2011-03

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RigbyJones, AE

10.1111/j.1460-9592.2010.03454.x
Pediatric Anesthesia
Wiley

	P A N	3 4 5 4	B	Dispatch: 8.11.10	Journal: PAN	CE: Suganya
	Journal Name	Manuscript No.		Author Received:	No. of pages: 9	PE: Jeyanthi

Pediatric Anesthesia 2010 doi:10.1111/j.1460-9592.2010.03454.x

Propofol and children – what we know and what we do not know

ANN E. RIGBY-JONES XX AND J. R. SNEYD XX

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

Section Editor: Brian Anderson

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, because of practical difficulties in 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.

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 nonventilated 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 1-h propofol infusion (4 $mg \cdot kg^{-1} \cdot h^{-1}$) administered to an adult [Diprifusor kinetics (1,13)] or to a 20-kg child [Kataria kinetics (5)]. The larger central compartment

Correspondence to: Dr. Ann E. Rigby-Jones, Anaesthesia Research Group, Peninsula Medical School, Peninsula College of Medicine & Dentistry, University of Plymouth, N31, ITTC Building, Tamar Science Park, Derriford, Plymouth PL6 8BX, UK (email: ann.rigby-jones@pms.ac.uk).

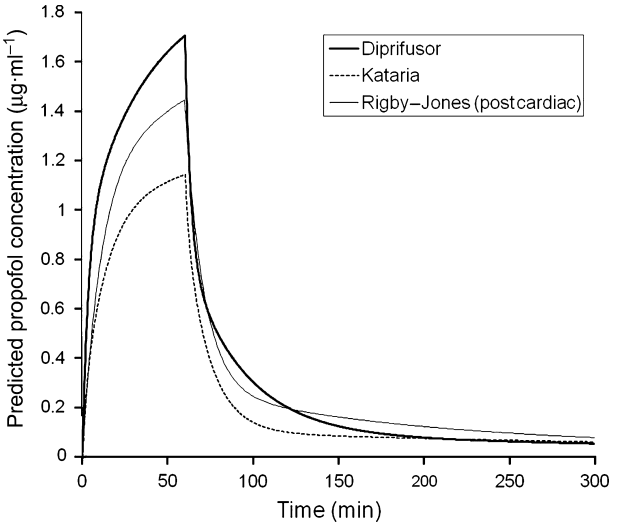

Figure 1
Simulation of the concentration vs time profile resulting from a 1-h propofol infusion (4 $mg \cdot kg^{-1} \cdot h^{-1}$) administered to a 20-kg child, using three different pharmacokinetic models. Diprifusor kinetics (adult) (1,13), Kataria (pediatric) (5), and Rigby-Jones (pediatric, postcardiac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

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 (15) 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. 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).

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

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

Propofol in neonates

The work of Allegaert and colleagues in recent years has done much to inform propofol disposition and metabolism in term and preterm neonates. Allegaert (11) described markedly reduced clearance in a group of nine neonates (4–25 days postnatal age) after bolus injection of propofol. After appropriate allometric scaling to 70 kg to allow comparison, the clearance value was approximately 32%, and the volume of distribution at steady state was approximately 44% of the corresponding values previously reported in infants. Scaled propofol clearance rates approach adult values within the first 3 months to 1 year of life (6,19), mirroring ontogenic development of hepatic enzyme systems (20).

For infants and older children, the inclusion of body weight alone as a model covariate accounts for much of the observed interindividual variability in propofol pharmacokinetics (5,8,9,19). Allegaert has demonstrated that for neonates, postmenstrual and postnatal age as markers of maturity, rather than body weight, were the most influential factors, with the youngest babies having the smallest clearance values. Anderson (21) further explored this finding, combining Allegaert's neonatal clearance data with

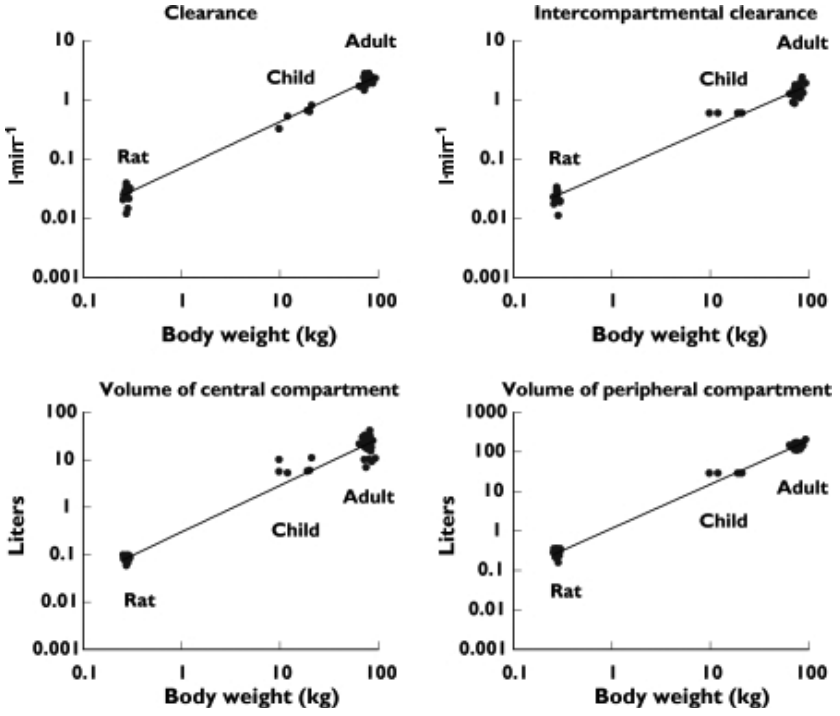

Figure 2
Evidence for applicability of allometric scaling of propofol pharmacokinetic parameters. Plots show clearance (upper left), intercompartmental clearance (upper right), volume of the central compartment (lower left), and volume of the peripheral compartment (lower right) of propofol vs body weight in rats (bolus injection), children (postcardiac surgery, 6-h infusion), and adults (post-CABG, 5-h infusion). Figure from Knibbe *et al.* (17).

clearance values derived from older children (5,6) and adults (13,22,23). A sigmoid E_{max} model was then applied to describe the maturation profile, Figure 3. In this analysis, the maturation half-time was calculated as 44 weeks. Anderson highlights the need for additional study of propofol disposition in infants to fully characterize the maturation profile in the first 2 years of life.

Pediatric critical care and propofol infusion syndrome (PRIS)

PRIS was first described in the literature in 1992 (24). Shortly after, the syndrome was defined by Bray (25) as a sudden onset of treatment-resistant bradycardia leading to asystole, combined with at least one of the following symptoms: lipemic plasma, clinically enlarged or fat infiltrated liver, metabolic acidosis or rhabdomylosis. The syndrome was associated with long-duration (more than 48 h), high-dose (more than 4 $mg \cdot kg^{-1} \cdot h^{-1}$) 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

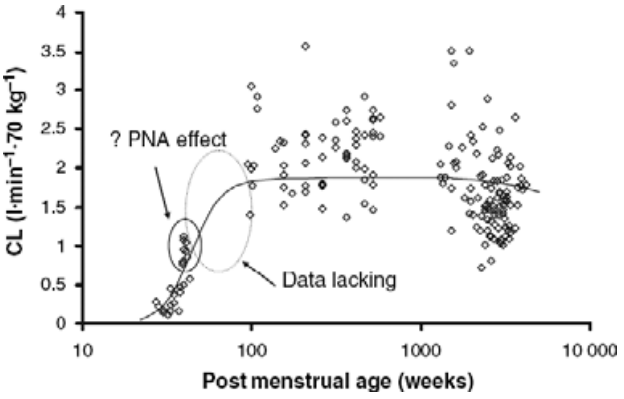

Figure 3
Propofol clearance rates, scaled to 70kg, derived from neonates, children, and adults. The solid line describes the maturation process as a sigmoid E_{max} function of postmenstrual age. Allegaert (10) hypothesizes that the influence of postnatal age (PNA) on clearance reflects ontogeny of glucuronidation activity during the first week of postnatal life. Figure from Anderson (21).

