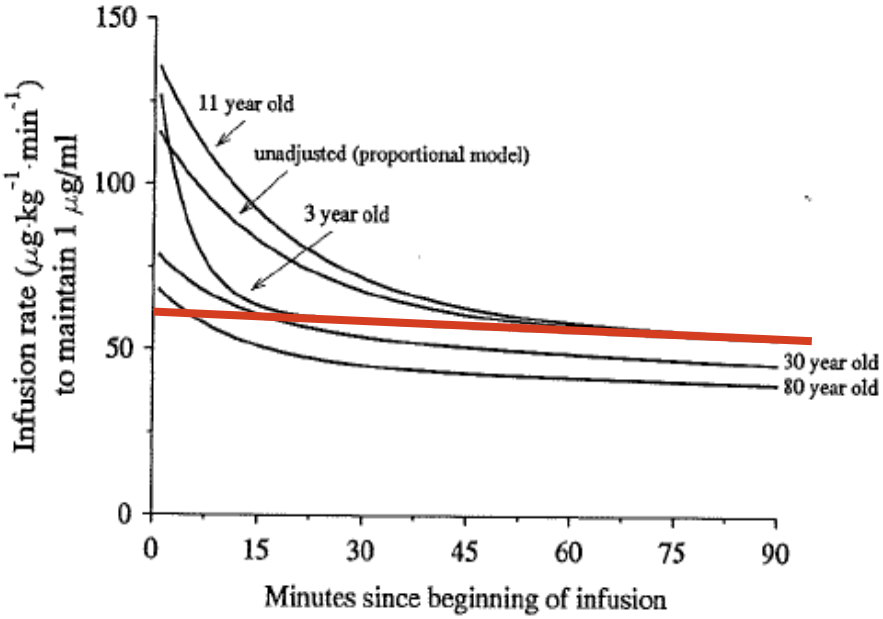
Modelling work is under way!

# Propofol Infusions:

# Manual control or TCI?

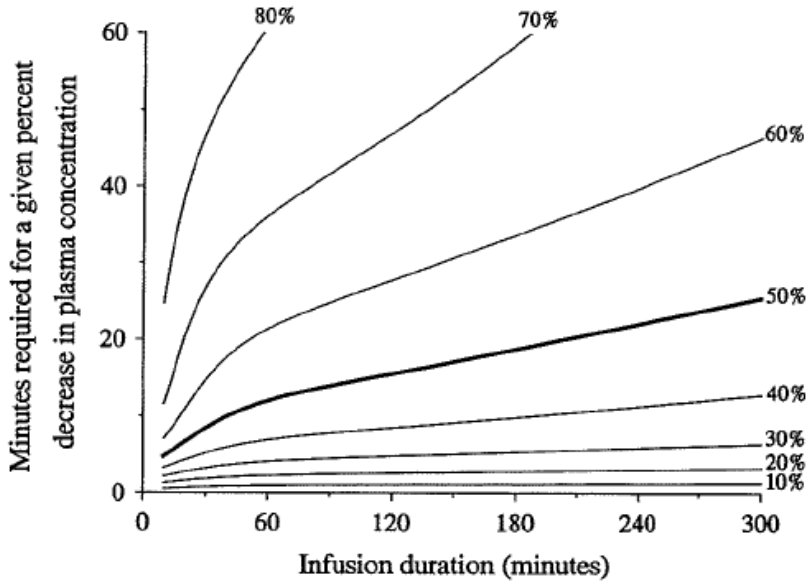
# What Parameters?

