



HAL
open science

Propofol and children - what we know and what we don't know

Ann Rigby-Jones, J Robert Sneyd

► **To cite this version:**

Ann Rigby-Jones, J Robert Sneyd. Propofol and children - what we know and what we don't know. *Pediatric Anesthesia*, 2010, 21 (3), pp.247. 10.1111/j.1460-9592.2010.03454.x . hal-00599902

HAL Id: hal-00599902

<https://hal.science/hal-00599902>

Submitted on 11 Jun 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Pediatric Anesthesia

Propofol and children – what we know and what we don't know

Journal:	<i>Pediatric Anesthesia</i>
Manuscript ID:	PAN-2010-0337.R1
Manuscript Type:	Review (commissioned)
Date Submitted by the Author:	13-Oct-2010
Complete List of Authors:	Rigby-Jones, Ann; Peninsula Medical School, Anaesthesia Research Group Sneyd, J; Peninsula College of Medicine & Dentistry, Anaesthesia
Key Words:	intravenous agents < Drugs, pharmacodynamics < Drugs, pharmacokinetics < Drugs, child < Age, infant < Age, neonate < Age

Propofol and children – what we know and what we don't know

Ann E Rigby-Jones

J Robert Sneyd

Anaesthesia Research Group, Peninsula Medical School, Peninsula College of Medicine & Dentistry, University of Plymouth, UK.

Corresponding Author

Dr Ann Rigby-Jones

N31, ITTC Building

Tamar Science Park

Derriford

Plymouth

PL6 8BX

E-mail: ann.rigby-jones@pms.ac.uk

Running title: Propofol kinetics and dynamics in children

Summary

The pharmacokinetics of propofol are relatively well-described in the pediatric population. Recent work has confirmed the validity of allometric scaling for predicting propofol disposition across different species and for describing pediatric ontogenesis. In the first year of life, allometric models require adjustment to reflect ontogeny of maturation. Pharmacodynamic data for propofol in children are scarcer, due to practical difficulties of data collection and the limitations of currently available depth of anesthesia monitors for pediatric use. Hence, questions relating to the comparative sensitivity of children to propofol, and differences in time to peak effect relative to adults, remain unanswered. K_{eo} half-lives have been determined for pediatric kinetic models using time to peak effect techniques but are not currently incorporated into commercially available target controlled infusion pumps. ~~Propofol injection pain remains a clinical problem, despite availability of propofol emulsions with a reduced free propofol concentration.~~

Keywords: propofol; children; pharmacokinetics; pharmacodynamics;

Pediatric pharmacokinetics

The pharmacokinetics of propofol are relatively well-described in children, having been investigated in healthy children (1-5), children with biliary atresia (3), small children suffering from burns (6), critically ill ventilated (7, 8) and non-ventilated children (9) and neonates (10, 11). Propofol disposition is generally best described by a 3-compartment mamillary model, with a rapidly equilibrating central compartment, a second larger peripheral compartment and a third, very large peripheral compartment. Propofol pharmacokinetics are altered in children, compared to adults. Comparative analyses have demonstrated that on a per kilogram body weight basis, children demonstrate increased clearance and larger volumes of distribution relative to adults. In particular, the volume of the central compartment is much greater than in adults (12). Consequently, children require higher induction and maintenance doses than adults to achieve the same propofol blood concentration.

The influence of the larger central compartment volume in children can be explored using pharmacokinetic simulation. Figure 1 compares the concentration versus time profile resulting from a one hour propofol infusion ($4\text{mg kg}^{-1}\text{ hr}^{-1}$) administered to an adult (Diprifusor kinetics (1, 13)) or to a 20kg child (Kataria kinetics (5)). The larger central compartment volume in children results in markedly reduced propofol plasma concentrations, relative to the adult.

Disentangling covariate effects

The evaluation of drug disposition in heterogeneous patients groups, such as those encountered in the pediatric ICU, can be complicated by the presence of confounding factors. How can one separate the influences that critical illness may have on pharmacokinetics, from the affects of body size and maturity? Body size and age are usually well correlated in pediatric populations. Allometric scaling is a useful and well-supported (14) approach to disentangle body size effects from other correlated covariables, such as age, in pediatric populations. Allometric scaling relates body mass to metabolic rate (and hence, to drug clearance) using Kleiber's Law. In 1932, Kleiber demonstrated that basal metabolic rate was proportional to body mass raised to the power 0.75, and that this relationship applied to animals ranging in size from a mouse to a whale (15). When deriving pharmacokinetic data from pediatric populations, if weight is selected as a initial covariate and the three-quarter power relationship applied *a priori* (to clearance parameters; volume parameters are scaled to the power of 1), this allows the influence of secondary covariates, which may be correlated to weight e.g. age, to be examined (16).

1
2
3 Knibbe and colleagues explored the application of allometric scaling to propofol
4 pharmacokinetic parameters obtained from rats, children (aged from 1 to 5 years) and adults
5 (17). This work demonstrated the validity of the allometric approach for predicting drug
6 disposition across different species and for describing within-species ontogenesis, Figure 2.
7
8
9

10
11 A recent publication by the same group has focused on defining the human body weight
12 range for which allometric scaling can accurately be applied to predict propofol clearance
13 (18). Allometric scaling alone could accurately predict propofol clearance in children older
14 than 2 years. However, adjustment of the model to reflect maturation was required to predict
15 clearance in children younger than 24 months, a demonstration that simple allometric scaling
16 reveals, but does not account for, age-related differences in pharmacokinetics.
17
18
19
20
21

22 23 *Propofol in neonates*

24
25 The work of Allegaert and colleagues in recent years has done much to inform propofol
26 disposition and metabolism in term and pre-term neonates. Allegaert described markedly
27 reduced clearance in a group of nine neonates (4-25 days postnatal age) after bolus
28 injection of propofol(11). After appropriate allometric scaling to 70kg to allow comparison,
29 the clearance value was approximately 32%, and the volume of distribution at steady-state
30 was approximately 44% of the corresponding values previously reported in infants . Scaled
31 propofol clearance rates approach adult values within the first three months to one year of
32 life (6, 19), mirroring ontogenic development of hepatic enzyme systems (20).
33
34
35
36
37
38
39

40 For infants and older children, the inclusion of body weight alone as a model covariate
41 accounts for much of the observed inter-individual variability in propofol pharmacokinetics (5,
42 8, 9, 19). Allegaert has demonstrated that for neonates post-menstrual and post-natal age
43 as markers of maturity, rather than body weight, were the most influential factors, with the
44 youngest babies having the smallest clearance values. Anderson (21) further explored this
45 finding, combining Allegaert's neonatal clearance data with clearance values derived from
46 older children (5, 6) and adults (13, 22, 23). A sigmoid E_{max} model was then applied to
47 describe the maturation profile, Figure 3. In this analysis, the maturation half-time was
48 calculated as 44 weeks. Anderson highlights the need for additional study of propofol
49 disposition in infants to fully characterise the maturation profile in the first two years of life.
50
51
52
53
54
55
56
57
58
59
60

Pediatric Critical Care & Propofol Infusion Syndrome

Propofol infusion syndrome (PRIS) was first described in the literature in 1992 (24). Shortly after, the syndrome was defined by Bray and colleagues as a sudden onset of treatment-resistant bradycardia leading to asystole, combined with at least one of the following symptoms; lipaemic plasma, clinically enlarged or fat infiltrated liver, metabolic acidosis or rhabdomyolysis (25). The syndrome was associated with long duration (more than 48 hours), high dose (more than $4 \text{ mg kg}^{-1}\text{hr}^{-1}$) propofol infusions in children under 12 years old. In 2001, reports of the same propofol-related syndrome occurring in adult ICU patients (26) led to the UK Commission on Human Medicines (then Commission on Safety of Medicines) to recommend that propofol infusion rates for sedation did not exceed $4 \text{ mg kg}^{-1}\text{hr}^{-1}$ (27). In the following year, the same committee announced the contraindication of propofol for the sedation of critically ill children (28).

Eight years later, what have we learned about PRIS? We know that it is a real phenomenon, with the consistency of clinical reports of the syndrome, the dose-dependency and the temporal association to propofol administration cited as reasons to strongly support a causal relationship (29). Plausible mechanisms have been suggested supporting the implication of the lipid component of currently available propofol formulations in the pathology of the syndrome (30, 31). Whether a lipid-free propofol formulation, such as fospropofol, would decrease the risk of PRIS, or avoid it entirely, is as yet unknown. However, the potential for direct toxicity related to propofol itself, rather than the vehicle, would remain (32).

In recent years, use of propofol sedation in critically ill children in the UK has been extremely limited in line with current recommendations (33). The knowledge base regarding the disposition of propofol in the critical care population is hence based on studies carried out prior to the 2002 contraindication. Reed and colleagues were first to study propofol disposition in a critically ill pediatric population, ranging from neonates to age 15 years (7). They concluded that the pharmacokinetics were not dissimilar to studies of healthy children but described substantial inter-patient variability that could not be attributed to age or other demographic effects. Rigby-Jones *et al* (8) described altered kinetics in very small babies (due to increased peripheral distribution volume) and reduced metabolic clearance in children recovering from cardiac surgery, both findings leading to prolonged propofol elimination times, see Figure 2. Body weight was the most influential model covariate and although a broad age range was studied (1 week to 12 years), no additional influence of age could be supported. In a non-ventilated, post-neurosurgical pediatric population (9) propofol

1
2
3 clearance values were reported to be twice as high as those previously described in
4 paediatric intensive care unit (PICU) patients (8), emphasising the impact that mechanical
5 ventilation and cardiac bypass have on propofol elimination during post-operative sedation.
6
7
8
9

10 *Pediatric Propofol Target Controlled Infusion (TCI)*

11

12
13 There are at least two pediatric pharmacokinetic models for propofol available for use in
14 commercially available TCI pumps; the Paedfusor (34, 35) and the Kataria kinetic set (5).
15 The Kataria model is based on data from 53 healthy children, ranging in age from three to 11
16 years. Mean post-dose sampling duration was 214 minutes (range 52 to 811). The
17 Paedfusor pharmacokinetic set was derived as a preliminary model (presumably based on
18 pediatric data only) by Schuttler and Ihmsen during their development of a pharmacokinetic
19 model based on pooled data from both adults and children (12). In Schuttler's analysis,
20 pediatric data comprised 96 children aged from two to 11 years, including the patient
21 population on which Kataria's model was based (5) and data from two further pediatric
22 studies (1, 2).
23
24
25
26
27
28
29
30

31 The Paedfusor model was prospectively validated in 29 children (1 to 15 years) undergoing
32 cardiac surgery or cardiac catheterisation procedures (34). In this small study, the
33 Paedfusor model's predictive performance was well within acceptable limits for clinical use.
34 A formal prospective analysis of the predictive performance of the Kataria model in children
35 has not been published to date. However, a study by Rigouzzo and colleagues involved TCI
36 administration of propofol to children (aged 6 to 13 years) using the Kataria model. Blood
37 samples for propofol plasma assay were collected (36). It was reported that measured
38 concentrations of propofol were consistently higher than those predicted by the Kataria
39 model, and that the margin of error increased with increasing propofol concentration.
40
41
42
43
44
45
46
47

48 The original analyses leading to the derivation of the Kataria and Paedfusor models were
49 based on pharmacokinetic data only. However, values for K_{e0} , the blood-brain equilibration
50 rate constant have been retrospectively generated for both models using the Time to Peak
51 effect (t_{peak}) (37) technique (38). T_{peak} is a model-independent pharmacodynamic parameter
52 that can be used to calculate a K_{e0} value for a given pharmacokinetic set, after
53 administration of a sub-maximal dose. The K_{e0} value derived is one that accurately predicts
54 t_{peak} (37). Muñoz's analysis revealed that the peak effect of propofol in children (132s)
55 occurs far later than in adults (80s). The explanation offered for this finding is that, relative
56 to adults (Schnider model), simulations using the pediatric model demonstrate a much
57
58
59
60

1
2
3 slower initial decline in plasma propofol concentrations, Figure 4. As the post-bolus t_{peak} is
4 the consequence of both decreasing plasma concentration and increasing effect site
5 concentration, this is a plausible mechanism.
6
7
8

9
10 The experimentally derived t_{peak} value of 132s extrapolated to a K_{e0} value for the Kataria
11 model of 0.41min^{-1} and for the Paedfusor model, 0.91min^{-1} . However, current commercially
12 available TCI devices incorporating the Kataria and Paedfusor models do not include K_{e0} i.e.
13 plasma is the target of the infusion, rather than the effect site, thus depriving pediatric
14 populations from the superior control offered by effect site targeting systems (39-41).
15
16
17

18 19 **Pediatric Pharmacodynamics (PD)**

20
21 Whilst the pharmacokinetics of propofol in the pediatric population are reasonably well-
22 described, there is a relative paucity of pharmacodynamic data (9, 38, 42).
23
24
25

26 *Limitations of Pediatric PD studies*

27
28
29 Undertaking pharmacodynamic studies can be very difficult in children and particularly so in
30 intensive care medicine. In a “real life” scenario, rather than a controlled volunteer study in
31 adults, it is often difficult or impossible to obtain data describing a full drug concentration
32 versus effect profile. This is required for adequately quantifying hysteresis and hence, the
33 derivation of K_{e0} . Arterial blood, the gold-standard matrix for sampling during PK-PD studies
34 of rapidly acting drug compounds, is highly unlikely to be available for children outside of
35 critical care. The insertion of a peripheral arterial line in children purely for research
36 purposes is classified as high risk and cannot be justified (43), further, arterial line insertion
37 is typically done after induction of anesthesia and the opportunity to populate the rising
38 phase of the hysteresis loop is lost. The use of venous blood sampling during pediatric
39 pharmacodynamic studies of intravenous sedative-hypnotics presents a limitation that can in
40 part be overcome by careful study design, such as the incorporation of equilibration stages
41 to accompanying changes in infusion rate. This stabilises arterial and venous blood
42 concentrations and minimises arterio-venous differences as far as possible.
43
44
45
46
47
48
49
50
51
52

53
54 The use of intermittent pharmacodynamic markers, such as sedation scores, can also make
55 it more difficult to capture rapidly changing drug effects. However, for extended continuous
56 infusion studies, COMFORT scores (44) can provide useful information and have been
57 successfully utilised as pharmacodynamic markers for the development of complex but
58 clinically informative models of propofol pharmacodynamics (9). Other limitations of
59
60

1
2
3 sedation scoring as a pharmacodynamic marker are inter- and intra-observer variance and
4 the impact that stimulation required as part of a scoring system may have on the underlying
5 depth of sedation.
6
7

8
9
10 Additionally, researchers are unlikely to be able to study single drug effects in children.
11 Hence, there is a need for pragmatism regarding the concomitant administration of other
12 drugs with sedating effects when evaluating propofol pharmacodynamics, such as
13 maintaining opioids infusions at a constant rate, so adjunct drug contribution to
14 pharmacodynamic effects are at least unchanging after a period of equilibration (45). In
15 another strategy to deal with multiple drug effects, Jeleazcov and colleagues assumed
16 additive interactions between propofol and co-administered opioids to derive
17 pharmacodynamic parameter values for each drug based on their combined sedative effect,
18 when measured using bispectral index (BIS) (46). They studied 59 children aged from 1 to
19 16 years undergoing general surgery. A two-stage pharmacodynamic analysis revealed an
20 age-dependency of the K_{e0} value for propofol, with K_{e0} decreasing with increasing age. T_{peak} ,
21 however, showed a trend of increasing with age. These findings may reflect true age-
22 dependent differences in propofol pharmacodynamics. Cortinez and colleagues have
23 suggested that children may be more sensitive to propofol than adults, based on higher
24 calculated CE_{50} values in adults than in children (3 to 11 years), resulting from a study
25 examining auditory evoked potentials (AEP) following a sub-maximal bolus propofol dose
26 (42). However, a second study by the same group which determined propofol effect site
27 concentrations at BIS value = 50 in adults and in children aged 3 to 11 did not demonstrate
28 significant differences in propofol requirements (47). In contrast, Rigouzzo *et al* suggested
29 that children may be *less* sensitive than adults to propofol. In their study of 45 children (6 to
30 13 years) and 45 adults anaesthetised with TCI propofol, children demonstrated higher
31 measured and predicted propofol plasma concentrations at a BIS value of 50 than the adult
32 patients (36). Conflicting results from such studies may be in part related to the choice of
33 depth of anesthesia monitor, and differences in the pharmacokinetic models used to
34 administer propofol and/or predict effect site concentrations.
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50

51
52 Recently, a second smaller study by Rigouzzo and colleagues attempted to identify the best
53 model for describing propofol PK-PD in pre-pubertal children (48). Propofol was
54 administered to pre-pubertal children (n=16, 6-12 years) by TCI using the Kataria model (5),
55 and to adults and post-pubertal children (n=13, 13-35 years) using the Schnider model (49).
56 BIS was used as an effect measure. The recorded BIS data from the pre-pubertal group
57 was then compared to predicted propofol concentrations generated using several
58
59
60

1
2
3 pharmacokinetic models; the Kataria model used to administer propofol but also the Marsh
4 (1), Schuttler (12) and Schnider models, to evaluate which model best described the data.
5 BIS data from the post-pubertal/adult cohort was compared to predicted concentrations
6 generated by the Schnider model only. The analysis revealed that the pre-pubertal BIS
7 versus predicted propofol concentration was best described by the adult Schnider model so
8 in a second stage of the analysis, the two cohorts were pooled so that the influence of
9 puberty on propofol pharmacodynamic parameter estimates could be examined. The
10 authors hypothesise that the lack of early sampling in the studies that led to the derivation of
11 the paediatric models tested, may explain their perceived weakness at describing the initial
12 phase of propofol distribution kinetics, and hence, the effect on BIS. Additionally, the
13 Schnider model is unique among those explored in Rigouzzo's analysis in that both age and
14 lean body mass are included as covariates, thus allowing a more precise tailoring of
15 individual predicted propofol concentrations. Analysis of the pooled data from both cohorts
16 using the Schnider model revealed that pubertal status was a significant pharmacodynamic
17 model covariate with both K_{e0} and C_{e50} varying between children and adults. The typical
18 value of C_{e50} was around 20% higher in children than in adults. T_{peak} was subsequently
19 derived and found to be significantly shorter in children at 0.71 min [0.37-1.64] median
20 [range] versus 1.73 [1.4-2.68] min in adults. This is in contrast to the findings by Munoz (38),
21 which the authors suggest may relate to differences in effect measure (BIS versus AEP) and
22 methodological differences, including the use of different pharmacokinetic models. The
23 shorter T_{peak} in younger children supports the findings of Jeleacov and colleagues (46).
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

41 ***Propofol, BIS & Children***

42 The technology of BIS monitoring is based on an algorithm developed from adults, hence its
43 usefulness as a measure of anaesthetic depth in children, and particularly in infants, has
44 long been questioned (50). Subsequent studies evaluating the relationship between the
45 bispectral index and established sedation measures such as the Observer's Assessment of
46 Alertness/Sedation (OAA/S) and the University of Michigan Sedation Scale (UMSS) have
47 provided evidence that BIS monitoring can be a useful measure of intravenous sedation in
48 children older than 2 years (51) (52). Currently, evidence to suggest that any of the
49 alternative depth of anesthesia monitors is more or less suitable than BIS for use in children
50 is limited (53-55).
51
52
53
54
55
56
57
58
59
60

Prospective BIS monitoring of children (n=12, 1-12 years) in PICU was performed to
investigate the incidence of over-sedation and periods of potential awareness during

1
2
3 neuromuscular blockade (56). Children were sedated with either midazolam or propofol
4 infusions, with supplemental doses of midazolam, fentanyl or morphine provided if additional
5 sedation was deemed necessary, based on physiological parameters. The BIS monitor was
6 concealed from clinical staff. During the 476 hours of sedation studied, over-sedation
7 (BIS<50) occurred 35% of the time, and under-sedation (periods of potential awareness,
8 BIS>71) comprised 8% of the time. Over-sedation was more likely to occur in patients
9 sedated with propofol, than with midazolam ($p<0.0001$). There are several limitations to this
10 study, not least the small cohort and the assumption that BIS is a 'gold standard' measure of
11 sedation in the patients studied. However, the study results suggest the need for a larger
12 prospective trial to establish the benefit of BIS-titrated sedation in pediatric patients during
13 the use of neuromuscular blocking agents.
14
15
16
17
18
19
20
21
22

23 Recently, Tirel and colleagues (57) used TCI propofol to evaluate the relationship between
24 age and BIS values, in a group of children aged from 3 to 15 years. Target propofol plasma
25 concentrations were held at 6, 4 and $2\mu\text{g mL}^{-1}$ during periods without surgical stimulation to
26 allow collection of BIS and raw EEG. In this study, there was no statistically significant
27 difference in BIS values at 4 and $6\mu\text{g mL}^{-1}$. BIS values at $2\mu\text{g mL}^{-1}$ were significantly
28 different to those achieved at the higher target concentrations but were also correlated with
29 the age of the children ($r^2=0.66$), with the highest BIS values being recorded in the youngest
30 children. Tirel *et al* suggest this may reflect a true pharmacodynamic difference between
31 younger and older children, or could be influenced by the underlying pharmacokinetics. The
32 Kataria model used for TCI does not include age as a covariate after it was demonstrated
33 that its inclusion only marginally improved the model.
34
35
36
37
38
39
40
41

42 Park *et al* (58) investigated the relationship between BIS values and predicted plasma
43 propofol concentrations in 30 children aged from 2 to 7 years during emergence from
44 anesthesia. The Marsh model was used to administer TCI propofol (1). On completion of
45 surgery, the target propofol concentration was reduced from $3\mu\text{g mL}^{-1}$ in $0.2\mu\text{g mL}^{-1}$ steps
46 and BIS values were recorded. The authors concluded that BIS was correlated with
47 predicted propofol concentration during emergence from anesthesia but that the correlation
48 was weaker than that observed with an adult population. Additionally, there was substantial
49 interindividual variability in the recorded BIS values at each predicted concentration.
50
51
52
53
54
55
56

57 These studies suggest caution when using BIS to titrate propofol infusions in children and
58 demonstrate a lack of sensitivity of the BIS system to discriminate at deep sedation levels in
59 children.
60

Pain on injection

Whilst propofol injection pain is highly unpleasant for adults, it becomes a real clinical problem when the drug is administered to children. Injection pain causes severe distress to the patient and often to an accompanying parent. Children are more susceptible to propofol induced pain than adults, with younger children likely to experience more severe pain than older children (59).

The addition of adjuvant drugs has been explored, with ketamine (60), lidocaine (59) and thiopental (61) all demonstrating some efficacy at reducing injection pain. It has been argued that if the use of adjuvant drugs for the reduction of propofol injection pain is to be recommended, their use must be evaluated from a medical risk-benefit perspective (62). Propofol injection pain may be related to the concentration of free propofol in the formulation (63) and direct dilution of propofol prior to administration has been reported to reduce the incidence of injection pain in children (64). The free propofol concentration is reduced in medium chain triglyceride (MCT)/long chain triglyceride (LCT) mixtures, relative to formulations containing only LCT (65). Theoretically, this should lead to a reduction in injection pain. However, in practice, there have been contradictory findings in adults relating to the proposed reduction in pain (66-70). Certainly, MCT-LCT propofol is associated with pain in children when injected without an adjunct drug. Nyman and colleagues injected either a plain solution of 3mg/kg MCT-LCT propofol or LCT propofol with added lidocaine (1mL of 1%) randomly to a group of 83 children (2-18 years). The incidence of injection pain was higher with the MCT-LCT group (66.6%) than in the LCT propofol/lidocaine group (39.0%)(71). A recent study of 84 children aged from 5 to 15 years reported no difference in the incidence or severity of pain when either pre-mixed lidocaine (1mL of 2%) and either a long chain triglyceride (LCT) propofol emulsion combination, a MCT/LCT propofol emulsion (20mL of 1%) combination were injected (72). This indicates that in pediatric clinical practice, there may be little difference in the experience of injection pain with different propofol emulsions. There is, however, good evidence for the effectiveness lidocaine (1mL of 1%) combined with 10mL of a medium chain triglyceride (MCT) propofol formulation for eliminating injection pain in pre-school children (73).

Conclusion

This review has sought to identify current gaps in the knowledge base of propofol use in the pediatric population, in particular, aspects relating to drug disposition and pharmacodynamic effect. Updated information on issues that impact on day-to-day clinical practice, such as injection pain and PRIS were also considered.

There are comprehensive data describing propofol disposition across the pediatric age range, as a result of much needed research in the neonatal population in recent years. In addition, based on demonstration of the applicability and limitations of allometric scaling, there is now better understanding of the mechanisms and predictability of changes in propofol pharmacokinetics from birth to maturity.

Given the practical restrictions described, and the continued lack of a gold-standard depth of anesthesia monitor for children, it is not surprising that much remains to be elucidated regarding the pharmacodynamics of propofol in the pediatric population. Indeed, the knowledge base relating to adult propofol pharmacodynamics has its own limitations, with genuine disagreement about the most appropriate values for time to peak effect and $t_{1/2k_{e0}}$ (74, 75).

Figures

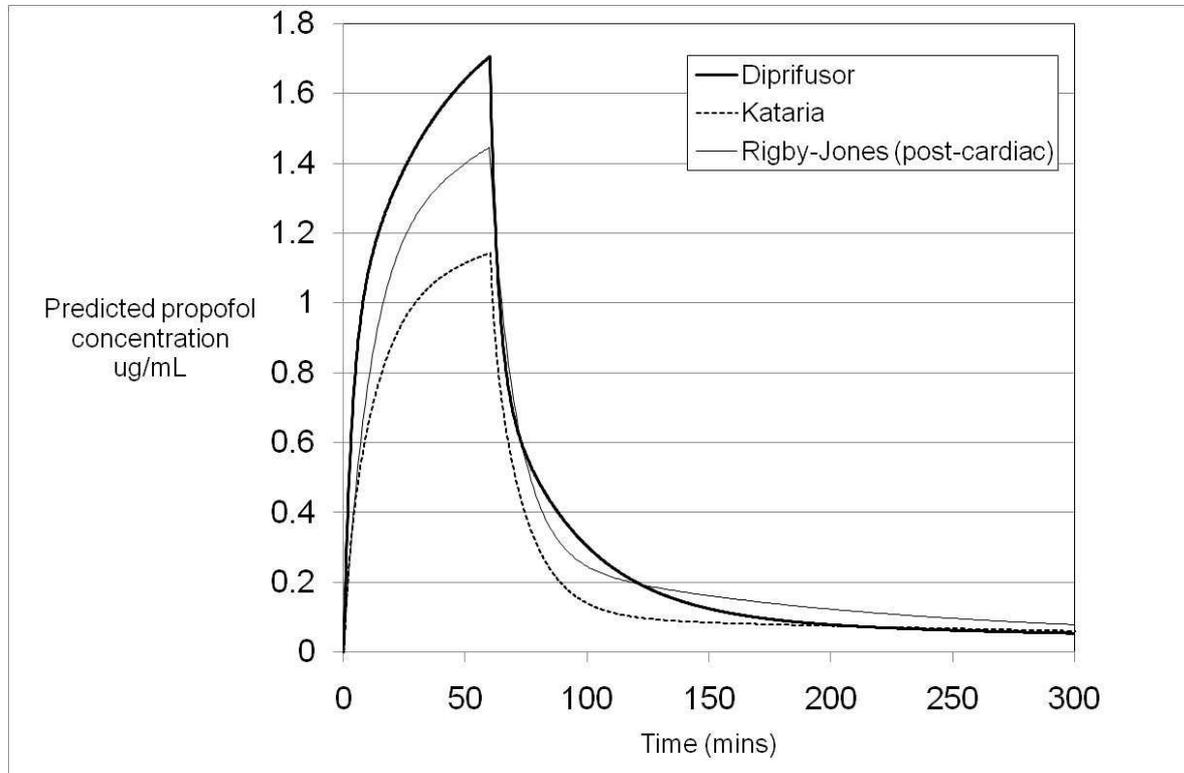


Figure 1

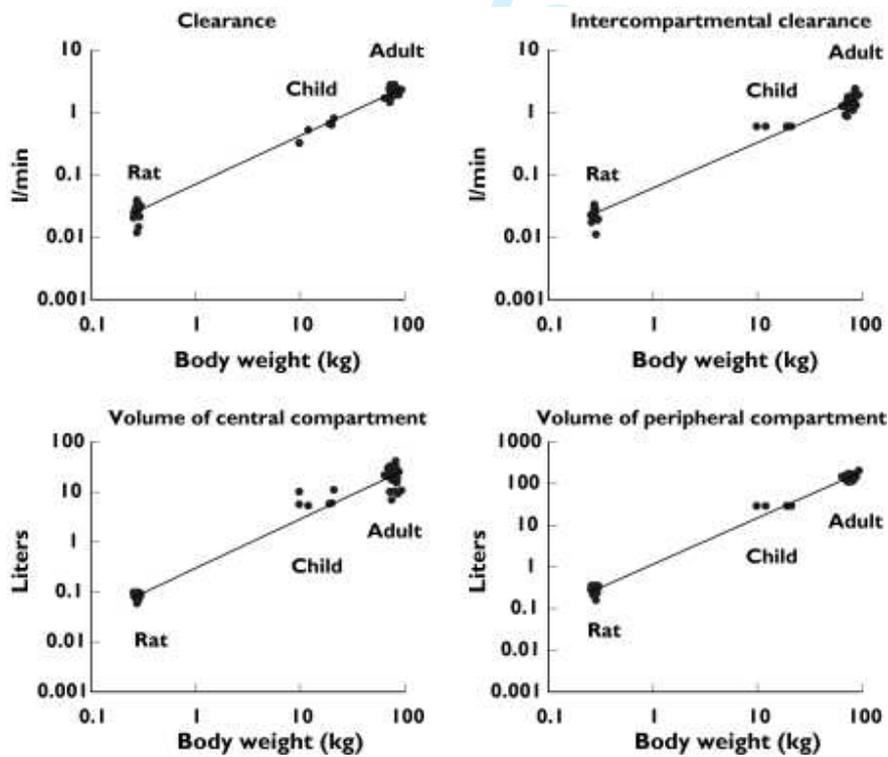


Figure 2

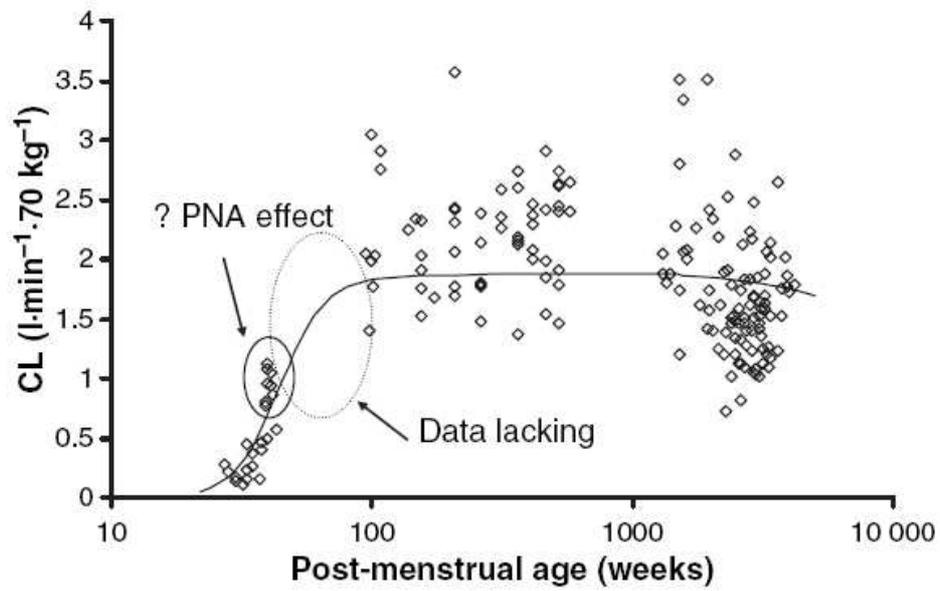


Figure 3

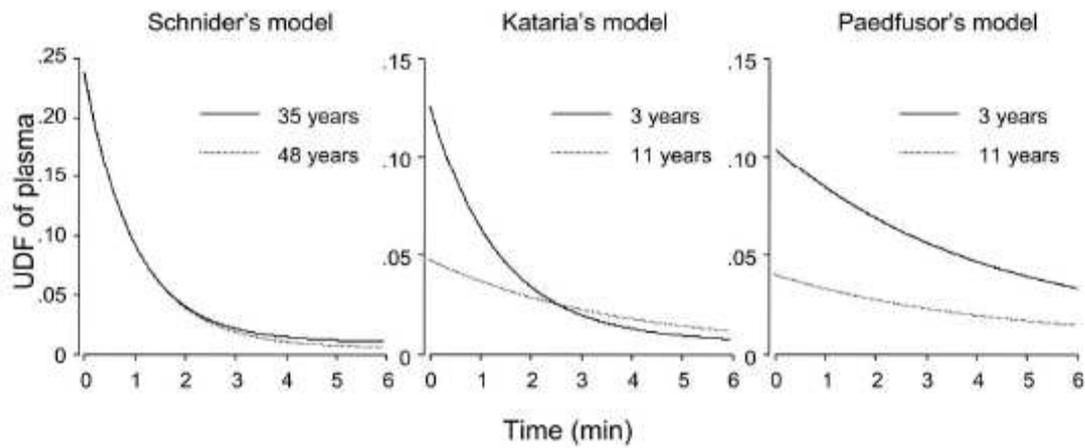


Figure 4

Figure Legends

Figure 1

Simulation of the concentration versus time profile resulting from a one hour propofol infusion ($4\text{mg kg}^{-1}\text{ hr}^{-1}$) administered to a 20kg child, using three different pharmacokinetic models. Diprifusor kinetics (adult)(1, 13), Kataria (pediatric) (5) and Rigby-Jones (pediatric, post-cardiac surgery)(8). The Diprifusor kinetics are linearly weight-scaled, hence the predicted profile shown would apply to any given body weight, adult or child.

Figure 2

Evidence for applicability of allometric scaling of propofol pharmacokinetic parameters. Plots show clearance (upper left), intercompartmental clearance (upper right), volume of the central compartment (lower left) and volume of the peripheral compartment (lower right) of propofol versus body weight in rats (bolus injection), children (post-cardiac surgery, 6 hr infusion) and adults (post-CABG, 5 hr infusion). Figure from Knibbe *et al* (17).

Figure 3

Propofol clearance rates, scaled to 70kg, derived from neonates, children and adults. The solid line describes the maturation process as a sigmoid E_{max} function of post-menstrual age. Allegaert (10) hypothesises that the influence of post-natal age (PNA) on clearance reflects ontogeny of glucuronidation activity during the first week of postnatal life. Figure from Anderson 2010 (21).

Figure 4

The unit disposition function of plasma versus time profile simulation with the Schnider model (adults) (22) and both the Kataria and Paedfusor models. A shallower decline in plasma concentration, and a larger variability related to patient age, is observed with the pediatric models. Figure from Munoz *et al* (38).

References

- 1 Marsh B, White M, Morton N, *et al.* Pharmacokinetic model driven infusion of propofol in children. *British journal of anaesthesia* 1991; **67**: 41-48.
- 2 Saint-Maurice C, Cockshott ID, Douglas EJ, *et al.* Pharmacokinetics of propofol in young children after a single dose. *British journal of anaesthesia* 1989; **63**: 667-670.
- 3 Raouf AA, van Obbergh LJ, Verbeeck RK. Propofol pharmacokinetics in children with biliary atresia. *British journal of anaesthesia* 1995; **74**: 46-49.
- 4 Jones RD, Chan K, Andrew LJ. Pharmacokinetics of propofol in children. *British journal of anaesthesia* 1990; **65**: 661-667.
- 5 Kataria BK, Ved SA, Nicodemus HF, *et al.* The pharmacokinetics of propofol in children using three different data analysis approaches. *Anesthesiology* 1994; **80**: 104-122.
- 6 Murat I, Billard V, Vernois J, *et al.* Pharmacokinetics of propofol after a single dose in children aged 1-3 years with minor burns. Comparison of three data analysis approaches. *Anesthesiology* 1996; **84**: 526-532.
- 7 Reed MD, Yamashita TS, Marx CM, *et al.* A pharmacokinetically based propofol dosing strategy for sedation of the critically ill, mechanically ventilated pediatric patient. *Critical care medicine* 1996; **24**: 1473-1481.
- 8 Rigby-Jones AE, Nolan JA, Priston MJ, *et al.* Pharmacokinetics of propofol infusions in critically ill neonates, infants, and children in an intensive care unit. *Anesthesiology* 2002; **97**: 1393-1400.
- 9 Peeters MY, Prins SA, Knibbe CA, *et al.* Propofol pharmacokinetics and pharmacodynamics for depth of sedation in nonventilated infants after major craniofacial surgery. *Anesthesiology* 2006; **104**: 466-474.
- 10 Allegaert K, Peeters MY, Verbesselt R, *et al.* Inter-individual variability in propofol pharmacokinetics in preterm and term neonates. *British journal of anaesthesia* 2007; **99**: 864-870.
- 11 Allegaert K, de Hoon J, Verbesselt R, *et al.* Maturational pharmacokinetics of single intravenous bolus of propofol. *Paediatric anaesthesia* 2007; **17**: 1028-1034.
- 12 Schuttler J, Ihmsen H. Population pharmacokinetics of propofol: a multicenter study. *Anesthesiology* 2000; **92**: 727-738.
- 13 Gepts E, Camu F, Cockshott ID, *et al.* Disposition of propofol administered as constant rate intravenous infusions in humans. *Anesthesia and analgesia* 1987; **66**: 1256-1263.
- 14 Anderson BJ, Allegaert K, Holford NH. Population clinical pharmacology of children: modelling covariate effects. *European journal of pediatrics* 2006; **165**: 819-829.
- 15 Kleiber M. Body size and metabolism. *Hilgardia* 1932; **6**: 315-333.
- 16 Anderson BJ, Holford NH. Mechanistic basis of using body size and maturation to predict clearance in humans. *Drug metabolism and pharmacokinetics* 2009; **24**: 25-36.
- 17 Knibbe CA, Zuideveld KP, Aarts LP, *et al.* Allometric relationships between the pharmacokinetics of propofol in rats, children and adults. *British journal of clinical pharmacology* 2005; **59**: 705-711.
- 18 Peeters MY, Allegaert K, Blusse van Oud-Alblas HJ, *et al.* Prediction of propofol clearance in children from an allometric model developed in rats, children and adults versus a 0.75 fixed-exponent allometric model. *Clinical pharmacokinetics*; **49**: 269-275.
- 19 Shangguan WN, Lian Q, Aarons L, *et al.* Pharmacokinetics of a single bolus of propofol in chinese children of different ages. *Anesthesiology* 2006; **104**: 27-32.
- 20 Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants: part I. *Clinical pharmacokinetics* 2002; **41**: 959-998.
- 21 Anderson BJ. Pediatric models for adult target-controlled infusion pumps. *Paediatric anaesthesia*; **20**: 223-232.
- 22 Schnider TW, Minto CF, Shafer SL, *et al.* The influence of age on propofol pharmacodynamics. *Anesthesiology* 1999; **90**: 1502-1516.

- 1
2
3 23 Struys MM, Coppens MJ, De Neve N, *et al.* Influence of administration rate on propofol
4 plasma-effect site equilibration. *Anesthesiology* 2007; **107**: 386-396.
- 5 24 Parke TJ, Stevens JE, Rice AS, *et al.* Metabolic acidosis and fatal myocardial failure after
6 propofol infusion in children: five case reports. *BMJ (Clinical research ed)* 1992; **305**: 613-616.
- 7 25 Bray RJ. Propofol infusion syndrome in children. *Paediatric anaesthesia* 1998; **8**: 491-499.
- 8 26 Cremer OL, Moons KG, Bouman EA, *et al.* Long-term propofol infusion and cardiac failure in
9 adult head-injured patients. *Lancet* 2001; **357**: 117-118.
- 10 27 MCA/CSM. Long term, high dose propofol (Diprivan) infusion. *Current Problems in*
11 *Pharmacovigilance* 2001; **27**.
- 12 28 MCA/CSM. Clarification: Propofol (Diprivan) infusion contraindication. *Current Problems in*
13 *Pharmacovigilance* 2002; **28**: 6.
- 14 29 Fudickar A, Bein B. Propofol infusion syndrome: update of clinical manifestation and
15 pathophysiology. *Minerva anesthesiologica* 2009; **75**: 339-344.
- 16 30 Wolf A, Weir P, Segar P, *et al.* Impaired fatty acid oxidation in propofol infusion syndrome.
17 *Lancet* 2001; **357**: 606-607.
- 18 31 Withington DE, Decell MK, Al Aayed T. A case of propofol toxicity: further evidence for a
19 causal mechanism. *Paediatric anaesthesia* 2004; **14**: 505-508.
- 20 32 Schenkman KA, Yan S. Propofol impairment of mitochondrial respiration in isolated perfused
21 guinea pig hearts determined by reflectance spectroscopy. *Critical care medicine* 2000; **28**: 172-177.
- 22 33 Jenkins IA, Playfor SD, Bevan C, *et al.* Current United Kingdom sedation practice in pediatric
23 intensive care. *Paediatric anaesthesia* 2007; **17**: 675-683.
- 24 34 Absalom A, Amutike D, Lal A, *et al.* Accuracy of the 'Paedfusor' in children undergoing
25 cardiac surgery or catheterization. *British journal of anaesthesia* 2003; **91**: 507-513.
- 26 35 Absalom A, Kenny G. 'Paedfusor' pharmacokinetic data set. *British journal of anaesthesia*
27 2005; **95**: 110.
- 28 36 Rigouzzo A, Girault L, Louvet N, *et al.* The relationship between bispectral index and propofol
29 during target-controlled infusion anesthesia: a comparative study between children and young
30 adults. *Anesthesia and analgesia* 2008; **106**: 1109-1116, table of contents.
- 31 37 Minto CF, Schnider TW, Gregg KM, *et al.* Using the time of maximum effect site
32 concentration to combine pharmacokinetics and pharmacodynamics. *Anesthesiology* 2003; **99**: 324-
33 333.
- 34 38 Munoz HR, Cortinez LI, Ibacache ME, *et al.* Estimation of the plasma effect site equilibration
35 rate constant (ke0) of propofol in children using the time to peak effect: comparison with adults.
36 *Anesthesiology* 2004; **101**: 1269-1274.
- 37 39 Wakeling HG, Zimmerman JB, Howell S, *et al.* Targeting effect compartment or central
38 compartment concentration of propofol: what predicts loss of consciousness? *Anesthesiology* 1999;
39 **90**: 92-97.
- 40 40 Struys MM, De Smet T, Depoorter B, *et al.* Comparison of plasma compartment versus two
41 methods for effect compartment--controlled target-controlled infusion for propofol. *Anesthesiology*
42 2000; **92**: 399-406.
- 43 41 Mortier E, Struys M. Effect site modelling and its application in TCI. *Acta anaesthesiologica*
44 *Belgica* 2000; **51**: 149-152.
- 45 42 Cortinez LI, Munoz HR, Lopez R. [Pharmacodynamics of propofol in children and adults:
46 comparison based on the auditory evoked potentials index]. *Revista espanola de anestesiologia y*
47 *reanimacion* 2006; **53**: 289-296.
- 48 43 Hull D. Guidelines for the ethical conduct of medical research in children. *Arch Dis Child*
49 2000; **82**: 177-182.
- 50 44 Marx CM, Smith PG, Lowrie LH, *et al.* Optimal sedation of mechanically ventilated pediatric
51 critical care patients. *Critical care medicine* 1994; **22**: 163-170.
- 52
53
54
55
56
57
58
59
60

- 1
2
3 45 Murray DM, Thorne GC, Rigby-Jones AE, *et al.* Electroencephalograph variables, drug
4 concentrations and sedation scores in children emerging from propofol infusion anaesthesia.
5 *Paediatric anaesthesia* 2004; **14**: 143-151.
- 6
7 46 Jeleazcov C, Ihmsen H, Schmidt J, *et al.* Pharmacodynamic modelling of the bispectral index
8 response to propofol-based anaesthesia during general surgery in children. *British journal of*
9 *anaesthesia* 2008; **100**: 509-516.
- 10
11 47 Munoz HR, Cortinez LI, Ibacache ME, *et al.* Effect site concentrations of propofol producing
12 hypnosis in children and adults: comparison using the bispectral index. *Acta anaesthesiologica*
13 *Scandinavica* 2006; **50**: 882-887.
- 14
15 48 Rigouzzo A, Servin F, Constant I. Pharmacokinetic-pharmacodynamic modeling of propofol in
16 children. *Anesthesiology*; **113**: 343-352.
- 17
18 49 Schnider TW, Minto CF, Gambus PL, *et al.* The influence of method of administration and
19 covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology* 1998; **88**: 1170-
20 1182.
- 21
22 50 Watcha MF. Investigations of the bispectral index monitor in pediatric anesthesia: first
23 things first. *Anesthesia and analgesia* 2001; **92**: 805-807.
- 24
25 51 Sadhasivam S, Ganesh A, Robison A, *et al.* Validation of the bispectral index monitor for
26 measuring the depth of sedation in children. *Anesthesia and analgesia* 2006; **102**: 383-388.
- 27
28 52 Overly FL, Wright RO, Connor FA, Jr., *et al.* Bispectral analysis during pediatric procedural
29 sedation. *Pediatric emergency care* 2005; **21**: 6-11.
- 30
31 53 Davidson AJ. Monitoring the anaesthetic depth in children - an update. *Current opinion in*
32 *anaesthesiology* 2007; **20**: 236-243.
- 33
34 54 Wallenborn J, Kluba K, Olthoff D. Comparative evaluation of Bispectral Index and Narcotrend
35 Index in children below 5 years of age. *Paediatric anaesthesia* 2007; **17**: 140-147.
- 36
37 55 Klockars JG, Hiller A, Ranta S, *et al.* Spectral entropy as a measure of hypnosis in children.
38 *Anesthesiology* 2006; **104**: 708-717.
- 39
40 56 Tobias JD, Grindstaff R. Bispectral index monitoring during the administration of
41 neuromuscular blocking agents in the pediatric intensive care unit patient. *Journal of intensive care*
42 *medicine* 2005; **20**: 233-237.
- 43
44 57 Tirel O, Wodey E, Harris R, *et al.* Variation of bispectral index under TIVA with propofol in a
45 paediatric population. *British journal of anaesthesia* 2008; **100**: 82-87.
- 46
47 58 Park HJ, Kim YL, Kim CS, *et al.* Changes of bispectral index during recovery from general
48 anesthesia with 2% propofol and remifentanyl in children. *Paediatric anaesthesia* 2007; **17**: 353-357.
- 49
50 59 Cameron E, Johnston G, Crofts S, *et al.* The minimum effective dose of lignocaine to prevent
51 injection pain due to propofol in children. *Anaesthesia* 1992; **47**: 604-606.
- 52
53 60 Barbi E, Marchetti F, Gerarduzzi T, *et al.* Pretreatment with intravenous ketamine reduces
54 propofol injection pain. *Paediatric anaesthesia* 2003; **13**: 764-768.
- 55
56 61 Cheng KI, Tang CS, Chiu SL, *et al.* Injection pain with propofol: the effectiveness of
57 thiopentone on induction. *The Kaohsiung journal of medical sciences* 1998; **14**: 480-485.
- 58
59 62 Akesson J. Pain on injection of propofol - why bother? *Acta anaesthesiologica Scandinavica*
60 2008; **52**: 591-593.
- 61
62 63 Klement W, Arndt JO. Pain on injection of propofol: effects of concentration and diluent.
63 *British journal of anaesthesia* 1991; **67**: 281-284.
- 64
65 64 Soltesz S, Silomon M, Graf G, *et al.* Effect of a 0.5% dilution of propofol on pain on injection
66 during induction of anesthesia in children. *Anesthesiology* 2007; **106**: 80-84.
- 67
68 65 Yamakage M, Iwasaki S, Satoh J, *et al.* Changes in concentrations of free propofol by
69 modification of the solution. *Anesthesia and analgesia* 2005; **101**: 385-388, table of contents.
- 70
71 66 Sundarathiti P, Boonthom N, Chalacheewa T, *et al.* A comparison of propofol-LCT with
72 propofol-LCT/MCT on pain of injection. *Journal of the Medical Association of Thailand = Chotmaihet*
73 *thangphaet* 2007; **90**: 2683-2688.

- 1
2
3 67 Burimsittichai R, Kumwilaisuk K, Charuluxananan S, *et al.* Pain on injection of propofol:
4 propofol LCT vs propofol MCT/LCT with or without lidocaine pretreatment. *Journal of the Medical*
5 *Association of Thailand = Chotmaihet thangphaet* 2006; **89 Suppl 3**: S86-91.
- 6
7 68 Allford MA, Mensah JA. Discomfort on injection: a comparison between two formulations of
8 propofol. *European journal of anaesthesiology* 2006; **23**: 971-974.
- 9
10 69 Suzuki H, Miyazaki H, Andoh T, *et al.* Propofol formulated with long-/medium-chain
11 triglycerides reduces the pain of injection by target controlled infusion. *Acta anaesthesiologica*
12 *Scandinavica* 2006; **50**: 568-571.
- 13
14 70 Kinoshita M, Morioka N, Takada M, *et al.* [The injection pain of propofol with different
15 emulsion]. *Masui* 2006; **55**: 338-343.
- 16
17 71 Nyman Y, von Hofsten K, Georgiadi A, *et al.* Propofol injection pain in children: a prospective
18 randomized double-blind trial of a new propofol formulation versus propofol with added lidocaine.
19 *British journal of anaesthesia* 2005; **95**: 222-225.
- 20
21 72 Varghese E, Krishna HM, Nittala A. Does the newer preparation of propofol, an emulsion of
22 medium/long chain triglycerides cause less injection pain in children when premixed with
23 lignocaine? *Paediatric anaesthesia*; **20**: 338-342.
- 24
25 73 Rochette A, Hocquet AF, Dadure C, *et al.* Avoiding propofol injection pain in children: a
26 prospective, randomized, double-blinded, placebo-controlled study. *British journal of anaesthesia*
27 2008; **101**: 390-394.
- 28
29 74 WorldSIVA. Open TCI Initiative <http://opentci.org/doku.php>. 2010.
- 30
31 75 Absalom AR, Mani V, De Smet T, *et al.* Pharmacokinetic models for propofol--defining and
32 illuminating the devil in the detail. *British journal of anaesthesia* 2009; **103**: 26-37.
- 33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60