Medicines) to recommend that propofol infusion rates for sedation did not exceed 4 $mg \cdot kg^{-1} \cdot h^{-1}$(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 with 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 availably 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 United Kingdom 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 *et al.* (7) were first to study propofol disposition in a critically ill pediatric population, ranging from neonates to children aged 15 years. 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 (because of 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 nonventilated, postneurosurgical, pediatric population (9), propofol clearance values were reported to be twice as high as those previously described in pediatric intensive care unit (PICU) patients (8), emphasizing the impact that mechanical ventilation and cardiac bypass have on propofol elimination during postoperative sedation.

Pediatric propofol target-controlled infusion (TCI)

There are at least two pediatric pharmacokinetic models for propofol available for use in commercially available TCI pumps: the Paedfusor (34,35) and the Kataria kinetic set (5). The Kataria model is based on data from 53 healthy children, ranging in age from three to 11 years. Mean postdose sampling duration was 214 min (range 52–811). The Paedfusor pharmacokinetic set was derived as a preliminary model (presumably based on pediatric data only) by Schuttler and Ihmsen (12) during their development of a pharmacokinetic model based on pooled data from both adults and children. In Schuttler's analysis, pediatric data comprised 96 children aged from 2 to 11 years, including the patient population on which Kataria's model was based (5) and data from two further pediatric studies (1,2).

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

The original analyses leading to the derivation of the Kataria and Paedfusor models were based on pharmacokinetic data only. However, values for K_{e0} and the blood–brain equilibration rate constant have been retrospectively generated for both models using the time to peak effect (t_{peak}) (37) technique (38). T_{peak} is a model-independent pharmacodynamic parameter that can be used to calculate a K_{e0} value for a given pharmacokinetic set, after administration of a submaximal dose. The K_{e0} value derived is one that accurately predicts t_{peak} (37). Muñoz's analysis revealed that the peak effect of propofol in children (132 s) occurs far later than in adults (80 s). The explanation offered for this finding

is that, relative to adults (Schnider model), simulations using the pediatric model demonstrate a much slower initial decline in plasma propofol concentrations, Figure 4. As the postbolus t_{peak} is the consequence of both decreasing plasma concentration and increasing effect site concentration, this is a plausible mechanism.

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

Pediatric pharmacodynamics (PD)

While the pharmacokinetics of propofol in the pediatric population are reasonably well described, there is a relative paucity of pharmacodynamic data (9,38,42).

Limitations of pediatric PD studies

Undertaking pharmacodynamic studies can be very difficult in children and particularly so in intensive care medicine. In a 'real life' scenario, rather than a controlled volunteer study in adults, it is often difficult or impossible to obtain data describing a full drug concentration versus effect profile. This is required for adequately quantifying hysteresis and hence the derivation of K_{e0}. Arterial blood, the gold-standard matrix for sampling during PK–PD studies of rapidly acting drug compounds, is highly unlikely to be available for children outside of critical care. The insertion of a peripheral arterial line in children purely for research purposes is classified as high risk and cannot be justified (43); further, arterial line insertion is typically carried out after induction of anesthesia, and the opportunity to populate the rising phase of the hysteresis loop is lost. The use of venous blood sampling during pediatric pharmacodynamic studies of intravenous sedative-hypnotics presents a limitation that can in part be overcome by careful study design, such as the incorporation of equilibration stages to accompanying changes in infusion rate. This stabilizes arterial and venous blood concentrations and minimizes arterio-venous differences as far as possible.

The use of intermittent pharmacodynamic markers, such as sedation scores, can also make it more difficult to capture rapidly changing drug effects. However, for extended continuous infusion studies, COMFORT scores (44) can provide useful information and have been successfully utilized as pharmacodynamic markers for the development of complex but clinically informative models of propofol pharmacodynamics (9). Other limitations of sedation scoring as a pharmacodynamic marker are inter- and intra-observer variance and the impact that stimulation required as part of a scoring system may have on the underlying depth of sedation.

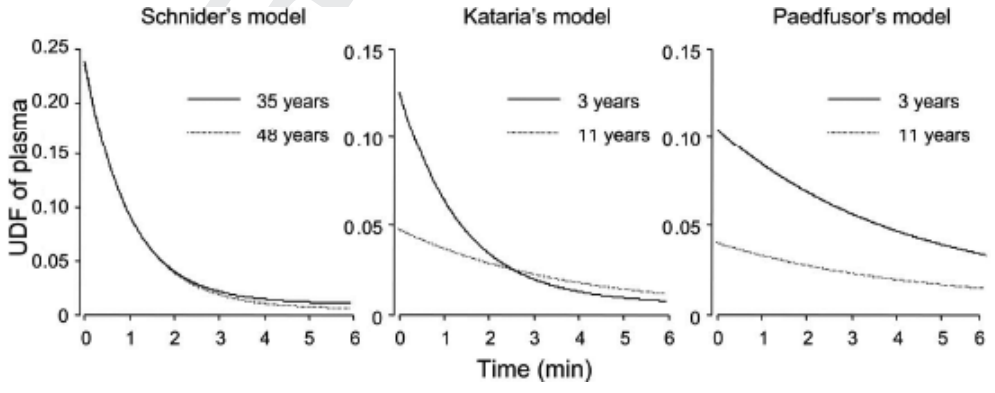

Figure 4
The unit disposition function of plasma vs time profile simulation with the Schnider model (adults) (22) and both the Kataria and Paedfusor models. A shallower decline in plasma concentration, and a larger variability related to patient age, is observed with the pediatric models. Figure from Munoz *et al.* (38).

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

Recently, a second smaller study by Rigouzzo *et al.* (48) attempted to identify the best model for describing propofol PK–PD in prepubertal children. Propofol was administered to prepubertal children (n = 16, 6–12 years) by TCI using the Kataria model (5) and to adults and postpubertal children (n = 13, 13–35 years) using the Schnider model (49). BIS was used as an effect measure. The recorded BIS data from the prepubertal group were then compared to predicted propofol concentrations generated using several pharmacokinetic models; the Kataria model used to administer propofol but also the Marsh (1), Schuttler (12) and Schnider models, to evaluate which model best described the data. BIS data from the postpubertal/adult cohort was compared to predicted concentrations generated by the Schnider model only. The analysis revealed that the prepubertal BIS vs predicted propofol concentration was best described by the adult Schnider model, so in a second stage of the analysis, the two cohorts were pooled so that the influence of puberty on propofol pharmacodynamic parameter estimates could be examined. The authors hypothesize that the lack of early sampling in the studies that led to the derivation of the pediatric models tested may explain their perceived weakness at describing the initial phase of propofol distribution kinetics, and hence the effect on BIS. Additionally, the Schnider model is unique among those explored in Rigouzzo's analysis in that both age and lean body mass are included as covariates, thus allowing a more precise tailoring of individual predicted propofol concentrations. Analysis of the pooled data from both cohorts using the Schnider model revealed that pubertal status was a significant pharmacodynamic model covariate with both K_{eO} and Ce_{50} varying between children and adults. The typical value of Ce_{50} was around 20% higher in children than in adults. T_{peak} was subsequently derived and found to be significantly shorter in children at 0.71 min [0.37–1.64] median [range] vs 1.73 [1.4–2.68] min in adults. This is in contrast to the findings by Munoz (38), which the authors suggest may relate to differences in effect measure (BIS vs AEP) and methodological differences, including the use of different pharmacokinetic models. The shorter T_{peak} in younger children supports the findings of Jeleacov and colleagues (46).

Propofol, BIS, and children

The technology of BIS monitoring is based on an algorithm developed from adults, hence its usefulness as a measure of anesthetic depth in children, and particularly in infants, has long been questioned

(50). Subsequent studies evaluating the relationship between the bispectral index and established sedation measures such as the Observer's Assessment of Alertness/Sedation (OAA/S) and the University of Michigan Sedation Scale (UMSS) have provided evidence that BIS monitoring can be a useful measure of intravenous sedation in children older than 2 years (51,52). Currently, evidence to suggest that any of the alternative depth of anesthesia monitors is more or less suitable than BIS for use in children is limited (53–55).

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

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

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

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

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 $t_{1/2}k_{eO}$ (59,60).

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Accepted 13 October 2010

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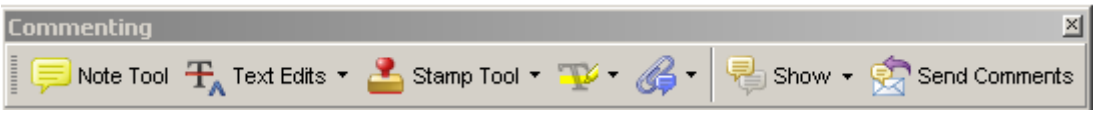
USING E-ANNOTATION TOOLS FOR ELECTRONIC PROOF CORRECTION

Required Software

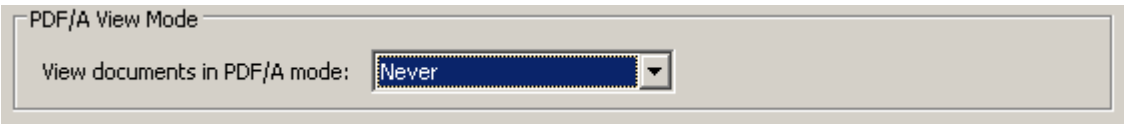
Adobe Acrobat Professional or Acrobat Reader (version 7.0 or above) is required to e-annotate PDFs. Acrobat 8 Reader is a free download: http://www.adobe.com/products/acrobat/readstep2.html

Once you have Acrobat Reader 8 on your PC and open the proof, you will see the Commenting Toolbar (if it does not appear automatically go to Tools>Commenting>Commenting Toolbar). The Commenting Toolbar looks like this:



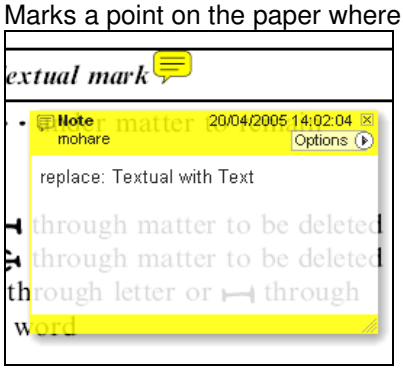
If you experience problems annotating files in Adobe Acrobat Reader 9 then you may need to change a preference setting in order to edit.

In the "Documents" category under "Edit – Preferences", please select the category 'Documents' and change the setting "PDF/A mode:" to "Never".



Note Tool — For making notes at specific points in the text

Marks a point on the paper where a note or question needs to be addressed.

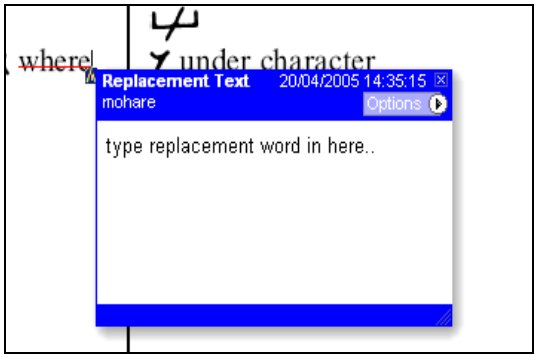


How to use it:

1. Right click into area of either inserted text or relevance to note
2. Select Add Note and a yellow speech bubble symbol and text box will appear
3. Type comment into the text box
4. Click the X in the top right hand corner of the note box to close.

Replacement text tool — For deleting one word/section of text and replacing it

Strikes red line through text and opens up a replacement text box.

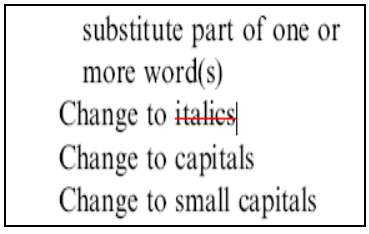


How to use it:

1. Select cursor from toolbar
2. Highlight word or sentence
3. Right click
4. Select Replace Text (Comment) option
5. Type replacement text in blue box
6. Click outside of the blue box to close

Cross out text tool — For deleting text when there is nothing to replace selection

Strikes through text in a red line.



How to use it:

1. Select cursor from toolbar
2. Highlight word or sentence
3. Right click
4. Select Cross Out Text

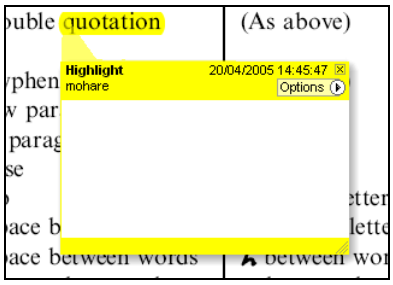
Approved tool — For approving a proof and that no corrections at all are required.

How to use it:

1. Click on the Stamp Tool in the toolbar
2. Select the Approved rubber stamp from the 'standard business' selection
3. Click on the text where you want to rubber stamp to appear (usually first page)

Highlight tool — For highlighting selection that should be changed to bold or italic.

Highlights text in yellow and opens up a text box.

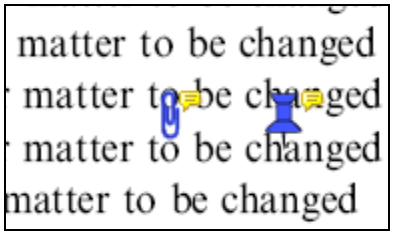


How to use it:

1. Select Highlighter Tool from the commenting toolbar
2. Highlight the desired text
3. Add a note detailing the required change

Attach File Tool — For inserting large amounts of text or replacement figures as a files.

Inserts symbol and speech bubble where a file has been inserted.

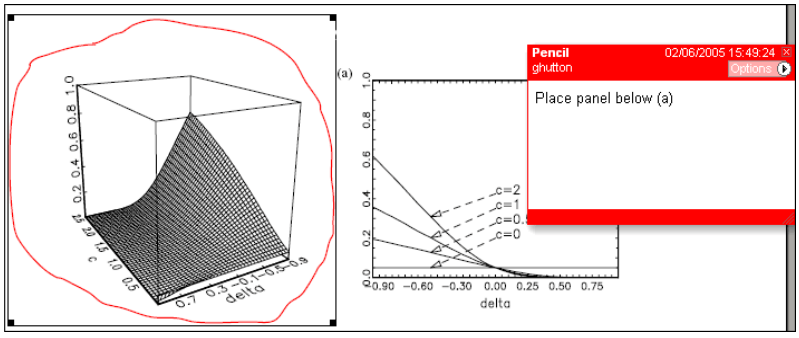


How to use it:

1. Click on paperclip icon in the commenting toolbar
2. Click where you want to insert the attachment
3. Select the saved file from your PC/network
4. Select appearance of icon (paperclip, graph, attachment or tag) and close

Pencil tool — For circling parts of figures or making freeform marks

Creates freeform shapes with a pencil tool. Particularly with graphics within the proof it may be useful to use the Drawing Markups toolbar. These tools allow you to draw circles, lines and comment on these marks.



How to use it:

1. Select Tools > Drawing Markups > Pencil Tool
2. Draw with the cursor
3. Multiple pieces of pencil annotation can be grouped together
4. Once finished, move the cursor over the shape until an arrowhead appears and right click
5. Select Open Pop-Up Note and type in a details of required change
6. Click the X in the top right hand corner of the note box to close.

Help

For further information on how to annotate proofs click on the Help button to activate a list of instructions: