 doi:10.20944/preprints202208.0135.v1

Article

The Impact of Low Cardiac Output on Propofol Pharmacokinetics across Age Groups - an Investigation using Physiologically based Pharmacokinetic Modelling

Karel Allegaert [1,2,3,4,*], Mohammad Yaseen Abbasi [5], Robin Michelet [6] and Olusola Olafuyi [7]

[1] Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, 3000 Leuven, Belgium; karel.allegaert@uzleuven.be
[2] Department of Development and Regeneration, KU Leuven, 3000 Leuven, Belgium
[3] Leuven Child and Youth Institute, KU Leuven, 3000 Leuven Belgium
[4] Department of Hospital Pharmacy, Erasmus Medical Center, 3015 GD Rotterdam, the Netherlands.
[5] Division of Clinical Pharmacology, Department of Medicine, Indiana University School of Medicine, 46202 Indianapolis, Indiana, USA; abbaiyaseen36@gmail.com
[6] Department of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, 12169 Berlin, Germany; rmichele@zedat.fu-berlin.de
[7] Division of Physiology, Pharmacology and Neurosciences, School of Life Sciences, University of Nottingham, NGT 2TQ Nottingham, United Kingdom; olusola.olafuyi@nottingham.ac.uk
*Correspondence: karel.allegaert@uzleuven.be; Tel.: +32-16342020

Abstract: Background: pathophysiological changes like low cardiac output (LCO) impact pharmacokinetics, but its extent may be different throughout pediatrics compared to adults. Physiologically based pharmacokinetic (PBPK) modelling enables further exploration. Methods: A validated propofol model was used to simulate the impact of LCO on propofol clearance across age groups using the PBPK platform, