Universitair Medisch Centrum Groningen
Afdeling Anesthesiologie

Intravenous induction and TIVA in paediatrics

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- Prof. Dr. A.R. Absalom (slides and discussion)
- No conflicts of interest to declare


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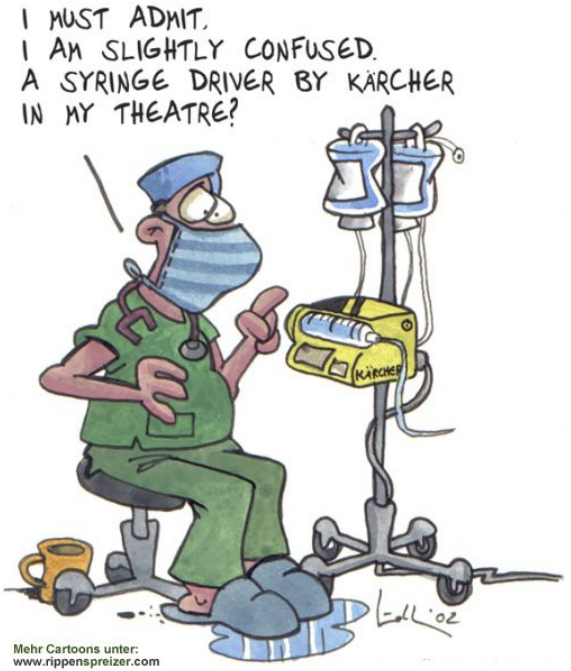
Topics

- Propofol and the foetus or neonate
- Propofol induction of anaesthesia
- Propofol maintenance
  - Pharmacodynamics
  - Pharmacokinetics



- TCI propofol in children as a convenient solution

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Propofol and the foetus or neonate

British Journal of Anaesthesia **109** (S1): i60–i67 (2012)
doi:10.1093/bja/aes424

BJA

Perioperative central nervous system injury in neonates

M. E. McCann[1,2] and S. G. Soriano[1,2*]

British Journal of Anaesthesia **110** (S1): i53–i72 (2013)
Advance Access publication 29 March 2013 · doi:10.1093/bja/aet054

BJA

Impact of anaesthetics and surgery on neurodevelopment: an update

R. D. Sanders[1,2,3*], J. Hassell[2], A. J. Davidson[4], N. J. Robertson[2] and D. Ma[5]

Propofol and the foetus or neonate

- Animal evidence clear
  - All anaesthetic agents “neurotoxic” – promote PCD
    - Exceptions: dexmedetomidine, xenon
    - No data to suggest benefit propofol vs volatiles
  - Only during peak synaptogenesis
- Human evidence equivocal
  - Ongoing multi-center RCTs
    - GAS study
    - PANDA

Propofol for induction of anaesthesia

- Practical issues:
  - The issue of intravenous access
  - Use anti-backflow valves on IV line

- Favourable pharmacokinetics
  - Rapid induction independent of breathing efficiency
    - mean ± standard deviation t_{peak} was 65 ± 14 s

Munoz et al, Acta Anaesth Scand 2009 (53) 883-890

  - PK differences cf adults – large V1
    - Larger bolus dose needed (2,5-3 mg/kg)
    - Shorter duration of initial effect after bolus dose

Marsh vs Kataria vs Paedfusor

	Marsh	Kataria	Paedfusor
V1	**0.228 L/kg**	**0.52 L/kg**	**0.458 L/kg**
V2	**0.463 L/kg**	**1.0 L/kg**	**1.34 L/kg**
V3	**2.893 L/kg**	**8.2 L/kg**	**8.20 L/kg**
K_{10} (min^{-1})	**0.119**	**0.066**	**70 x Weight $^{-0.3}$/458.4**
K_{12} (min^{-1})	**0.112**	**0.113**	**0.12**
K_{13} (min^{-1})	**0.042**	**0.051**	**0.034**
K_{21} (min^{-1})	**0.055**	**0.059**	**0.041**
K_{31} (min^{-1})	**0.0033**	**0.0032**	**0.0019**

Propofol for induction of anaesthesia

- Pharmacodynamics
  - Fast induction (t_{peak} was 65 ± 14 s)
  - Pain on injection
    - Many cofactors involved
    - IV location, speed of injection, MCL, Aquatic phase
    - R/ Lidocaine 0,2 mg/kg (!!!) in children or mixture 10mg in 2 mg/kg prop
  - Muscle relaxation
  - Less epileptiform changes in EEG
    - >> Sevoflurane
  - Myoclonic movements blunted by opioids (etiology?)

Tan et al, Anaesthesia 1998,(53)5: 468-476

Constant, Ped Anesthesia, 2005

Propofol for maintenance of anaesthesia

- Pharmacodynamics
  - Avoidance of volatile agents
    - Less PONV
    - Pleasant emergence
    - Less emergence agitation
    - Environmental issues
    - Applicable in distant locations

COHEN IT et al: Paediatr Anaesth; 2003, 13:63-67

Propofol for maintenance of anaesthesia

- Pharmacodynamics
  - Avoidance of volatile agents
  - Protection against ischaemia-reperfusion injury
    - Free radical scavenger, enhanced tissue antioxidant capacity
    - Inhibition of plasma membrane calcium channels
    - Inhibition of MPTP opening
    - Antiapoptotic properties

Wong, Ped Anesthesia 2011

Propofol for maintenance of anaesthesia

- Pharmacodynamics
  - Avoidance of volatile agents
  - Protection against ischaemia-reperfusion injury
  - Beneficial cerebrovascular effects
    - Parallel reductions in metabolism and flow
    - Reduced cerebral blood volume and intracranial pressure

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Propofol for maintenance of anaesthesia

- Pharmacodynamics
  - Avoidance of volatile agents
  - Other beneficial effects
  - No analgesic effect/weak effect on spinal reflexes
  - Propofol infusion syndrome?

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PRIS – propofol infusion syndrome

Paediatric Anaesthesia 1998 8: 491–499

Propofol infusion syndrome in children

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Department of Anaesthesia, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne NE1 4LP, UK

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PRIS

Does it occur with Anaesthesia?

Age (yrs)	Diagnosis	Prop dose (mg/kg/hr)	Prop duration (hours)	Signs of PRIS
3	Cerebral aneurysm	6.5	8	A, HT, ↑CPK
7	Osteogenesis imperfecta	13.5	2.5	LA
12	Mitral valve disease	<3	15	LA
16	Mitral valve disease	<3	8	LA

Kill, Ped Anesth 2003; *Westhout, J Neurosurg 2007*

Adapted from O. Bagshaw

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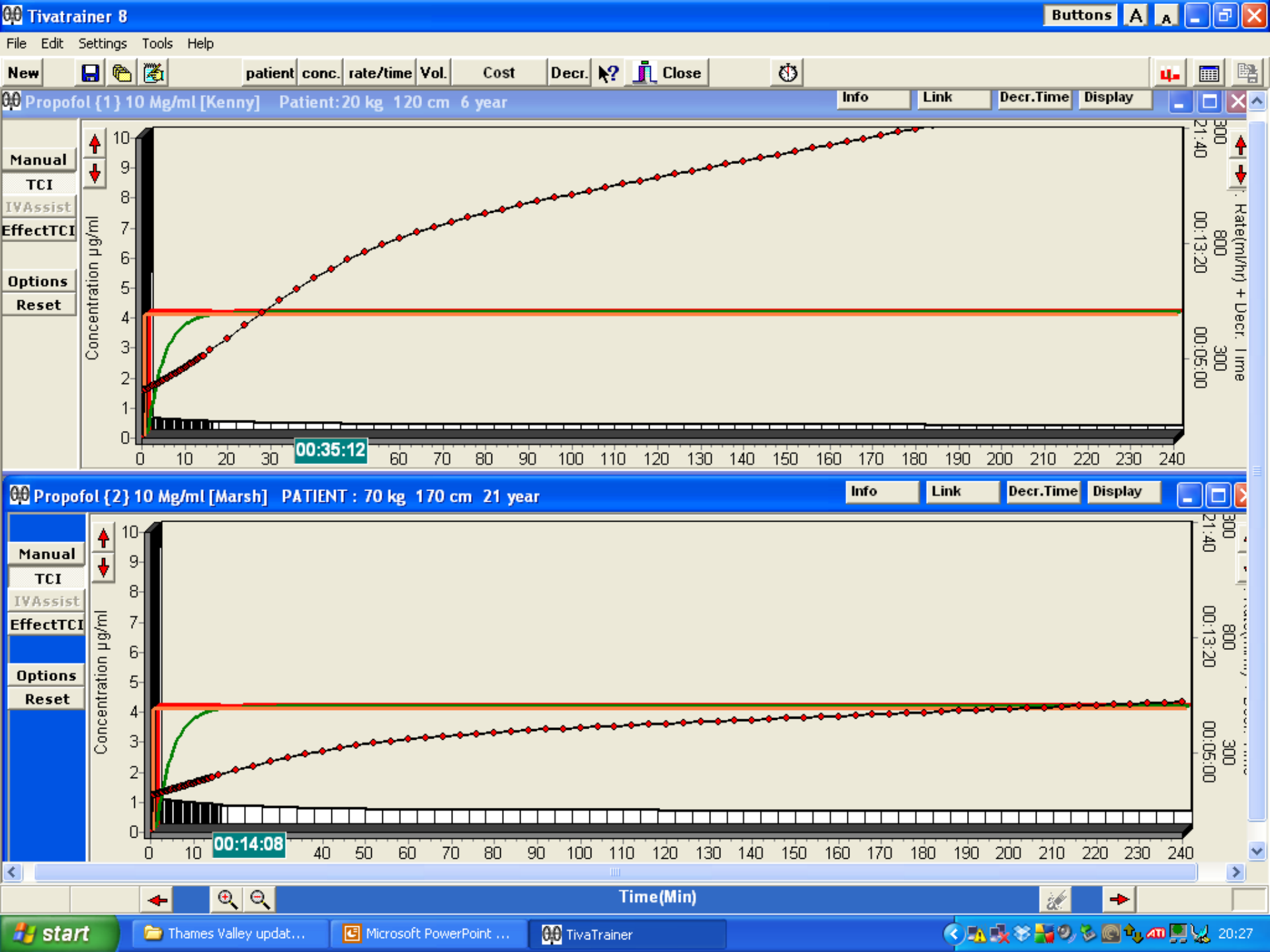
PRIS
Features

- Very rare during propofol anaesthesia
- Clinical features
  - Metabolic (lactic) acidosis
  - Lipaemic serum
  - Circulatory failure requiring inotropic support
  - Bradyarrythmias progressing to asystole
  - Unresponsive to conventional treatment
- Recovery possible if propofol stopped early

Propofol for maintenance of anaesthesia

- Pharmacokinetics
  - More accumulation than in adults
    - Greater context-sensitivity than in adults
    - Relatively large V2 and V3, cf metabolism
    - Longer time to steady state with fixed infusion rate
    - Longer wake-up times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Propofol {2} 10 Mg/ml [Marsh] PATIENT : 70 kg 170 cm 21 year
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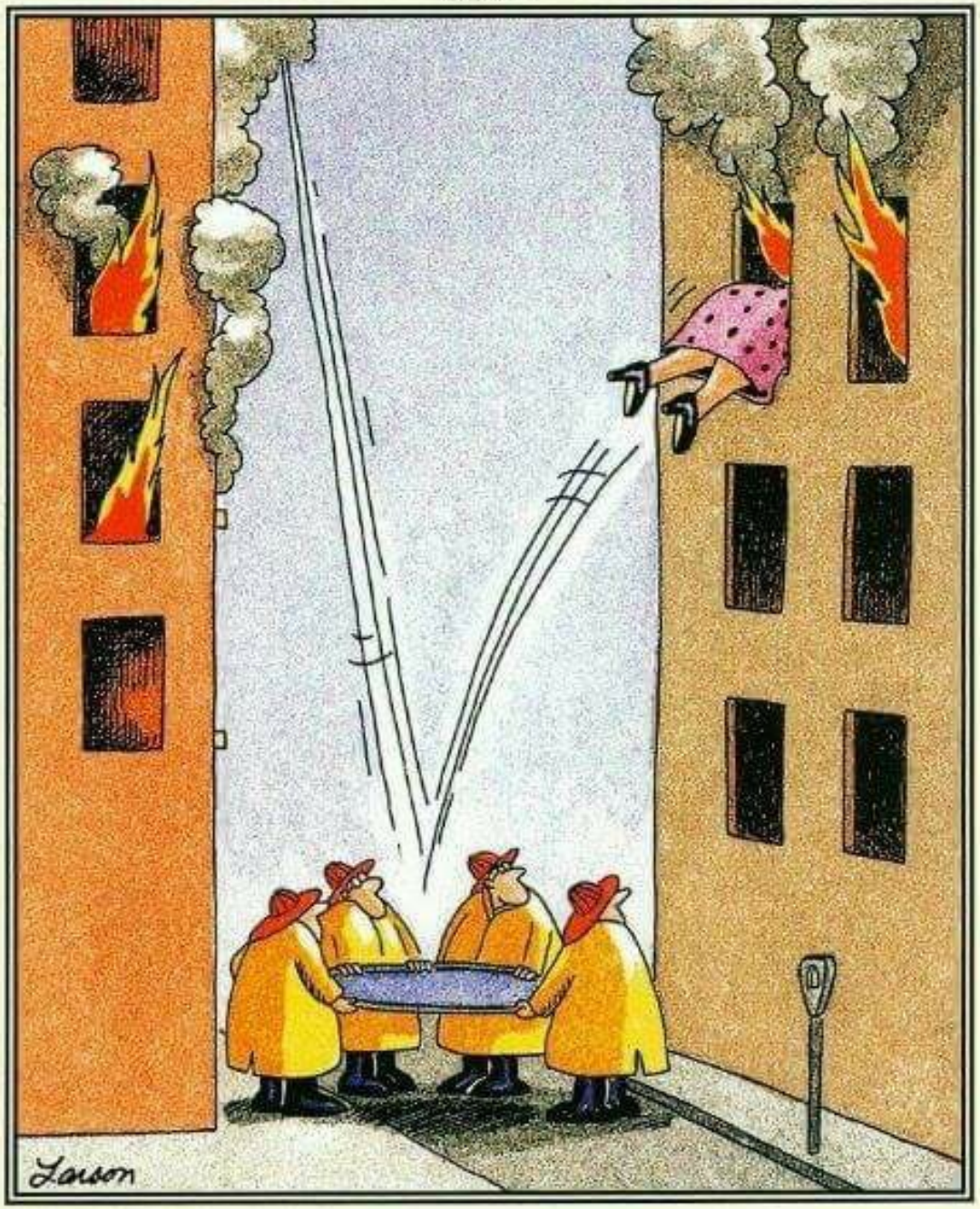
Propofol for maintenance of anaesthesia

- Pharmacokinetics
  - More accumulation than in adults
  - Slowly reduce infusion rates during long cases
  - TCI is useful to assist in dose adaptation
  - Time course of accumulation predicted at bedside
  - Recovery can be anticipated better using TCI
  - But how good are the current models?

3/31/81

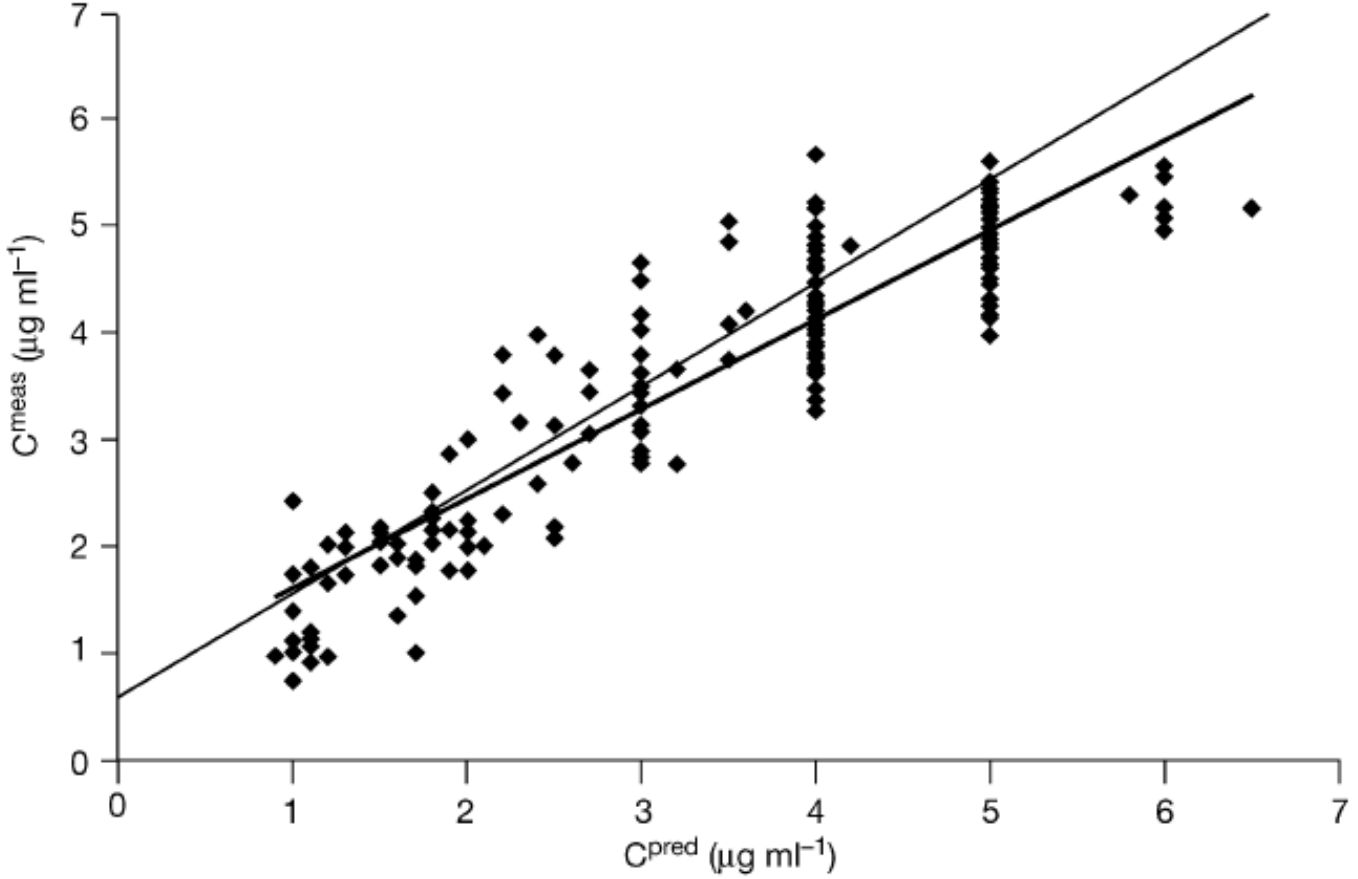


British Journal of Anaesthesia **91** (4): 507–13 (2003)
DOI: 10.1093/bja/aeg220

BJA

Accuracy of the 'Paedfusor' in children undergoing cardiac surgery or catheterization

A. Absalom[1]*, D. Amutike[1 4], A. Lal[2], M. White[3] and G. N. C. Kenny[1]

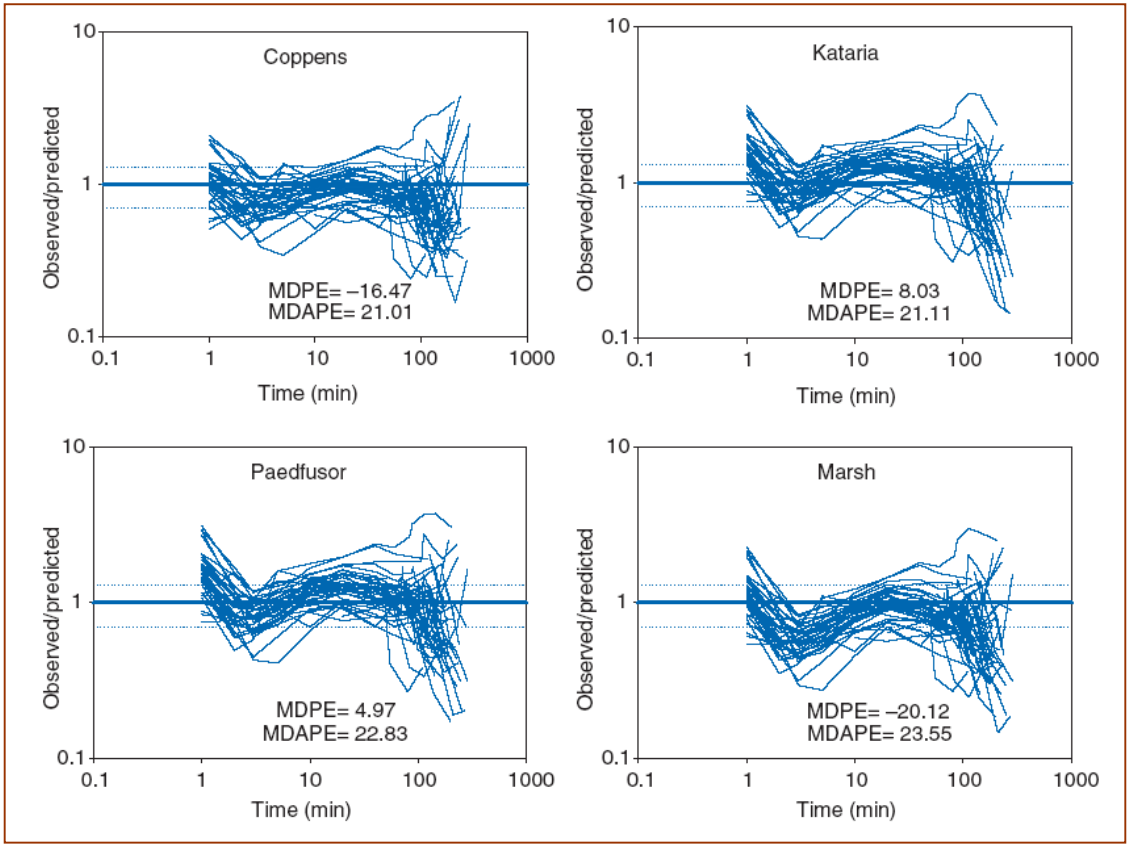


British Journal of Anaesthesia Page 1 of 8
doi:10.1093/bja/aer198

BJA

Performance evaluation of paediatric propofol pharmacokinetic models in healthy young children

P. Sepúlveda[1], L. I. Cortínez[2*], C. Sáez[1], A. Penna[4], S. Solari[3], I. Guerra[3] and A. R. Absalom[5]



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Propofol for maintenance of anaesthesia

- Pharmacokinetics
  - More accumulation than in adults
  - Slowly reduce infusion rates during long cases
  - TCI is useful to assist in dose adaptation
  - Time course of accumulation predicted at bedside
  - Recovery can be anticipated better using TCI
  - TCI useful, but how good are the current models?
    - Current models imperfect
    - Maturation effects
    - Linear versus allometric scaling
    - Separate paediatric model versus adult model

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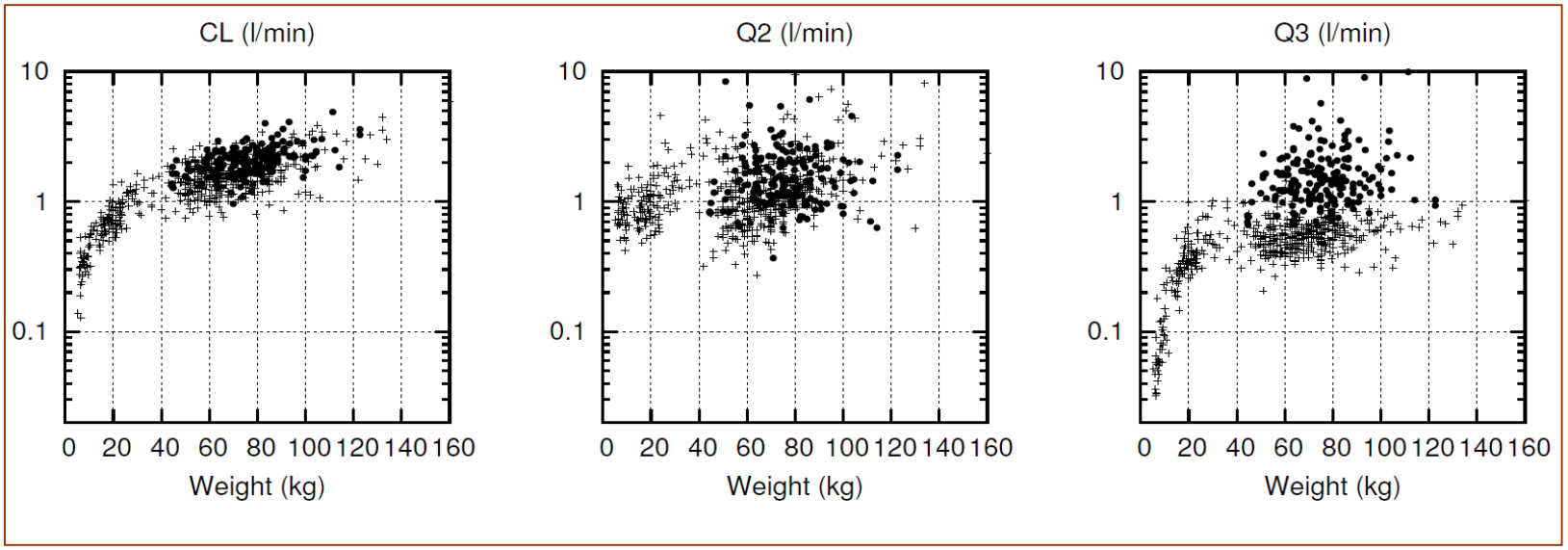
Basis for allometric exponents

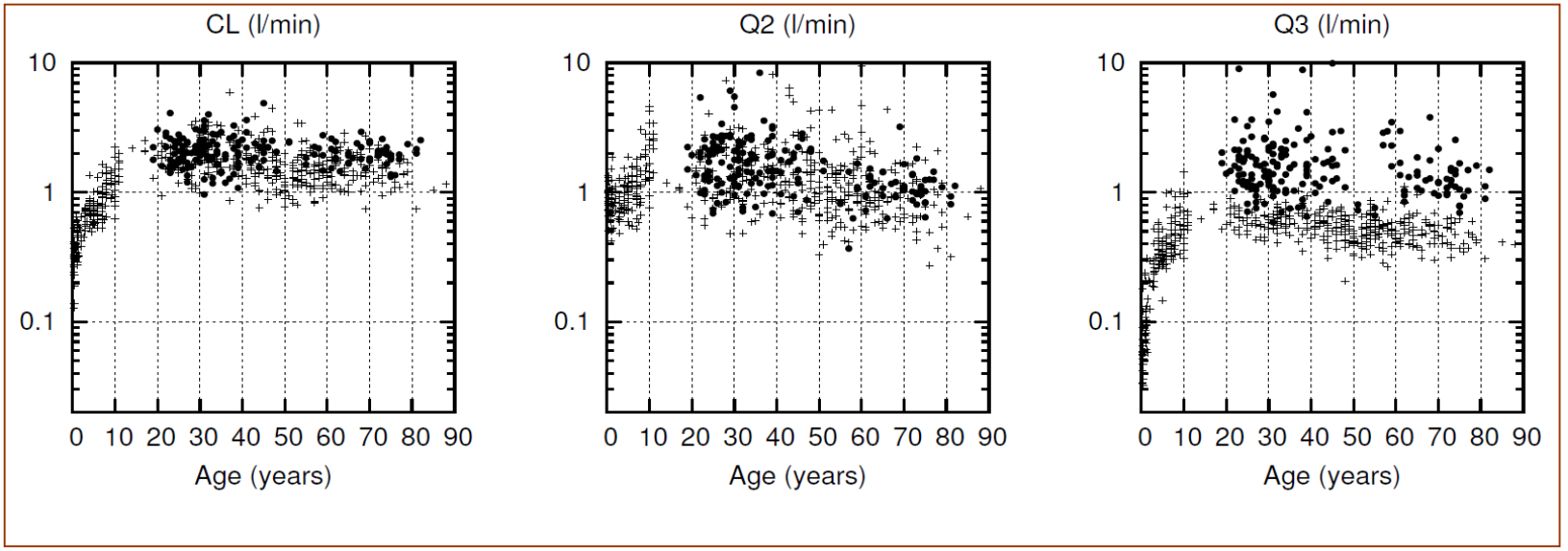
- Invariant properties across organisms
  - Branching, capillaries, efficiency, heat production
- Theory suggests:
  - Volumes (linear): V = const x (Weight/70)^1.0
  - Clearance (sub-linear): Cl = const x (Weight/70)^0.75

THE FOURTH DIMENSION OF LIFE:
FRACTAL GEOMETRY AND
ALLOMETRIC SCALING OF ORGANISMS

Geoffrey B. West[1,2] *, James H. Brown[2,3], Brian J. Enquist[2,3]

June 9, 1999





Eleveld et al. A general purpose pharmacokinetic model for propofol. ANESTHESIA AND ANALGESIA.(2014). 118(6). p.1221-1237

Predictive performance of Eleveld 'general purpose' propofol model

Subgroup	Model	MDPE (%)	MDAPE (%)	Good prediction error (APE<=20%)	Poor prediction error (APE>60%)	Predictive performance metric (%)
Young children	final model	-3.8	18.0	54.5	7.0	47.5
	Coppens	-15.3	23.0	44.3	8.1	36.2
	Short	2.4	20.9	47.6	11.6	36.0
	Rigby-Jones	-9.3	22.8	45.0	10.7	34.3
	Knibbe	-7.4	24.5	42.2	11.1	31.1
Children	final model	-3.7	19.3	52.3	5.5	46.8
	Coppens	-10.8	19.7	50.9	6.4	44.5
	Marsh (children)	-11.3	20.7	48.3	5.4	42.8
	Paedfusor	-9.3	23.0	44.8	6.0	38.8
	Rigby-Jones (multicenter)	3.8	22.3	45.3	7.5	37.8

Are there still limitations for the use of target-controlled infusion in children?

Brian J. Anderson[a] and Bryan Hodkinson[b]

Current Opinion in Anaesthesiology 2010, 23:356–362

- No integrated parameter estimates to be programmed over the broad paediatric age range.
- The six pharmacokinetic parameter sets available for children out of infancy all differ.
- Validation studies are few.
- Estimates in neonates and infants are dependent on maturation and size considerations that have not yet been elucidated.
- There remains a need for specific neonate-derived algorithms if electroencephalogram (EEG)-derived anaesthesia depth monitors are to be used for neonates or infants.
- Hardware limitations
- Monitoring issues restrict use.

Not every issue solved

Global purpose model is a step in the good direction?

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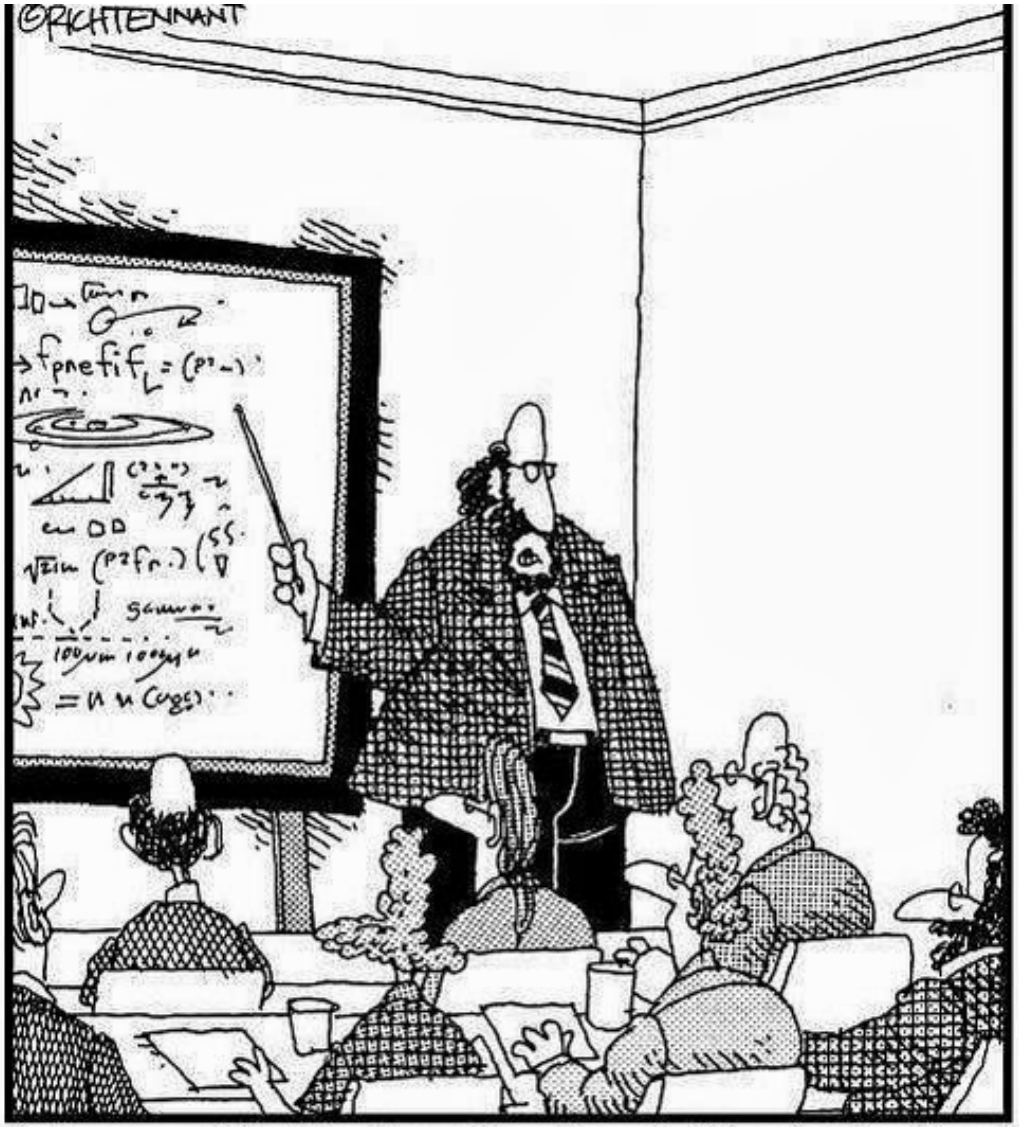
TCI propofol in paediatrics

- Several paediatric pharmacokinetic models
  - Paedfusor & Kataria available in some TCI pumps
  - None perfect
  - Incompletely validated (puberty?)
  - None use allometric scaling
- Some published PD parameters (keo values)
  - Validation needed
  - Not yet commercially available

In conclusion

- Practical concerns can be resolved
- Propofol is a convenient and safe induction agent
- It has advantages over inhaled anaesthesia
- Accumulation should be anticipated
- TCI assists in optimal dosing and anticipating recovery
- PRIS is rare when moderate dose and short duration
- Room for improvement in PKPD models for children



"Along with 'Antimatter,' and 'Dark Matter,' we've recently discovered the existence of 'Doesn't Matter,' which appears to have no effect on the universe whatsoever."