CNS Drugs (2015) 29:543–563
DOI 10.1007/s40263-015-0259-6

REVIEW ARTICLE

Propofol: A Review of its Role in Pediatric Anesthesia and Sedation

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Published online: 20 August 2015

Abstract Propofol is an intravenous agent used commonly for the induction and maintenance of anesthesia, procedural, and critical care sedation in children. The mechanisms of action on the central nervous system involve interactions at various neurotransmitter receptors, especially the gamma-aminobutyric acid A receptor. Approved for use in the USA by the Food and Drug Administration in 1989, its use for induction of anesthesia in children less than 3 years of age still remains off-label. Despite its wide use in pediatric anesthesia, there is conflicting literature about its safety and serious adverse effects in particular subsets of children. Particularly as children are not "little adults", in this review, we emphasize the maturational aspects of propofol pharmacokinetics. Despite the myriad of propofol pharmacokinetic-pharmacodynamic studies and the ability to use allometrical scaling to smooth out differences due to size and age, there is no optimal model that can be used in target controlled infusion pumps for providing closed loop total intravenous anesthesia in children. As the commercial formulation of propofol is a nutrient-rich emulsion, the risk for bacterial contamination exists despite the Food and Drug Administration mandating addition of antimicrobial preservative, calling for manufacturers' directions to discard open vials after 6 h. While propofol has advantages over inhalation anesthesia such as less postoperative nausea and emergence delirium in children, pain on injection remains a problem even with newer formulations. Propofol is known to depress mitochondrial function by its action as an uncoupling agent in oxidative phosphorylation. This has implications for children with mitochondrial diseases and the occurrence of propofol-related infusion syndrome, a rare but seriously life-threatening complication of propofol. At the time of this review, there is no direct evidence in humans for propofol-induced neurotoxicity to the infant brain; however, current concerns of neuroapoptosis in developing brains induced by propofol persist and continue to be a focus of research.

Key Points

Pharmacokinetic studies in children have shown that the use of allometric scaling between adults and children seems to be an adequate tool for the development of rational dosing schemes for children of varying body weights.

Propofol has mitochondrial inhibitory functions that contraindicate its use in patients with mitochondrial disease and may play a role in deaths from propofol infusion syndrome.

Despite concerns for propofol causing cell damage to developing brains, change in indications for propofol use in pediatrics is unwarranted until conclusive human studies prove otherwise.

1 Introduction

Propofol, commonly dubbed as "milk of anesthesia", is one of the most popular intravenous anesthetic agents in modern medicine. The mechanisms of action on the central

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nervous system are rather complex with interactions at various neurotransmitter receptors [1]. Propofol has many pharmacologic advantages over other anesthetic agents such as rapid effect, short action, and fewer side effects such as postoperative nausea. The efficacy of propofol as a sedative for children has been established in several clinical trials and case series since the 1990s [2–4]. Pediatric use of propofol includes induction and maintenance of general anesthesia as well as sedation during non-surgical intervention and intensive care [5, 6]. Despite the above, there have been supporting, and discouraging literature regarding its use in children. The use of propofol in certain age groups continues to be off-label as it has US Food and Drug Administration (FDA) approval for maintenance of anesthesia only in children ≥2 months of age and for induction of anesthesia in children ≥3 years of age [7]. There are a number of review articles covering the features of propofol [8, 9], but not a comprehensive one covering its present use in pediatric anesthesia, which is the main focus of this review.

2 History

Propofol was originally developed in the UK by Imperial Chemical Industries following research into the sedative effect of phenol derivatives in animal models. Its anesthetic properties were first reported in January 1973 [10, 11]. Initial clinical trials of propofol used an emulsion containing polyethoxylated castor oil (Cremophor EL). However, this formulation was withdrawn as the stabilizing agent was found to cause anaphylactic reactions [12]. Later trials using other water- and lipid-based emulsions were conducted in Europe in 1983 and in the USA in 1984. These preparations were found to be as effective as propofol in Cremophor but they were not associated with a similar rate of anaphylactic reactions [13]. In 1986, propofol was introduced for therapeutic use as a lipid emulsion in the UK and New Zealand. Propofol (Diprivan®) received FDA approval in October 1989.

3 Structure and Physical Properties

Propofol is chemically described as 2,6-diisopropylphenol (Fig. 1) and has a molecular weight of 178.27. The octanol/water partition coefficient for propofol is 6761 at a pH of 6–8.5. Being insoluble in water, it is formulated in a white oil-in-water emulsion with a pKa of 11. The emulsion form makes it very useful for the intravenous delivery of fat-soluble agents but also inherently unstable vehicles, which provide fertile media for bacterial proliferation and carry the potential risk of iatrogenic sepsis after contamination. It

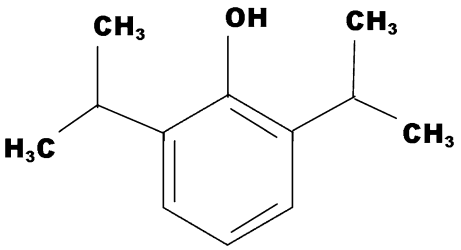

Fig. 1 Chemical structure of propofol (2,6-diisopropylphenol) depicting the key propofol moieties, most notably, the phenolic hydroxyl group (–OH) and the number and arrangement of methyl groups ($–CH_3$) at the 2- and 6-positions that determine the potency and the efficacy of the receptor–drug interaction

appears white in color because light is scattered by the small droplets of lipid suspended in the liquid medium. Propofol is readily oxidized to quinone, which turns the suspension yellow in color after approximately 6 h of exposure to air. Most formulations include an emulsifier and bacteriostatic agents such as ethylene-di-amine-tetra-acetic acid, sodium metabisulfite, or benzyl alcohol. The chemical reaction to quinone is enhanced by the presence of sodium metabisulfite [14].

4 Commercially Available Formulations

There are several commercial formulations of propofol available.

4.1 Diprivan

The original formulation, Diprivan® 1 % (Astra-Zeneca, Cheshire, UK) is the most common preparation for propofol. It is a 1 % emulsion in 10 % soyabean oil. This includes an emulsifier (1.2 % egg lecithin) along with agents to regulate the tonicity (2.25 % glycerol) and pH (sodium hydroxide) of the mixture. It also contains ethylene-di-amine-tetra-acetic acid, a chelation agent with bacteriostatic activity.

4.1.1 FDA Advisory

After reports of several clusters of patients who experienced chills, fever and body aches after receiving propofol for sedation or general anesthesia in recent years, the FDA tested the vials for contamination but did not find any. However, to minimize the potential for bacterial contamination when using propofol for general anesthesia or procedural sedation, the FDA recommends that:

- both the vial and prefilled syringe formulations be used on only one patient;

- administration commence immediately after the vial or syringe has been opened; and
- administration from a single vial or syringe must be completed within 6 h of opening.
- ICU sedation with propofol administered directly from a vial must be limited to only one patient, must commence immediately on opening the vial, and must be completed within 12 h of opening the vial to minimize the risk of product contamination (http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm125817.htm).

4.2 Propoven®

Propoven® 1 % (Fresenius-Kabi AG, Bad Homburg, Germany) is a generic version of the original formulation without an antimicrobial retardant, approved in European countries. This formulation was imported into the USA when the FDA exercised its regulatory enforcement discretion to fill a gap in supply when two companies decided to recall or stop production of propofol for different reasons [15].

4.3 Lipuro®

Lipuro® 1 % (B-Braun, Melshungen AG, Germany) contains a mixture of long- and medium-chain triglycerides (LCT/MCTs) and is reported to reduce injection pain [16, 17]. A multicenter double-blinded trial compared the dose of propofol for induction [using a closed loop infusion guided by the bispectral index (BIS)] and patient discomfort with and without lidocaine and found that the different formulations were not equipotent—Propoven® required a higher dose for induction (2.2 ± 0.1 mg/kg) than Diprivan® (1.8 ± 0.1 mg/kg) or Lipuro® (1.7 ± 0.1 mg/kg; $P = 0.02$); however, induction doses were similar when propofol formulations were mixed with lidocaine [18].

A water-soluble prodrug form, fospropofol, has been developed and tested with positive results. Fospropofol is rapidly broken down by the enzyme alkaline phosphatase to form propofol. Marketed as Lusedra, this new formulation may not produce the pain at injection site that often occurs with the traditional form of the drug [19] The FDA approved the product in 2008.

5 Mechanism of Action

Similar to other intravenous anesthetic agents such as benzodiazepines and barbiturates, propofol exerts its hypnotic actions by activation of the central inhibitory neurotransmitter, gamma-aminobutyric acid (GABA) [20]. The first evidence of this effect was provided by Collins et al. [21]. $GABA_A$ receptors are ligand-gated ion channels composed of various subunits (α1–6, β1–4, γ 1–3, δ, ε, and ρ 1–3) forming a pentameric structure containing a central chloride channel [22, 23] (Fig. 2). Binding of the propofol molecule to the receptor leads to increased chloride ion influx and hyperpolarization of the neuron, leading to unresponsiveness to external stimuli. Propofol influences also presynaptic mechanisms of GABAergic transmission such as GABA uptake and GABA release [1]. Not only does propofol facilitate GABAergic transmission by both presynaptic and postsynaptic mechanisms, it has also been shown to selectively block release of acetylcholine in the baso-cortical and septo-hippocampal pathways, which are under tonic innervation by GABAergic input [24].

The potency and the efficacy of the receptor–drug interaction is dependent on key propofol moieties, most notably, the phenolic hydroxyl group and the number and arrangement of alkyl groups at the 2- and 6-positions that flank it (Fig. 1) [25]. Of note, its site of action at the $GABA_A$ receptor is different from benzodiazepine recognition sites [26]. There is evidence that α, β, and γ subunits all contribute to $GABA_A$ receptor sensitivity to propofol. It seems that propofol was less efficacious at β1-containing receptors than at those containing β2 or β3 subunits [27].

Moreover, propofol also results in a concentration-dependent activation of inhibitory glycine receptors at the spinal cord level [28], serotonin (5-hydroxy trytophan) receptors that might explain its anti-emetic action [29] with mild activity at excitatory glutamate/*N*-methyl D-aspartate receptors [30].

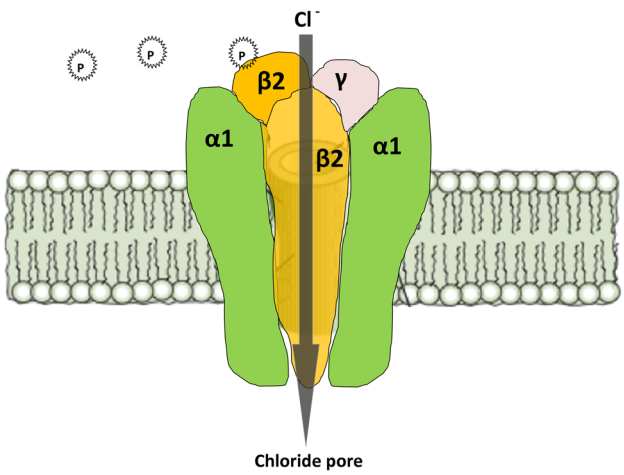

Fig. 2 Diagrammatic representation of the gamma-aminobutyric acid $(GABA)_A$ receptor in the cell membrane with its α, β, and γ subunits where propofol mainly interacts to cause its anesthetic effect in the central nervous system. The "*P*" *starred structures* represent propofol drug molecules. On interacting with the $GABA_A$ receptor, chloride ion influx happens through the central chloride channel (represented by *arrow*)

6 Propofol Pharmacokinetics and Pharmacodynamics in Children

The primary elimination pathway of propofol is by glucuronidation; only 0.3 % of the administered dose is excreted unchanged in urine [31]. It has a high hepatic extraction ratio (0.87 ± 0.09) and hence hepatic clearance is blood flow limited [32]. Because the clearance of propofol (30 mL/kg/min) is higher than the accepted hepatic blood flow (21 mL/kg/min), extrahepatic elimination sites have been investigated. While pulmonary metabolism of propofol was substantiated by Dawidowicz et al. [33] who reported higher propofol concentration in blood from right atrium than from radial artery (6.17 ± 2.15 and 3.49 ± 1.38 μg mL^{-1}) during propofol infusion, with a pulmonary extraction ratio ≈0.3–0.4, this is still controversial and has not been proven in other studies [34] which reported no pulmonary extraction at pseudo-steady state. Furthermore, the kidneys likely account for about one-third of total body propofol clearance in patients undergoing cardiac surgery [35].

The pharmacokinetics (PK) of propofol are usually described using a three-compartmental model: a large central compartment, a peripheral relatively less perfused compartment (lean tissues), and a deep compartment with limited perfusion (fat) [36]. High lipophilicity ensures rapid onset of action at the brain, and rapid redistribution from central to the peripheral compartment causes quick offset of anesthetic action. Peripheral fat compartments act as reservoirs and redistribution from these compartments to the central compartment can take much longer especially in obese and critically ill children, after prolonged infusions [37, 38].

6.1 Hepatic Enzymes in Propofol Metabolism

About 53 % of injected propofol is excreted in urine as a glucuronide [38]. The main enzyme that plays a role in the glucuronidation of propofol in hepatic as well as renal cortical microsomes is *Uridine Glucuronyltransferase UGT1A9*. Hydroxylation accounts for 38 % of the excreted metabolites of propofol and is mainly brought about by the cytochrome P250 (CYP) system (*CYP2B6, CYP2C9*) in the liver [38]. Available data on the developmental maturation of the *CYP2B6* reveals that infants younger than 10 months of age have only 10 % and at 1.3 years, about 50 % of adult activity levels [39], while not much is known about developmental changes in *UGT1A9*. However, the important factor remains that there is a 100-fold inter-individual differences in activity of these enzymes throughout life, and propofol clearance varies more than 300 % in the neonatal period, which makes the variability more a function of inter-individual differences rather than age [40, 41].

6.2 Maturation and Propofol Pharmacokinetics

As we know, children are not "little adults". Along with differences in body composition, childhood is also period of physiological maturation and changes in height, fat composition, weight, changes in hepatic and renal function, as well as cerebral cortical effects. During maturation, from birth to the age of 15 years, many changes influence PK and metabolism [42]. Basically, three periods may be distinguished, the neonate, the infant, and the prepubertal children. Neonates: clearance is only 10 % of the mature value at 28 weeks gestation, 38 % at term, and 9 0 % of adult levels by 30 weeks post-natal age in a term neonate [40, 43]. Infants are characterized by increased volume of distribution for propofol in the first year of life and a fast maturational increase in clearance, which is completed in the first 6 months [43]. Propofol clearance in a 2-year-old child could be 22.2–41.8 mL/kg/min depending on the PK model used to estimate clearance [44]. In fact, when metabolic clearance of propofol was calculated using an allometric exponent of 0.75 for weight, it reaches adult rates at approximately 50 weeks of age [43]. In older prepubertal children (from 3 years to puberty) volumes are nearly twice greater and inter-compartmental clearance 50 % greater than in adults [36, 45]. In fact, it has been proposed that the use of allometric scaling between adults and children seems to be an adequate tool for the development of rational dosing schemes for children of varying body weights [46].

6.3 Propofol Anesthetic Effects in Children

Neonates are characterized by an increased sensitivity to intravenous anesthetics and anesthetic doses have to be decreased to reach and maintain a given target concentration, which tends to be lower than in older children [47]. The influence of propofol on the cerebral cortex is often assessed by using the BIS, an electroencephalography-based monitor of depth of anesthesia, a reliable tool of propofol effect in children and adults [48–50]. The effect-site concentration of propofol at half-maximal effect (EC50) was found to be 3.71–3.85 μg mL^{-1} in children [51, 52] while in adults it ranges from 2.19 to 3.07 μg mL^{-1} [53, 54]. A prospective study compared the relationship between propofol concentrations and BIS in children (aged 6–13 years) and post-pubertal young adults (14–32 years) and found that the plasma concentrations at targeted BIS of 50 was higher in the children (4.3 ± 1.1 μg mL^{-1} vs. 3.4 ± 1.2 μg mL^{-1}, $p < 0.05$). They concluded that children are less sensitive to propofol [49]. McFarlan et al. found that children required infusion rates about 50 % above those of adults to maintain a steady-state concentration of 3 μg mL^{-1} [55]. However,

using a different PK model, Munoz et al. did not find any differences in EC50 between children and adults [56]. The Ke0 for propofol, a measure of equilibration half-life between the central and effect compartments, was shown to be age dependent in one study, a decrease from approximately 0.91 min^{-1} at 1 year to 0.15 min^{-1} at 16 years [48].

6.4 Effect of Severe Obesity on Propofol PK/PD

The prevalence of obesity in children in the USA is currently alarming (16.9 %) [57] and there is a corresponding 5-fold increase in bariatric surgeries performed in severely obese adolescents [58]. Propofol is a commonly used anesthetic in this population and its dosing in this population poses serious dilemmas. While it is reported that clinical titration of propofol in severely obese adolescents caused overdosing associated with delayed emergence, increased postoperative somnolence and incidence of postoperative adverse respiratory events [59], in obese adults, inadequate anesthesia from propofol under-dosing has been reported to cause intra-operative awareness [60]. Hence clinical trials for evaluating propofol dosing in obese children is necessary. A recent retrospective study concluded that overweight/obese children are more likely to receive doses of common anesthetic medications outside recommended doses potentially adding risk of adverse outcomes in these children [61]. Ingrande et al. recommended that lean body mass (LBM) correlates well with cardiac output and is more suitable for weight based induction of anesthesia with propofol [62–64]. The reasoning was that because cardiac output is a determinant of the initial concentration of propofol after the administration of a short intravenous infusion, as during induction of anesthesia [62], and obesity-related increase in LBM appears to be the main determinant of cardiac output, LBM may be a better scalar for dosing propofol induction doses. In practice, it may be best to titrate propofol induction to patient response. Propofol clearance has been found to increase with body weight according to a power function in several studies in obese adults and adolescents [65–67]. Hence, it is suggested that maintenance of propofol anesthesia should be scaled to total body weight (TBW) in an allometric fashion [68]. A population PK meta-analysis of propofol to characterize the influence of body size measures and age in morbidly obese and nonobese adults, adolescents, and children included data from 60 morbidly obese and nonobese adult patients (55–167 kg; 21–79 years) and 34 morbidly obese and nonobese adolescents and children (37–184 kg; 9–20 years). The results show that clearance increased with TBW in an allometric function while age was found to influence clearance in a bilinear fashion with two distinct slopes, reflecting an initial increase and subsequent decrease as a result of aging (Fig. 3) [69].

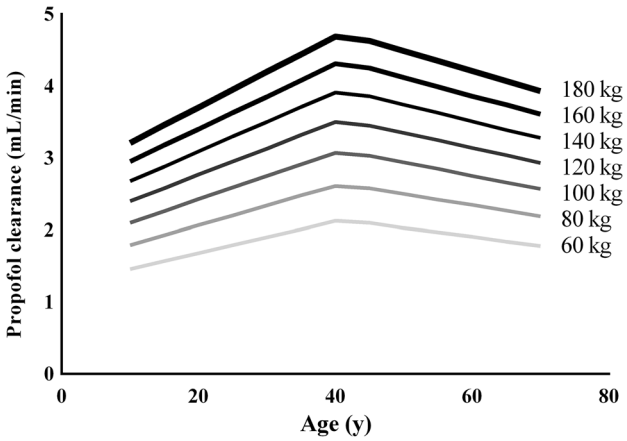

Fig. 3 Model-based predictions of population clearance estimates of propofol vs. age for patients with different total body weights show both the allometric increase of propofol clearance with total body weight as the distance between the weight classes decreases with increasing total body weight, and the bilinear relationship of propofol clearance with age (reprinted unchanged from Diepstraten et al. [69], p 5, published by Nature Publishing Group, licensed for reprinting under a Creative Commons Attribution-Noncommercial-No Derivative Works 3.0 License)

7 Dosing and Total Intravenous Anesthesia in Pediatric Anesthesia

Total intravenous anesthesia (TIVA) has the advantages of reduced postoperative nausea, reduced emergence delirium, and decreased atmospheric pollution in peripheral locations, and is especially necessary for anesthetic care of children susceptible to malignant hyperthermia and scoliosis surgery with intraoperative neuro monitoring. While BIS is one method of monitoring anesthetic depth, expired propofol concentration may be potentially another guide of propofol administration in the future [70, 71]. Target controlled infusion (TCI) pumps are used in Europe for administering TIVA but unfortunately, there are no integrated PK/pharmacokdynamic (PD) analyses providing validated parameter estimates that can be programed into TCI pumps for plasma or effect-site concentration over the broad pediatric range [72]. Popular pediatric programs used for propofol infusion targeting a plasma concentration are based on data from Marsh et al. [73], Gepts et al. [74] (Diprifusor), Kataria et al. [45], or Absalom et al. (Paedfusor) [75]. In children, the predicted concentration/effect relationships were best described with an adult Schnider PK model in few studies [52, 76, 77]. Propofol concentration of 2–3 μg mL^{-1} is commonly targeted for sedation, whereas 4–6 μg mL^{-1} is used for anesthesia. Both the loss

and return of consciousness occur at similar target effect-site propofol concentrations (2 ± 0.9 μg mL^{-1} vs. 1.8 ± 0.7 μg mL^{-1}) in adults [78] and a 'wake-up' concentration of 1.8 μg mL^{-1} is described in children [79]. Moreover, the half-life Ke_0 of propofol has not been adequately described in children, which when combined with the interactions that propofol has with opioids when administered together for TIVA purposes [80], makes use of TCI for TIVA even more complicated. As mentioned before, much PK parameter variability in children attributable to size and age, can be reduced by application of allometric theory and maturation models, which can then be incorporated into TCI pumps for pediatric TIVA, once drug maturation is characterized [44]. A summary of different pediatric PK/PD models that are commonly used, are provided in Table 1 for comparison of parameters.

Although closed-loop control of anesthesia would be expected to decrease drug dosage and improve dosing tailored to response, thus increasing patient safety, it has been deemed a challenging task because of the interpatient variability in drug sensitivity. This was demonstrated by Heusden et al. who presented 47 validated models describing the effect of propofol infusions in children aged 6–16 years, where induction clinical data were used to identify the model [81]. Therefore, in conclusion, the use of TCI or closed loop control of propofol anesthesia in children remains a challenge.

8 Effects on Different Organ Systems

8.1 Cardiovascular Effects

Propofol has a number of effects on the cardiovascular system, but the precise underlying mechanisms are not yet fully understood. They appear a few minutes after the hypnotic effect. The most significant hemodynamic effect is a decrease in arterial blood pressure. An induction dose of 2–2.5 mg/kg produces a 25–40 % reduction in systolic blood pressure [82] as well as a fall in mean and diastolic blood pressure. This is mainly because of arterial vasodilation due to reduced vascular sympathetic tone, but propofol may also affect myocardial contractility and autonomic control of cardiac output [83]. Propofol reduces both preload and afterload, because of a fall in arterial and venous systemic vascular resistance. It has also been noted to cause a fall in pulmonary arterial and capillary wedge pressure in cases of valvular heart disease [84]. These effects depend on the plasma concentration and are therefore more pronounced during induction compared with maintenance of anesthesia. However, it can be exaggerated in hypovolemia, older patients, or those with significant preexisting cardiac disease. This hypotensive effect can also be potentiated by other drugs such as opioids, benzodiazepine, anti-hypertensives, and beta blockers. A fall in blood pressure is also accompanied by reduced cardiac output, cardiac index, and stroke volume index [84].

Propofol also reduces systemic vascular resistance, which is an important effect in children with congenital heart disease. In cases of a cyanotic cardiac shunt, a fall in the ratio of pulmonary to systemic blood flow can lead to arterial desaturation [85]. Propofol has no significant effect on the heart rate mainly because it prevents an appropriate cardiac response to a fall in blood pressure [86]. However the heart rate may still vary during anesthesia owing to other compensatory systemic changes or the effect of other drugs administered at the same time. Propofol has a dose-dependent effect on the cardiac rhythm. It shows both arrythmogenic and anti-arrhythmic effects depending on its concentration within the blood. There is also evidence to suggest that propofol can convert supraventricular and ventricular tachycardia and may inhibit the conduction system of the heart. This may be because of its effect on the autonomic nervous system of the heart as well as myocardial ion channels [87].

8.2 Central Nervous System Effects

Propofol causes significant cerebral vasoconstriction, which is directly proportional to the administered dose. This is associated with a fall in cerebral blood flow, metabolic demand for oxygen, and any pre-existing cerebral edema [88, 89]. However, cerebral autoregulation and cerebrovascular reactivity to CO_2 appear unaffected [90]. Propofol causes a fall in normal or raised intracranial pressure along with a decrease in cerebral perfusion pressure [91]. Propofol may also have some effect on normal neurological function but its clinical significance is not clear. Its use in children to achieve prolonged sedation has been associated with adverse neurological outcomes, including prolonged sedation in a premature infant [92], impaired motor function, and blindness in a 23-month-old infant [93], muscle weakness and twitching that lasted 9–18 days as well as seizures [94], ataxia, and hallucinations in a 6-year-old child after propofol infusions [95]. However, a case of series of 20 children receiving propofol infusion did not show any negative neurological sequelae [96]. Although animal studies suggest that propofol increases neurodegeneration in a dose-dependent manner [97], current evidence fails to reveal injurious effects of propofol on neuronal survival, arborization, and electrophysiological function and the case reports are limited by the lack of detailed follow-up [98, 99].

Currently, there is much controversy regarding the use of anesthetics including propofol on neurocognitive development in young children. This has been discussed

Table 1 Comparison of propofol pharmacokinetic/pharmacodynamic models evaluated in the pediatric literature [42, 72]

References	V_1	V_2	V_3	CL (L/min)	Q2 (L/min)	Q3 (L/min)	K_{10} (min^{-1})	K_{12} (min^{-1})	K_{21} (min^{-1})	K_{13} (min^{-1})	K_{31} (min^{-1})
PK parameters based on commonly used PK models for propofol in children (parameters for a child aged 6 years and 20 kg are presented in bold)											
Kataria [45]	**10.4**	**20.2**	**164**	**0.68**	**1.16**	**0.52**	**0.097**	**0.166**	**0.072**	**0.066**	**0.0041**
	0.52 × WGT	1.01 × WGT	8.2 × WGT	34 mL/kg/min	58 mL/kg/min	26 mL/kg/min					
Schuttler [36]	**7.68**	**20.74**	266	**0.56**	**1.036**	**0.46**	**0.073**	**0.135**	**0.052**	**0.059**	**0.0017**
	$9.3 \times PWT^{0.71} \times (AGE/30)^{-0.39} \times (1 + BOL \times 1.61)$	$44.2 \times PWT^{0.61} \times (1 + BOL \times 0.73)$		$1.44 \times PWT^{0.75}$	$2.25 \times PWT^{0.62} \times (1 - VEN \times 0.40) \times (1 + BOL \times 2.02)$	$0.92 \times PWT^{0.55} \times (1 + BOL \times -0.48)$					
Marsh [73]	**6.8**	**17.6**	**40.68**	**0.68**	**0.58**	**0.14**	**0.1**	**0.0855**	**0.1092**	**0.0392**	**0.0049**
	0.343 L/kg										
Paedfusor [75]	**9.2**	**18.98**	**116.58**	**0.568**	**1.044**	**0.384**	**0.063**	**0.114**	**0.055**	**0.0419**	**0.0033**
	0.4584 L/kg/min						$0.1527 \times WGT^{-0.3}$				
Schnider [77]	**4.27**	**37.3**	**238**	**0.37**	**2.42**	**0.836**	**0.086**	**0.565**	**0.196**	**0.065**	**0.0035**
		$18.9 - 0.391 \times (AGE-53)$		$1.89 - 0.0456 \times (WGT - 77) - 0.0681 \times (LBM - 59) + 0.0264 \times (HGT - 177)$	$1.29–0.024 \times (AGE - 53)$						

References	Population	V_1	V_2	V_3	CL L/min	Q_2 (L/min)	Q_3 (L/min)	Ke_0/min	EC_{50} (Mcg/ml)	γ	E_0	Conclusions
PK–PD parameters from propofol PK–PD studies with bispectral index as a PD parameter in children												
Coppens [76]	Non-obese children	0.174 L/kg	0.234 L/kg	0.951 L/kg	0.0393 L/kg/min	0.102 L/kg/min	0.0333 L/kg/min	**0.79** (0.33–3.30)	**3.85** (2.78–4.52)	**1.50** (1.02–2.07)		Using population PK models from the literature instead of the 'true' PK model led to better predictions of BIS while incorrectly estimating the PD parameters
Riguozzo [52]		PK parameters of Schnider's model used						0.272 (A) **1.770 (C)**	3.07 (A) **3.71 (C)**		95.8 (A) **95.2 (C)**	In children, the predicted concentration–effect relationships were best described using the Schnider model
Cortinez-Eleveld [213, 214]	All patients	3.9 (1–34.5)	16.5 (8.9–16.4)	80.8 (47.7–87.6)	2.1 (1.6–2.7)	4.8 (3.8–6.0)	0.9 (0.8–1.3)	**0.190**	**3.29**	**1.59**	**97**	The Eleveld allometric PK model proved to be superior to all other tested models using TBW. No relevant effect of obesity on the propofol concentration–BIS relationship
Chidambaran [68]	Obese adolescents	14	56.9	247	1.65 L/70 kg/min	4	1.50	**0.61**	**3.12**	**1.32**	**95**	TBW is the major determinant of CL using allometric function with an exponent of 0.75. No significant covariates for other PK/PD parameters

BOL bolus, *CL* clearance, V_1 volume of distribution of the central compartment, V_2 volume of distribution of the first peripheral compartment, V_3 volume of distribution of the second peripheral compartment, Q_2 inter-compartmental clearance from the central compartment to the first peripheral compartment, Q_3 inter-compartmental clearance from the central compartment to the second peripheral compartment, *LBM* lean body mass, *PWT* population median weight, *VEN* venous, LBM_{male} $1.1 \times WGT - 128 \times (WGT/HGT)^2$, LBM_{female} $1.07 \times WGT - 148 \times (WGT/HGT)^2$, *PWT* WGT/70, *K10, K12, K21, K13, K31* rate constants describing movement of propofol between the different compartments in a three-compartmental model, *PD* pharmacodynamics, *PK* pharmacokinetics, Ke_0 first-order equilibrium constant linking the central pharmacokinetic compartment to the effect-site compartment, EC_{50} propofol concentration at half-maximum effect, γ Hill coefficient, *BIS* bispectral index, E_{max} maximal reduction in BIS, E_{min} minimal BIS attainable due to propofol, E_0 baseline BIS, *A* adult, *C* child, *TBW* total body weight, *WGT* weight in kilograms, *AGE* subject age in years, *HGT* subject height in cm

later in this review. It is as yet uncertain if propofol has any neuroprotective effects in the setting of compromised cerebral function as a result of trauma, hypoxia, or ischemia. Animal models suggest that it may reduce hypoxic upregulation of lactate dehydrogenase, reduce cellular injury, and increase neurogenesis [100–102]. The effect of propofol on epileptogenic cerebral activity is poorly understood. It appears to have a dose-dependent anticonvulsant effect. It may act by enhancing the effect of GABA, inhibiting NMDA receptors, and modulating slow calcium ion channels. However, this GABA agonism and concomitant glycine antagonism may also induce seizures and cause epileptiform changes in electroencephalography [103]. The latter is more likely to occur during induction or emergence from anesthesia. Propofol has also been used to induce epileptic activity for cortical mapping of epileptogenic foci.

8.2.1 Propofol Effects on Intraoperative Neurophysiological Monitoring

Intraoperative neurophysiological monitoring (IONM) has become the standard of care for many neurosurgical procedures. The main modalities are: somatosensory evoked potentials (SSEPs), motor evoked potentials (MEPs), and electromyography (EMGs) [104]. Both inhaled and intravenous agents depress signal attainment; however, for equal MAC concentrations, inhaled agents result in greater signal depression [105]. On comparison of sevoflurane and propofol effects on SSEP during scoliosis corrective surgery, the authors found that propofol and sevoflurane depressed SSEP amplitude by 18.0 ± 3.5 to 28.7 ± 5.9 %, respectively and increased SSEP latency by 1.3 ± 0.4 to 2.6 ± 1.2 %, respectively [106]. Although propofol does demonstrate a dose-dependent reduction in MEP amplitude without effect on latency, it has repeatedly been shown to produce a more stable neurophysiologic environment for monitoring, when compared with inhalational anesthetics [107].

8.3 Respiratory System

The usual induction dose of propofol of 1–3 mg kg^{-1} results in most patients becoming apneic for a few minutes. The incidence and duration of apnea depends on dose, speed of injection, and concomitant premedication [108]. The effects of propofol on a decrease in tidal volume, minute ventilation, and ventilatory drive and an increased $PaCO_2$ are dose dependent. Patients with chronic obstructive pulmonary disease have an exaggerated response to the ventilatory depressant effects of propofol. A maintenance infusion of propofol (100 μg kg^{-1} min^{-1}) results in a 40 % decrease in tidal volume and a 20 % increase in respiratory frequency, with an unpredictable change in minute ventilation. Doubling the infusion rate from 100 to 200 μg kg^{-1} min^{-1} causes a further moderate decrease in tidal volume but no change in respiratory frequency [109]. Propofol (50–120 μg kg^{-1} min^{-1}) also depresses the ventilatory response to hypoxia, presumably by a direct action on carotid body chemoreceptors [110]. The ventilatory depressant effects of propofol are accompanied by a decrease in protective airway reflexes. An increasing depth of propofol anesthesia is associated with the increased collapsibility of the upper airway [111]. This dose-related inhibition is likely to be the combined result of the depression of central respiratory output to the upper airway dilator muscles and the upper airway reflexes. Propofol potentiates hypoxic pulmonary vasoconstriction. The potentiated response in response to hypoxia, as during one lung ventilation or lung disease, appears to be caused by inhibition of adenosine triphosphate-sensitive potassium channel-mediated pulmonary vasodilation [112]. Propofol does not alter airway mechanics in asthmatic patients and is superior to etomidate and thiopentone; however, there have been case reports of bronchospasm in susceptible patients [113].

9 Clinical Uses and Propofol Dosage in Pediatric Anesthesia

9.1 General Anesthesia

The rapid recovery characteristics, and relatively small accumulation that propofol undergoes, even after prolonged infusions make it an extremely useful drug for inducing and maintaining general anesthesia. Loss of consciousness occurs within one arm-brain circulation time and cessation of effect after a single dose is usually determined by rapid redistribution. The induction dose of propofol in children is increased (2–5 mg kg^{-1}) compared with adults, primarily because of PK differences, smaller central compartment, increased metabolic clearance, and larger volumes of distribution [114]. Premedication with a benzodiazepine or an opioid, or both significantly reduces the induction dose. Increased clearance rates in children contribute to the requirements of an increased rate of maintenance infusion doses. In children less than 3 years of age divided into groups of <3, 3–6, 6–12 months, and 1–3 years, a dosage scheme was described by Steur et al. in 50 pilot patients and then evaluated in 2271 children (mostly mechanically ventilated) to provide safe and smooth anesthesia [115]. They found that relatively more propofol was needed, especially in the youngest age groups, to fill the central compartments, but with a longer duration the dosage had to be reduced relative to older

Table 2 Propofol induction and maintenance dosing in children of different ages (<3 months to 11 years) and adolescents (severely obese) (propofol doses for infusions are mg kg^{-1} h^{-1}). Valid under conditions applied by authors of respective studies

Age	First 10 min	Second 10 min	Third 10 min	Fourth 10 min	Consecutive 1 h	Remarks
Propofol maintenance dosing in children <3 months to 3 years of age[a]						
<3 months	25	20	15	10	5	Relatively more propofol was needed in the youngest age groups to fill the central compartments, but with a longer duration the dosage had to be reduced relative to older patients
3–6 months	20	15	10	[b]	5	
6–12 months	15	10	[b]	[b]	5	
1–3 years	12	9	[b]	[b]	[b]	

Age	Loading dose	First 15 min	Next 15–30 min	Next 30–60 min	Next 1–2 h	Next 2–4 h
Propofol dosing in children 3–11 years of age[c]						
3–11 years	2.5 mg/kg	15	13	11	10	9

	Loading dose	First 20 min	20–40 min	40–120 min
Propofol dosing for severely obese adolescents (aged 9–18 years) based on PK–PD model simulations in a hypothetical obese female adolescent (15.6 years, 130 kg weight, height 166 cm)[d]				
Obese adolescent	1.4 mg/kg ABW	9.3 (DW)	7.2 (DW)	5.1 (DW)

ABW adjusted body weight, *DW* dosing weight = 70 × (total body weight/70)$^{0.75}$ kg, *PK* pharmacokinetics, *PD* pharmacodynamics

[a] Adapted from Steur et al. [115]

[b] Dosage and corresponding time period not applied

[c] McFarland et al. [55]

[d] Chidambaran et al. [68]

patients (Table 1). McFarlan et al. used PK simulation programs to target plasma propofol concentrations of 3 μg mL^{-1} and have published a dosing guide in children 3–11 years of age, which indicate need for higher infusion rates than adults to maintain same concentrations [55]. They also found that the context sensitive half-time in children was longer than in adults, rising from 10.4 min at 1 h to 19.6 min at 4 h compared with adult estimates of 6.7 and 9.5 min, respectively. Based on a prospective PK–PD study in severely obese children aged 9–18 years, simulations were performed in a representative hypothetical, obese, female adolescent (total body weight = 130 kg, age 15.67 years, and height 166 cm) and a dosing regimen proposed to target a median BIS of 50 (personal communication from Dr. Chidambaran). Table 2 provides a summary of the various dosing regimens recommended by the above said studies.

9.2 Propofol for Procedural Sedation

Propofol is commonly used for sedation for procedures and imaging by anesthesiologists and intensivists [116]. Frequently, an opioid is given to relieve the discomfort that may accompany a noxious procedure as well as decrease the required dose of the sedative. Intermittent bolus administration of propofol has a greater risk than continuous infusion because it is easier to overshoot and produce periods of unconsciousness that may be accompanied by diminished or absent airway patency. Prospective evaluation of propofol sedation in children undergoing airway endoscopies concluded that TIVA with propofol in patients breathing spontaneously was an effective technique [117]. In comparison to dexmedetomidine, propofol provided faster anesthetic induction and recovery times for sedation in children undergoing magnetic resonance imaging, although it caused more hypotension and desaturation [118]. Similarly, Wu et al. found that in comparison to dexmedetomidine infusion, use of propofol 2 mg kg^{-1} loading dose (after sevoflurane induction) followed by an infusion of 200 μg kg^{-1} min^{-1} yielded better outcomes in terms of emergence time, parental satisfaction, timeliness, and postoperative behavioral disturbances [119]. Propofol infusion was also found an acceptable sedative technique for magnetic resonance imaging sleep studies in children with obstructive sleep apnea, with no significant changes in airway dimensions for the doses used [120]. The question about non-anesthesia personnel providing propofol sedation for non-operating room procedures was independently evaluated using a large database of 49,836 sedations from 37 locations [121] and 91,189 pediatric procedural sedation by critical care physicians using the Pediatric Sedation Research Consortium multicenter database [122], both studies provided confidence that this was a safe practice, without any significantly increased risks compared to anesthesia providers. A study of propofol sedation by emergency physicians similarly observed a low adverse

event prevalence [123]. However, it is important for the providers to select patients wisely, be skilled in airway management, and use capnography to improve safety.

9.3 ICU Long-term Sedation

Propofol is routinely used in the ICU for long-term (sometimes weeks) sedation. Use of propofol was prospectively evaluated in 174 children aged 2 months to 16 years, duration of propofol infusion 13 h (range 16–179 h), and dose of propofol 2.9 mg/kg/h (range 0.3–6.5 mg/kg/h), and concluded that it was safe to use propofol in this setting. Long-term infusion of propofol may result in a very large dose of lipid, and this has been associated with hypertriglyceridemia and pancreatitis [124]. The use of propofol for sedation in pediatric intensive care unit patients has been associated with an increase in mortality, although a causal relationship has not been established [125]. Propofol infusion syndrome in children has been described consisting of myocardial infarction, metabolic acidosis, and rhabdomyolysis and is discussed in more detail later in this review [125]. Although no such cases have been reported in healthy children during routine anesthesia care, one child with a genetic defect in lipid metabolism who received approximately 150 μg kg^{-1} - min^{-1} (~9 mg kg^{-1} h^{-1}) for 6.5 h during scoliosis repair was reported [126]. This case report along with one other suggests caution in the use of propofol in children with known defects in lipid metabolism, which may include some forms of mitochondrial disease, and has been detailed in a later section.

10 Other Advantages of Propofol TIVAA

10.1 Less Postoperative Nausea and Vomiting

The postoperative nausea and vomiting (PONV) rate in children aged ≥3 years can be almost twice as high as in adults [127]. The risk of PONV is rare in children less than 2 years of age. Several studies have demonstrated that propofol has antiemetic properties, including when administered in the subhypnotic dose range [128]. Low-dose intraoperative propofol infusion (bolus of 1 mg/kg followed by an infusion of 20 μg kg^{-1} min^{-1}), has been shown to reduce PONV when used by itself or when combined with other antiemetics [129, 130]. Additionally, small doses of propofol used as rescue therapy (20 mg as needed) has been found to be as effective as ondansetron [131]. However, it should be noted that duration of effect of low doses of propofol is brief. In a randomized controlled trial, Apfel et al. studied six interventions for the prevention of PONV and found that the use of propofol reduced risk for PONV by 19 % [132]. A quantitative review of randomized controlled studies that reported PONV after propofol anesthesia compared with other anesthetics showed a decrease in the incidence of early (occurring within the first 6 h) of PONV, with a number needed to treat = 5.53 [133, 134]. In fact, recent "Consensus Guidelines for the Management of Postoperative Nausea and Vomiting" (2014) of the Society of Ambulatory Anesthesiology recommend regional anesthesia or TIVA with propofol if patients are at high risk for PONV [135]. Although the guidelines are not specifically geared towards children, it is likely they will benefit children aged older than 3 years.

10.2 Less Emergence Delirium

Emergence delirium (ED) is a well-documented phenomenon occurring in about 12–13 % of children in the immediate postoperative period. It is defined as a dissociated state of consciousness in which the child is inconsolable and irritable [136]. Although generally self-limiting (5–15 min), it may result in physical harm to the child, including to the site of surgery. ED can also predispose children to the development of negative postoperative behavioral changes [137]. Chandler et al. compared TIVA with propofol and remifentanil to inhalational sevoflurane in a randomized trial of children between the age groups of 2 and 6 years who underwent strabismus repair. The study concluded that there was as lower incidence of ED after TIVA [138]. It has also been shown that the addition of a subhypnotic dose of propofol (1 mg kg^{-1}), at the end of sevoflurane-based general anesthesia for diagnostic imaging, is effective in significantly decreasing the incidence of ED without delaying recovery or discharge time [139].

11 Adverse Effects

11.1 Pain on Injection

Without doubt, pain associated with a propofol injection is the most common adverse effect of propofol. About 85 % of pediatric patients experience pain on injection with a higher incidence in younger children [140, 141]. The cause of pain is still unknown, but many mechanisms have been proposed. Many factors appear to affect the incidence and severity of pain which include, but are not limited to: size of the vein, site of the injection, speed of the injection, speed of the intravenous carrier fluid, and the concomitant use of drugs such as local anesthetics, nonsteroidal anti-inflammatory drugs, ketamine, and opiates [142].

In 1981, Briggs et al. were the first to report increased incidence of pain with propofol administration in the

dorsum of the hand than in the antecubital vein [143], a finding that was replicated in 1991 by Hannallah et al. in the pediatric population [144]. Further studies by Scott et al. pointed out that vein size is an important factor in the causation of pain [145]. There was no pain associated with injecting propofol into a large vein such as the antecubital fossa presumably because the drug was injected into the midstream and, thus, had minimal contact with the vein wall. Additionally, the composition of nociceptors along the endothelial wall may differ between small and large veins [146]. It was suggested that pain originates from the contact of propofol with the neural elements within the vein and is related to the propofol concentration in the free aqueous phase [147, 148]. Nakane et al. concluded that the lipid solvent in propofol results in plasma Kallikrein–Kinin cascade activation and, production of bradykinin which modifies the local vein by its vasodilatory and hyperpermeability actions, thus increasing the contact between the aqueous phase propofol and free nerve endings [149].

Several interventions have been studied to improve the perioperative experience by alleviating the pain associated with propofol injection including: a lidocaine-propofol admixture, pretreatment with lidocaine (with and without venous occlusion), opioids, ketamine, or non-steroidal anti-inflammatory drugs, and propofol emulsions containing medium and long-chain triglycerides MCT/LCT [142].

Diluting propofol with saline or glucose solution, using cold or warm propofol, and the use of topical analgesia were studied, but did not provide significant efficacy [150–154]. Numerous studies investigated the effect of lidocaine on injection pain with favorable outcomes. In multiple studies, lidocaine-propofol admixtures resulted in lower pain incidence when compared with controls [155, 156]. In a large systematic review of 6264 patients, lidocaine-propofol admixture was found similar in efficacy to pretreatment with lidocaine without venous occlusion, yet less efficacious than pretreatment with lidocaine (0.5 mg per kg) with venous occlusions [141]. Tan et al. recommended a combination technique that included: alfentanil pretreatment, mixing lidocaine with propofol, and injecting the mixture into a large vein with no carrier fluid to decrease the incidence and severity of propofol injection pain [157]. Effect of different formulations of propofol was evaluated on propofol injection pain, especially the MCT/LCT propofol formulation. However, a higher incidence of pain was reported with MCT/LCT propofol than LCT propofol in the pediatric population in a prospective randomized double-blind trial in children aged 2–18 years, and concluded that lidocaine is more effective in reducing pain than MCT/LCT propofol [158]. In contrast, Rochette et al. in another prospective, randomized, double-blinded, placebo-controlled study in preschool children, reported that MCT/LCT propofol caused significantly less pain than LCT propofol alone and that the combination of MCT/LCT propofol with lidocaine led to a further significant decrease of pain [159]. Varghese et al., however, found no difference in the incidence or severity of injection pain when lidocaine is added to both MCT/LCT propofol and LCT propofol [160]. A systematic review and meta-analysis recommends that the use of a small dose of opioids before induction of anesthesia and to use an antecubital vein instead of a hand vein for the propofol lidocaine admixture administration is a simple and effective way to avoid pain. The authors also recommended using lidocaine in conjunction with venous occlusion if a hand vein is chosen [142]. Besides, there are case reports of inadvertent intra-arterial injection of propofol in children, while no irreversible effects have been described, pain and cutaneous sequelae have been reported [161, 162].

11.2 Propofol Anaphylaxis

Propofol anaphylaxis, mediated by IgE, occurs in 1 in 60,000 patients, accounting for 2 % of all cases of perioperative anaphylaxis [163]. Because the most commonly used preparation of propofol contains 10 % soyabean oil with 1.2 % egg lecithin as the emulsifying agent and there is an increasing number of children presenting with food allergies, especially towards egg, soybean, and peanuts, the safety of administering propofol in these allergic children has been debated. Common food allergies during early childhood, affecting approximately 0.4 % of preschool children, are those to soy and peanuts [164] and there is a risk of cross-allergy reactions between peanut oil and soy bean oil [165]. While allergic reactions are precipitated by the protein particles in soy, the emulsion of propofol emulsion is refined soya oil that contains negligible traces of protein, suggesting that the drug is unlikely to trigger an anaphylactic reaction in patients with a soy allergy or a cross-reactivity reaction to patients with a peanut allergy [166].

Unlike lecithin, a purified egg yolk component present in propofol, the egg proteins, ovoalbumin, ovomucoid, and conalbumin, were found to be the triggering agents in an egg anaphylaxis [167]. In a study of 25 patients with a documented egg allergy, skin and intradermal testing with propofol and its lipid vehicle were found to be negative [168]. In a recent retrospective study, 28 patients with egg allergy with propofol administration were identified, no adverse reactions were noted except one non-anaphylactic reaction of a child with a history of egg anaphylaxis [169]. In a study of 14 patients with a documented propofol allergy, allergic reactions were shown to be triggered by the isopropyl or phenol groups, rather than the lipid vehicle of propofol [170].

Therefore, current literature does not support the belief that egg-allergic patients are more prone to propofol

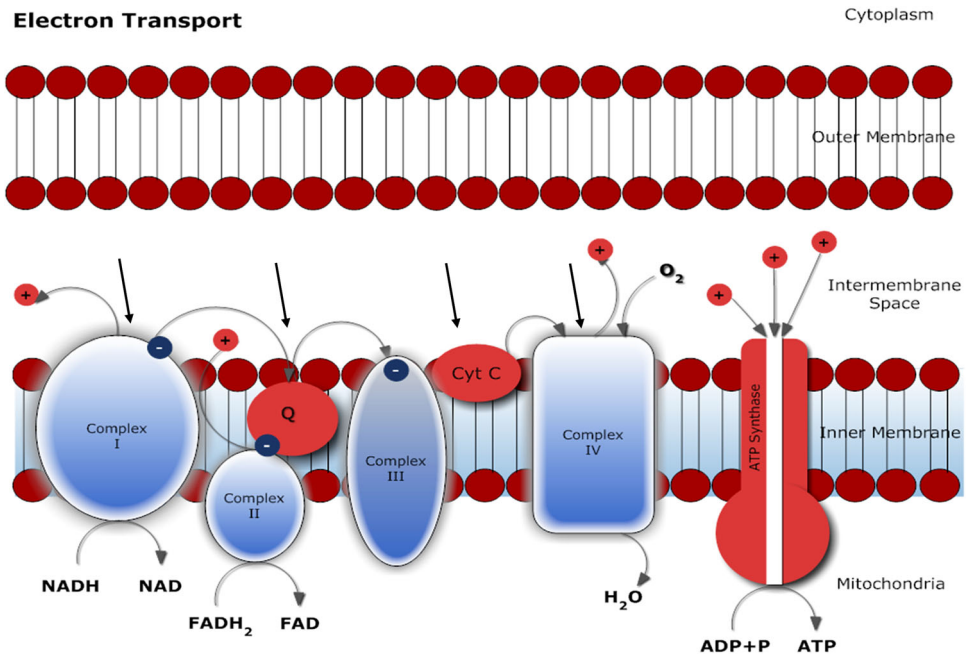

Fig. 4 Diagrammatic representation of propofol effects on the mitochondrial electron transport chain: the electron transport chain is located in the inner membrane of mitochondria: during oxidative phosphorylation, electrons from reduced coenzyme nicotinamide adenine dinucleotide (NADH) and succinate (formed from citric acid cycle) enter the electron transport chain via complex I and II respectively. Electrons are then fed to coenzyme Q, which passes them to complex III, cytochrome C, and complex IV sequentially. This electron flow leads to proton translocation and build-up in the intermembrane space creating an electromechanical gradient that drives the synthesis of adenosine triphosphate (ATP) by ATP synthase. Propofol brings about uncoupling of oxidative phosphorylation by its inhibitory effects on various complexes involved in the process (denoted by *black arrows*). *NAD* Nicotinamide adenine dinucleotide, *$FADH_2$* Flavin Adenine Dinucleotide, *FAD* Flavin Adenine Dinucleotide, *ADP* Adenosine Diphosphate, *Cyt C* Cytochrome C, *Q* Ubiquinone

anaphylaxis. However, caution should be exercised when administering propofol to children with a history of egg anaphylaxis.

12 Propofol and Mitochondria

Propofol has been shown to affect mitochondrial function by uncoupling oxidative phosphorylation. To understand the proposed mechanisms, it is important to understand the background processes in the mitochondria. The mitochondria are responsible for generating adenosine triphosphate (ATP), the main source of cellular energy for muscle and nerve cells, via the citric acid cycle, fatty acid oxidation, and oxidative phosphorylation. During oxidative phosphorylation, electrons from reduced coenzyme nicotinamide adenine dinucleotide and succinate (formed from citric acid cycle) enter the electron transport chain via complex I and II respectively. Electrons are then fed to coenzyme Q, which passes them to complex III, cytochrome C, and complex IV sequentially. This electron flow leads to proton translocation and build-up in the intermembrane space creating an electromechanical gradient that drives the synthesis of ATP by ATP synthase (Fig. 4).

Though an exact mechanism is still unknown, propofol has been shown to depress mitochondrial function by inhibiting complex I, complex IV, cytochrome c, and the acylcarnitine transferase in the mitochondria, as well as acting as an uncoupling agent in oxidative phosphorylation [171–175]. Recently, Vanlander et al. proposed a pathogenic mechanism that involves interrupting the electron flow in the mitochondrial membrane at the site of coenzyme Q, which transfers electrons from complex II to complex III [176].

12.1 Mitochondrial Diseases

Mitochondrial diseases are groups of disorders that arise as a result of mitochondrial respiratory chain dysfunction affecting 1 in 4000 children [177]. They are caused by a variety of mutations in either nuclear or mitochondrial DNA leading to a wide range of neurologic, muscular, cardiac, and endocrine disorders. Previously, patients with mitochondrial diseases were thought to be at a higher risk of developing malignant hyperthermia when exposed to volatile agents, therefore they were mainly managed with TIVA mainly propofol. With no evidence of association between mitochondrial disease and MH, the safety of

propofol use was questioned. In a large case series, the authors studied 122 children with confirmed MD. Propofol was used for induction in 17 patients and for maintenance in 15 patients with no severe morbidity and mortality related to anesthesia [178]. It is likely that some types of defects, especially those in the oxidative phosphorylation system, are more sensitive to the inhibitory effects of propofol than others [179]. It has been proposed that children with mitochondrial disease are more prone to metabolic decompensation with propofol infusion and hence, patients with abnormal responses to propofol should be tested for mitochondrial defects [180].

Based on the current literature, propofol may not be the anesthetic of choice in patients with mitochondrial disorders and especially prolonged infusions of propofol should be avoided in such populations. Titrated administration of a single bolus of propofol is acceptable if warranted provided the patient is closely monitored except for children on a ketogenic diet.

12.2 Propofol-Related Infusion Syndrome

Propofol-related infusion syndrome (PRIS) is a very rare, but serious and life-threatening complication with a lethal outcome that can occur with prolonged propofol infusion. In 1992, Parke et al. reported the death of five children as a result of myocardial failure after receiving long-term, high-dose propofol infusion [181]. Several pediatric reports followed describing propofol-related deaths in children with a similar constellation of symptoms including metabolic acidosis, dysrhythmias, rhabdomyolysis, and lipemic plasma. In 1998, Bray et. al. reviewed all these pediatric cases and formulated diagnostic criteria for PRIS, which included refractory bradycardia associated with one of the following conditions: (1) hepatomegaly or fatty liver, (2) lipemic plasma, (3) metabolic acidosis, and (4) skeletal muscle breakdown evident by rhabdomyolysis or myoglobinuria [125]. In addition, PRIS-associated clinical manifestations include hypotension, cardiac arrhythmias (Brugada-like ECG pattern, bradycardia, asystole, pulseless electrical activity, ventricular fibrillation, or sustained ventricular tachycardia), myocardial failure, renal failure, elevation in serum creatinine, hyperkalemia, hepatic transaminitis, hypertriglyceridemia, and hyperthermia [125, 182].

PRIS appears to be dose dependent and strongly associated with propofol infusion at a mean dose greater than 4 mg/kg/h for at least 48 h [125]. However, additional other factors may play a role, because not all children who have received more than the recommended dose developed the syndrome. In an unpublished, randomized, controlled clinical trial on the use of propofol in 327 patients in the pediatric intensive care unit, a significant concentration-dependent increase of the 28-day mortality in propofol-treated patients was recognized. The trial was terminated early and, as a result, in 2001, the FDA warned against the use of propofol for prolonged sedation in the pediatric intensive care unit [183]. In 2002, a retrospective study by Cornfield et al. reviewed 142 critically ill children who were sedated with propofol infusion at doses less than 3 mg/kg/h for less than 24 h, and found no evidence of metabolic acidosis or hemodynamic instability related to propofol infusion [184]. Appropriate monitoring for PRIS is still warranted.

The incidence of PRIS has been reported from 1.1 to 4.1 %, with mortality rates as high as 64 %; however, the true incidence is still unknown [185, 186]. The exact pathophysiologic mechanism of PRIS is still unknown, although most hypotheses point to the direction of propofol effects on the mitochondria as elucidated in the previous section. Critical illness has been proposed to be an essential prerequisite for the PRIS to develop and that high-dose propofol, catecholamines, and glucocorticoids act as triggering agents for this syndrome [187]. Propofol infusions should be stopped and alternative sedatives should be used once PRIS is suspected. Cardiorespiratory support, hemodialysis, or hemofiltration have been effective and are usually required in severe PRIS cases [181, 188, 189]. Mechanical circulatory support, such as ventricular assist devices and extracorporeal membrane oxygenators have been necessary in severe cardiovascular collapse [190].

In conclusion, preventive measures are the mainstay of the treatment. Propofol infusions of doses greater than 4 mg/kg/h for more than 48 h should be avoided [125, 191, 192]. However, it should be borne in mind that in critically ill children, development of PRIS has been reported even after 3–5 h of high-dose propofol anesthesia and rates as low as 1.4 mg kg^{-1} h^{-1} [193]. Alternative sedatives should be considered in patients with increased requirements of vasopressor or inotropic support with cardiac failure during high-dose infusions. Arterial blood gases (pH), serum lactate, creatinine kinase, electrolytes, and liver and kidney functions should be monitored during propofol infusions. Maintaining an adequate carbohydrate load will prevent the increase in fatty acids and thus, help prevent the onset of PRIS [194].

13 Propofol and Pain Modulation

Propofol has long been thought to have analgesia-enhancing properties owing to activation of the GABA type A receptor, a mechanism that may counteract the pronociceptive systems. It was also shown to inhibit the NMDA receptor, presumably via inhibitory effects on NMDA-receptor NR1 subunit phosphorylation, which is thought to depress nociceptive transmission and promote analgesia [195, 196]; the

above findings led to studies to evaluate the effect of propofol on the nociceptive response and modulation.

While few studies observed analgesic effect and reduction of postoperative opioid requirement after propofol anesthesia when compared with volatile anesthetic anesthesia [197], others showed no effects on analgesia [198] or even enhanced pain sensitivity [199]. Patients who had general anesthesia with isoflurane or sevoflurane were found to report more postoperative pain and require more morphine than those anesthetized with propofol [200, 201]. Additonally, sub-hypnotic doses of propofol were found to increase the pain threshold in human pain models to laser stimulation and decreased the amplitude of pain-evoked potential significantly [197]. In contrast, a prospective blind randomized trial reported no difference or even less analgesia among patients anesthetized with propofol compared with volatile anesthetics [202, 203].

There have also been a few studies investigating propofol effect on opioid-induced hyperalgesia. A randomized, double-blind and placebo-controlled study in an experimental pain model showed that co-administration of propofol with remifentanil did attenuate, but did not eliminate the opioid-induced post-infusion hyperalgesia, but in fact caused a secondary hyperalgesic effect [204]. These findings were replicated by Bandschapp et al., who concluded that propofol administration in hypnotic doses exert a short-term antihyperalgesic effect that disappears once propofol concentration decreases [205]. In the pediatric population, a study that examined 88 children who had anesthesia maintenance with propofol had significantly lower postoperative pain scores following inguinal hernia repair than those who had sevoflurane anesthesia [206].

The only study that provides some explanation of these contradictory findings of propofol effects on pain was given by an experimental study in rats, Wang et al. reported an interesting finding that sub-hypnotic doses of propofol produced hyperalgesia, possibly owing to the inhibitory effect of propofol on the endogenous pain descending inhibition system at the supraspinal level. In contrast, anesthetic doses produced analgesia at the spinal level by inhibiting the ascending nociceptive signals [207].

Much controversy still exists regarding the propofol analgesic effect, though several clinical studies point to this direction. Clinical studies are still warranted especially in the pediatric population to further establish the effect of propofol on the nociceptive system.

14 Propofol and Neurotoxicity

Propofol has a neuroprotective role in pathogenic situations, yet, mounting data from animals (rodents and non-human primates) and epidemiological human studies in children have raised concerns regarding neurotoxic changes in the developing brain with its use and the possible neurocognitive decline as a result [208]. In 1999, Ikonomidou et al. raised concerns about the safe use of anesthetic drugs in neonates and young children [209]. The effect of propofol was studied in 15 % of the studies investigating the effect of different drugs on the developing brain. In infant rodents, propofol induced neuroapoptosis in one fourth the dose required for surgical anesthesia [210]. Creeley et al. later showed a significant increase in apoptosis of neurons and of oligodendrocytes in the developing non-human primate brain after exposure to propofol anesthesia for 5 h [211]. In the non-human primate fetus, neuroapoptosis was more pronounced in the subcortical and caudal regions while in the neonate, it was more pronounced in the cerebral cortex. As a result of these studies, in 2012, the FDA, Smart Tots, and the American Academy of Pediatrics released a consensus statement in which they recommended that elective surgical procedures performed under anesthesia for children less than 3 years of age should be avoided (http://www.smarttotts.org).

The mechanism by which propofol neurotoxicity occurs is not fully understood, yet GABA agonism is thought to play a crucial role. Recently, Pearn et al. proposed a mechanism of propofol neurotoxicity mediated by p75 neurotrophin receptor activation [212].

Despite all the emerging data and the current epidemiological and preclinical studies in animals, the use of propofol in children is safe and any change in the indications of propofol use will be unwarranted until conclusive human studies are done and a safer alternative anesthetic drug is available.

15 Conclusion

Propofol, chemically described as 2,6-diisopropylphenol, is a commonly used intravenous anesthetic agent in pediatric practice. Sterile practices have been proposed to reduce the risk for bacterial contamination of propofol vials including single-use and administration within 6 h of opening a vial in the procedural room. Clearance is only 10 % of the mature value at 28 weeks gestation, 38 % at term, and 90 % of adult levels by 30 weeks post-natal age in a term neonate, and reaches adult values by about 50 weeks. PK studies in children have shown that the use of allometric scaling between adults and children seems to be an adequate tool for the development of rational dosing schemes for children of varying body weights. Neonates show an increased sensitivity to propofol while older children may be less sensitive than adults, with a higher effect site concentration at half-maximal effect (≈ 3.8 μg mL^{-1}). Unfortunately, the use of target-controlled infusions or closed loop control of

propofol anesthesia in children remains a challenge and needs further investigation, as there is a need to investigate propofol effects in severely obese smaller children. The effects of propofol on the organ systems mimic those in adults and advantages remain its rapid recovery characteristics, less postoperative nausea and vomiting, and decreased emergence delirium compared with volatile anesthetics. Current literature does not support the belief that egg-allergic patients are more prone to propofol anaphylaxis. However, caution should be exercised when administering propofol to children with a history of egg anaphylaxis. One main contraindication for propofol infusions remain in children with mitochondrial disorders as propofol has been shown to depress mitochondrial function by inhibiting complex I, complex IV, cytochrome c, and the acylcarnitine transferase in the mitochondria, as well as acting as an uncoupling agent in oxidative phosphorylation. Propofol-related infusion syndrome, characterized by lipemic plasma, metabolic acidosis, rhabdomyolysis, arrhythmias, and fatty liver, has been reported from 1.1 to 4.1 %, with mortality rates as high as 64 %; it is a dose-dependent phenomenon and preventive measure recommended include avoidance of propofol infusions at doses greater than 4 mg/kg/h for more than 48 h. Propofol and its effects on nociception and opioid hyperalgesia are still controversial and need to be further explored. While propofol has been implicated in causing neuroapoptosis in developing non-human brains, concern for detrimental effects of propofol are not validated in a clinical setting and any change in indications for propofol use in pediatrics are unwarranted until conclusive human studies prove otherwise.

Compliance with ethical standards

Funding Preparation of this manuscript was supported by the Department of Anesthesia, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA. No financial support except departmental salary support for the authors VC, AC, and AD. The writing of the review article was also facilitated by protected research time supported by Eunice Kennedy Shriver National Institute Of Child Health and Human Development of the National Institutes of Health under award number K23HD082782 (PI: VC)

Conflicts of interest All authors (VC, AC, and AD) listed in this manuscript have no conflicts of interest relevant to this article to disclose.

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