# 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

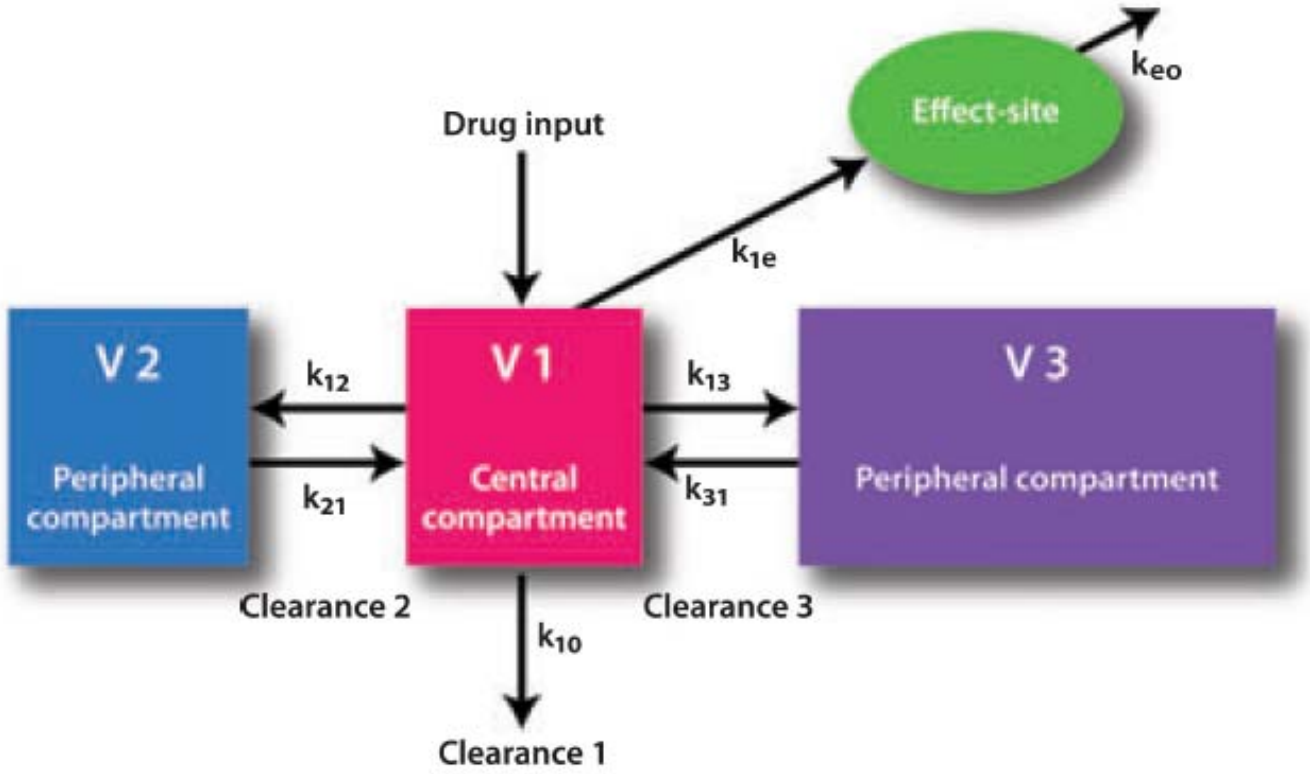
**(Examples: estimated Cp 3 mcg/ml)**

**Complex**

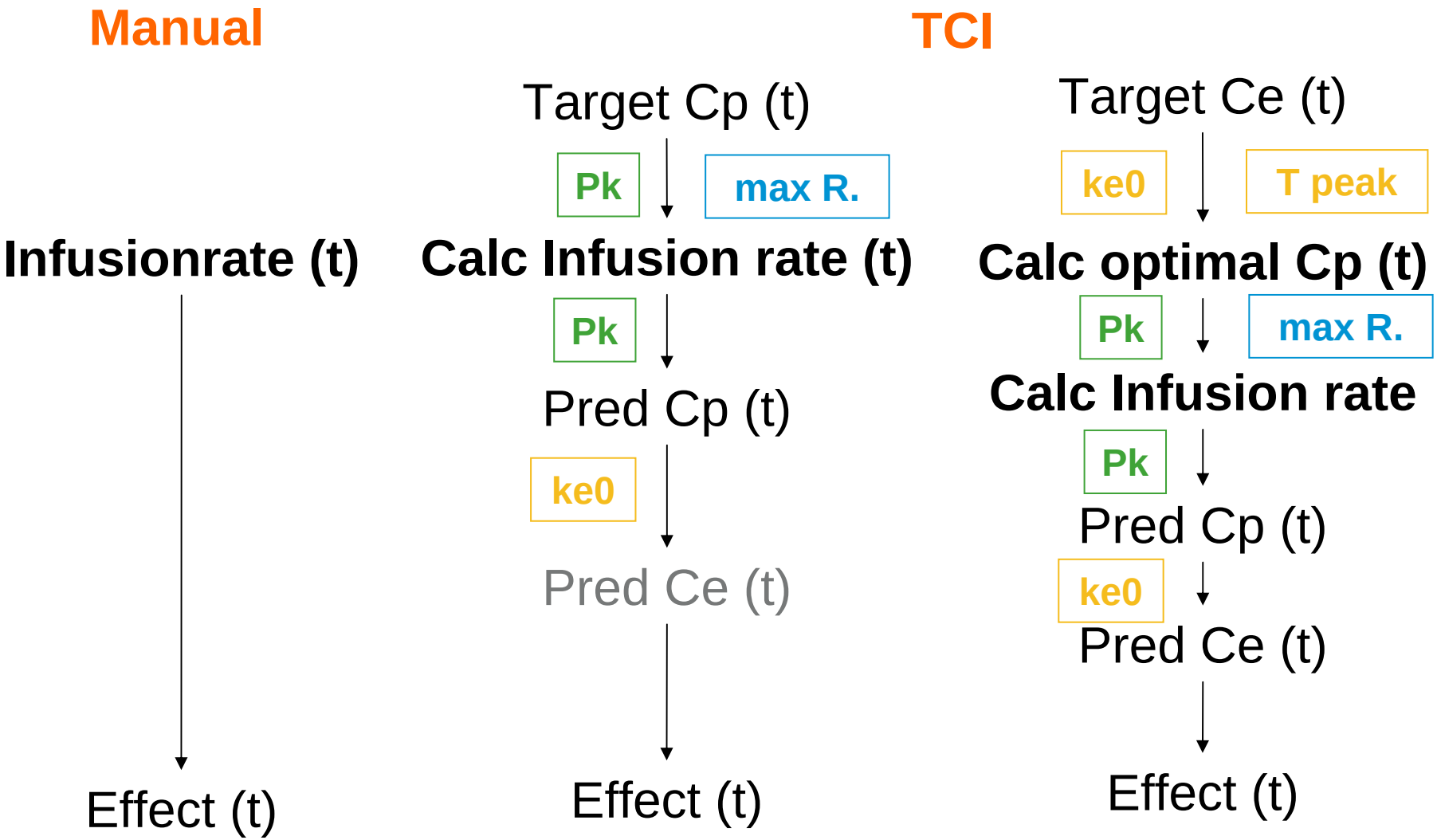
**Risk of errors !**

- **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:**

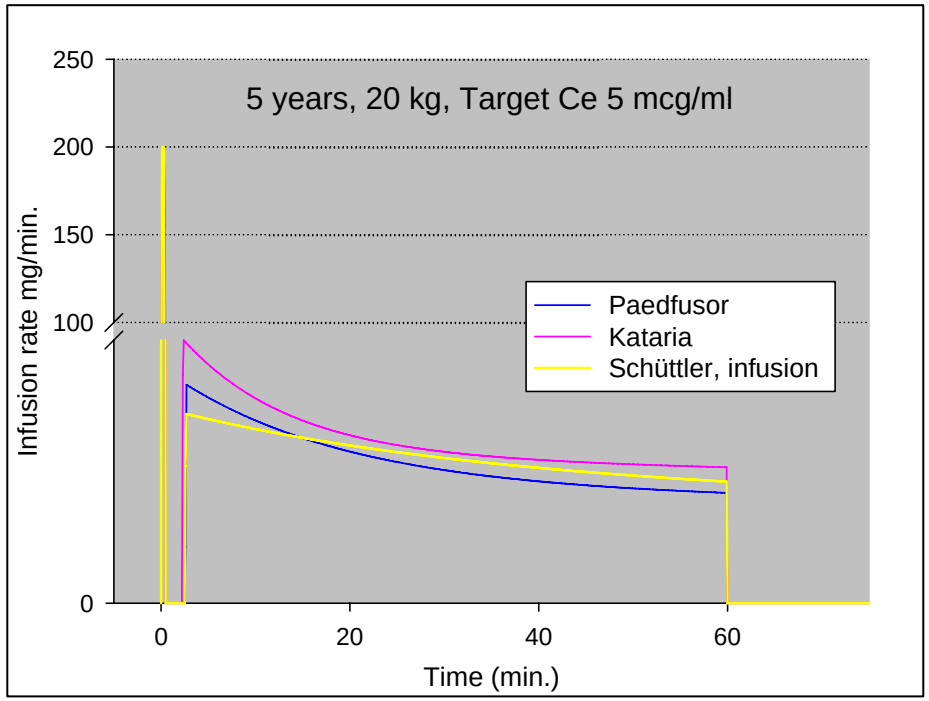
13y: 0.400xweight, 14y: 0.342xweight, 15y: 284xweight, 16y:229xweight

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

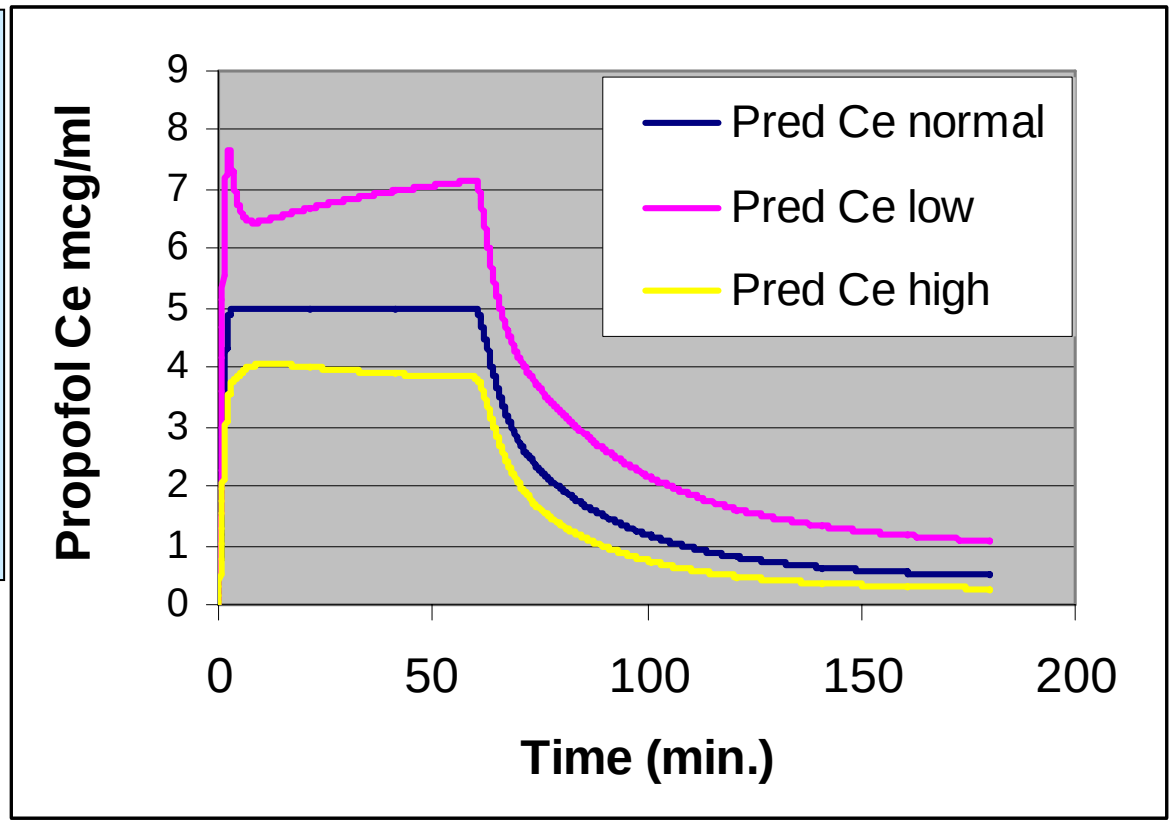
Simulation: 5y, 20 kg

V1 and Cl1

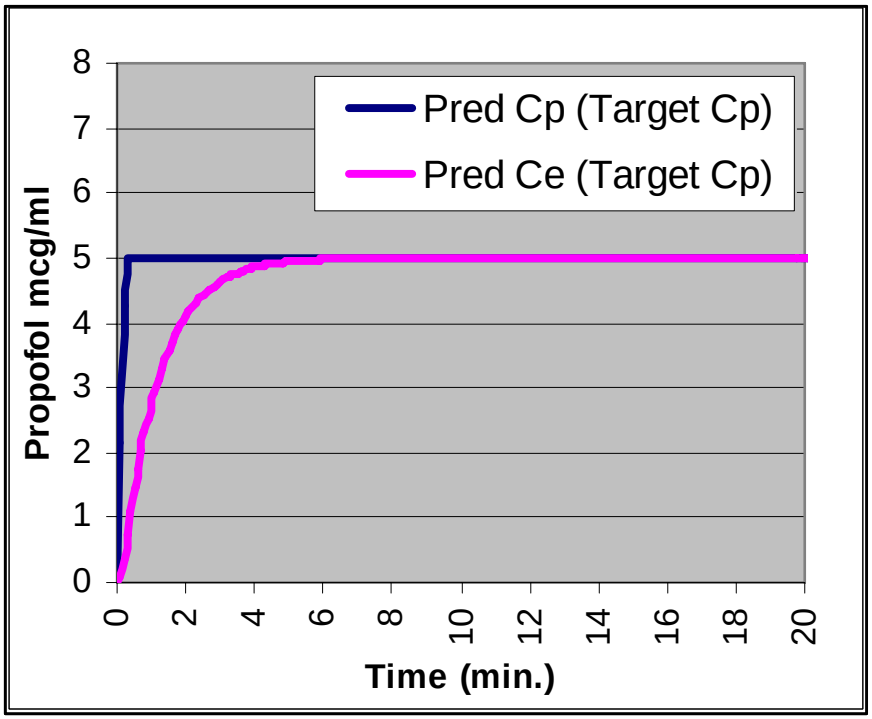
- 50%
- 100%
- 150%

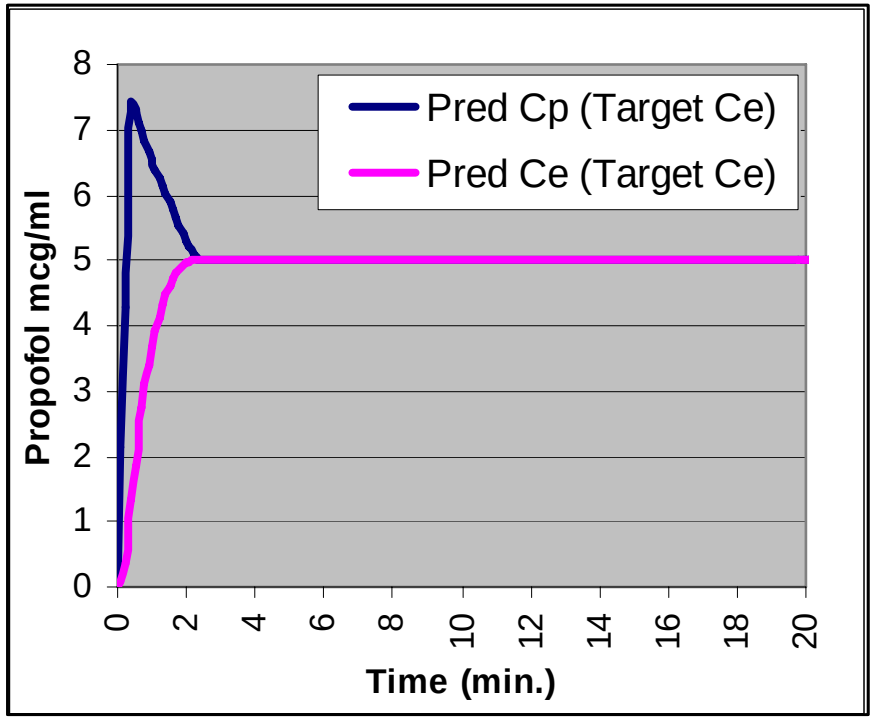
} of population

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)

**Munoz, Anesthesiology 2004**

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

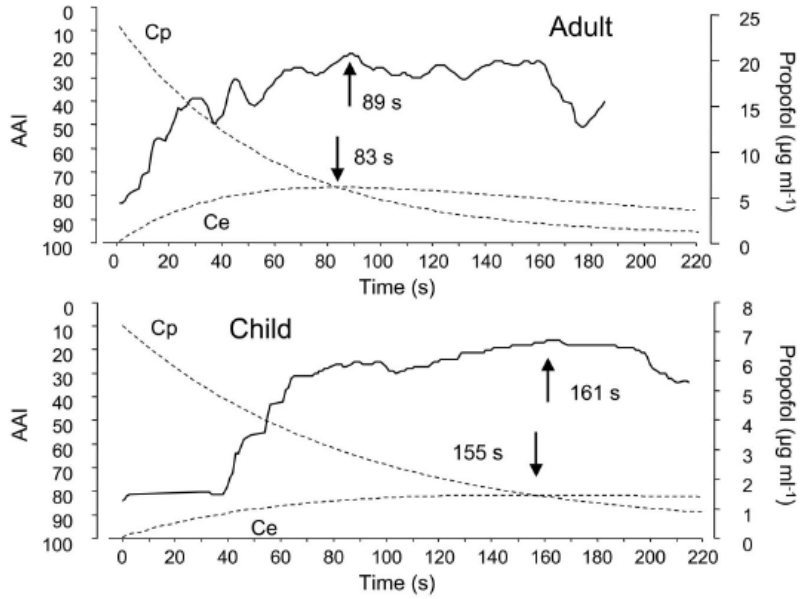
**“sub-maximal bolus”**

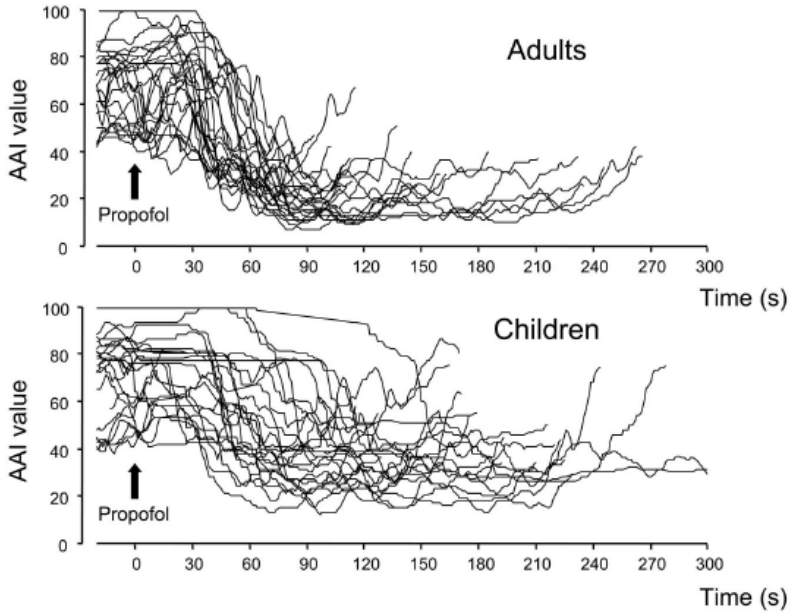
**Pk: Paedfusor and Kataria**

**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**

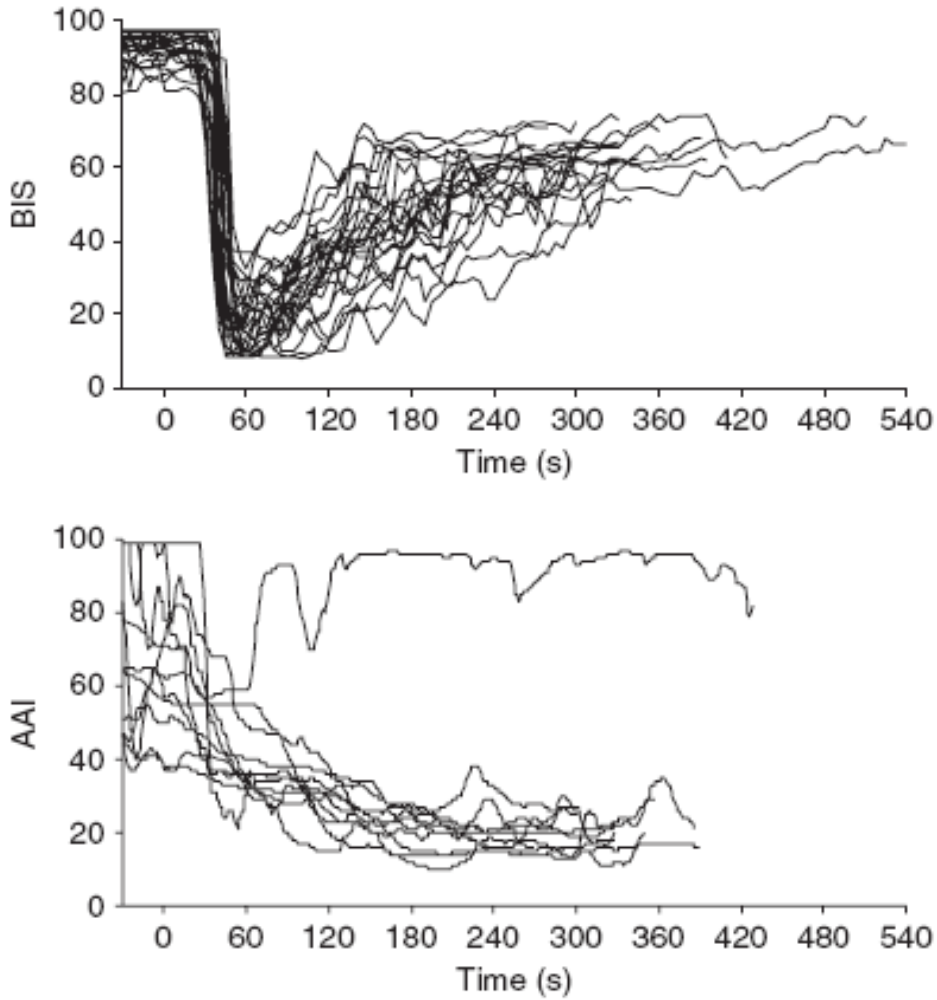
**Tpeak true > Tpeak pred**

*Table 2*

Measurements of performance during the induction.

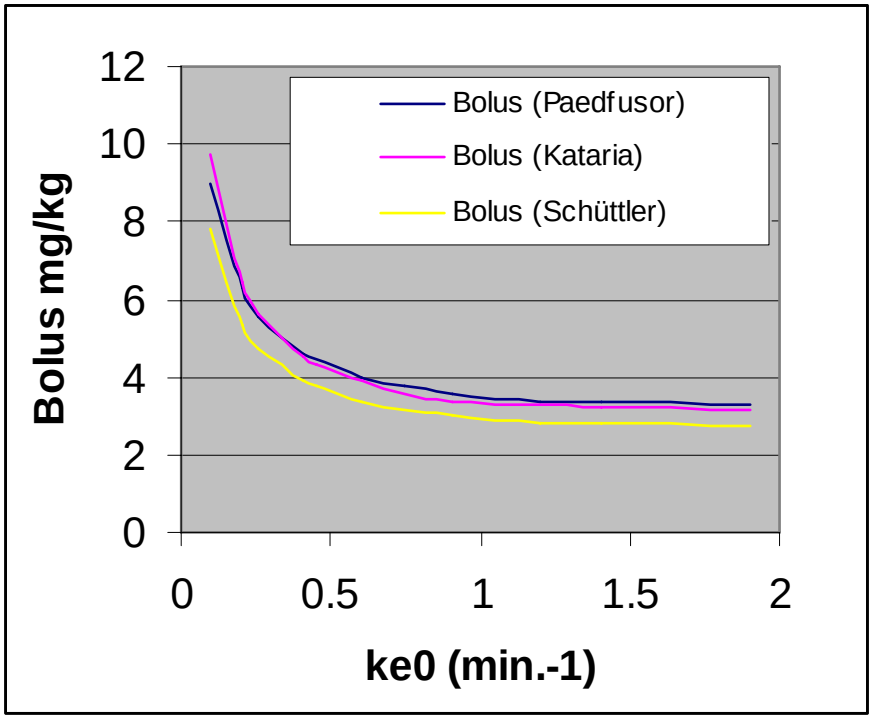
| | Kataria ($n = 20$) | Paedfusor ($n = 20$) |
|---|---|---|
| MD $t_{error}$ (s)* | −7.5 (−27.0–9.0) | −11.0 (−36.0–11.0) |
| MDA $t_{error}$ (s)* | 9.0 (0.0–27.0) | 11.5 (0.0–36.0) |
| MDPE (%)* | 9.4 (−11.4–33.8) | 14.2 (−13.6–46.6) |
| MDAPE (%)* | 11.2 (0.0–33.8) | 14.6 (0.0–46.6) |

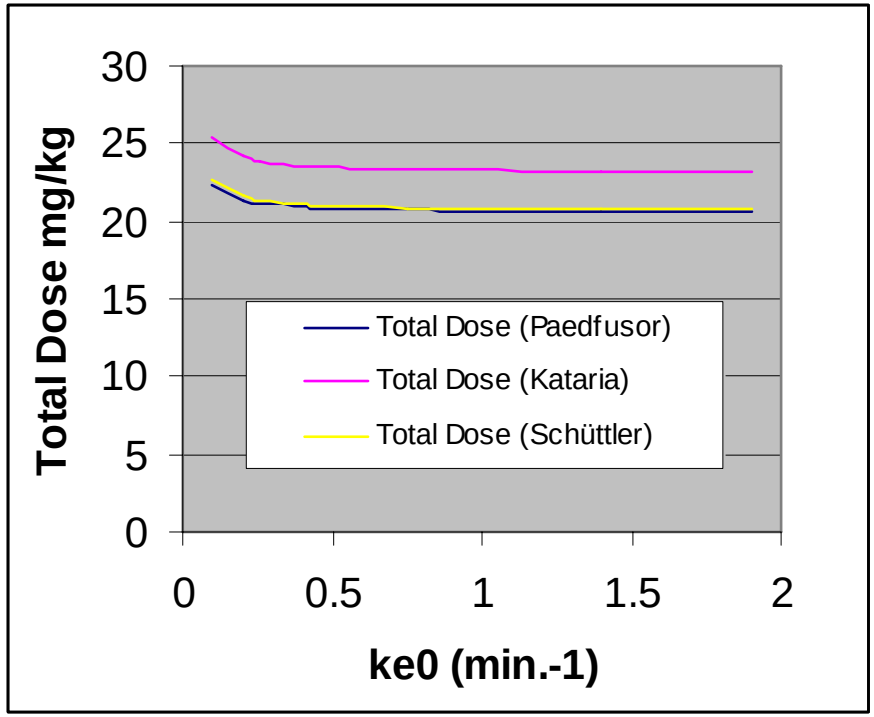
*Values are median (range).
MD,median; MDA; absolute median; MDPE, median prediction error; MDAPE, absolute median prediction error.



# 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

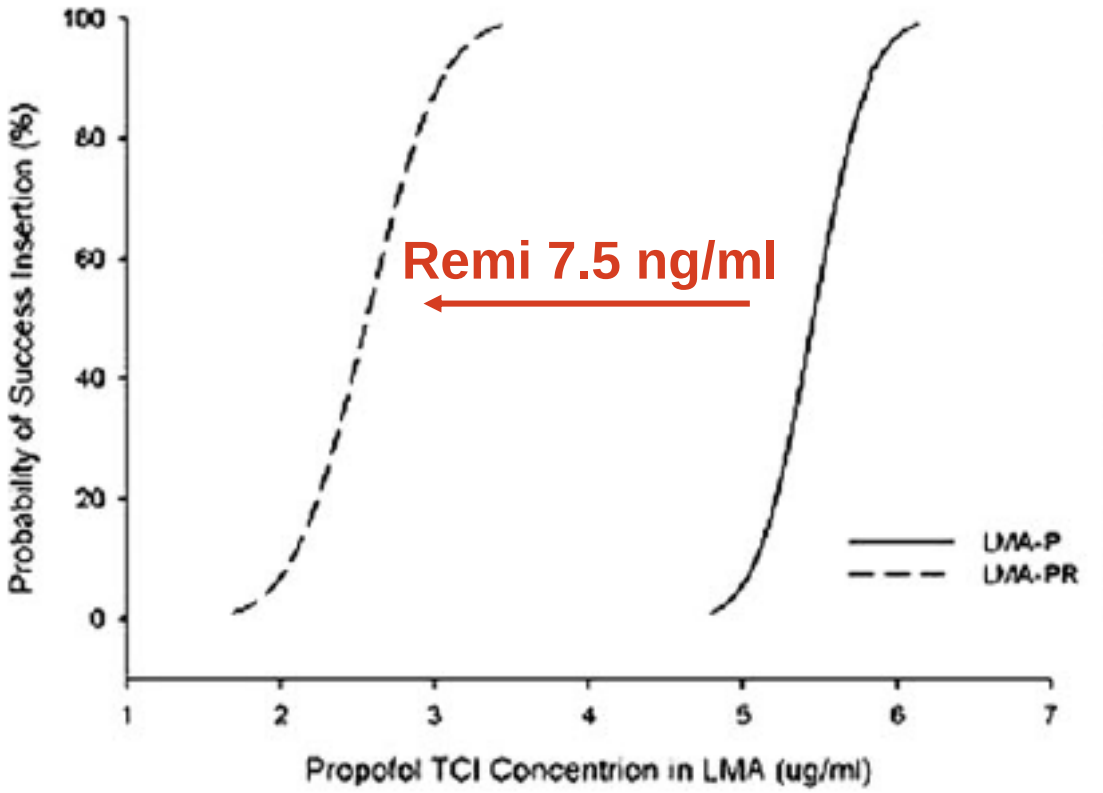
# Propofol Pharmacodynamics: What Concentrations are needed?

# 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



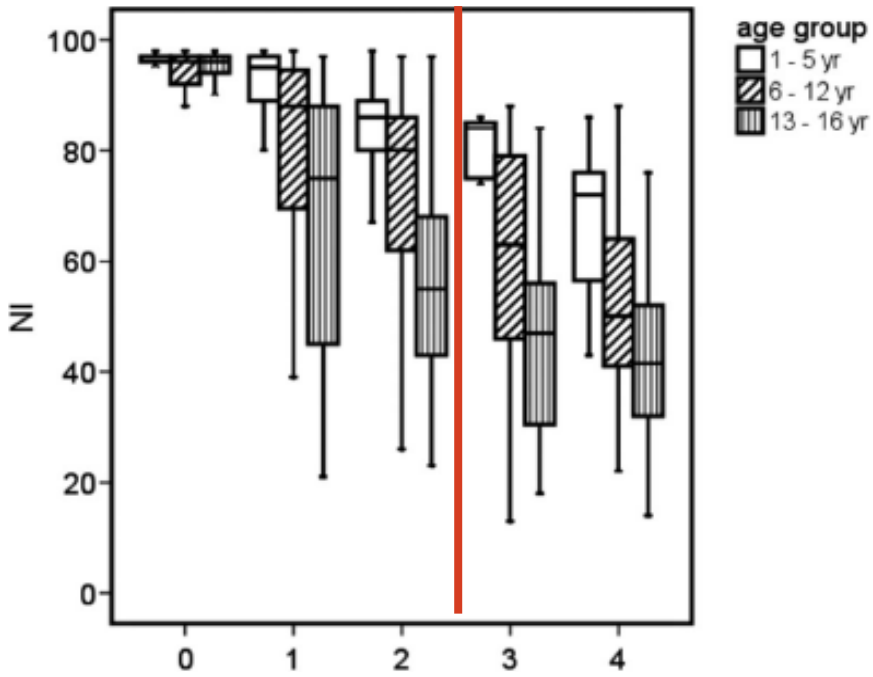
# Loss of consciousness (Münte et al, A&A 2009)

## 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

**Tirel et al. BJA 2008**

**Pseudo steady state**

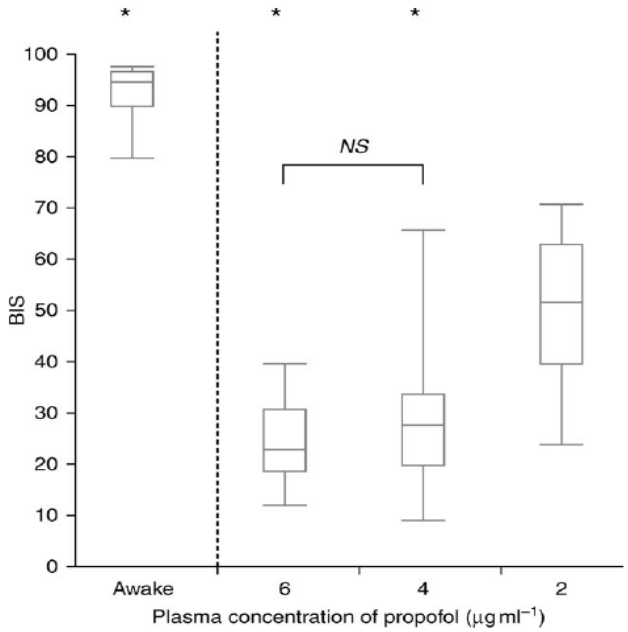
**Kids 3-15 y, N=50, Kataria**

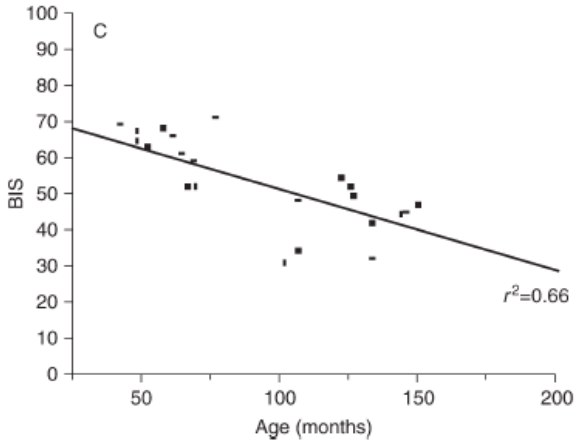
**Remifentanil 1 mcg/kg followed by 0.2 mcg/kg/min.**

**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!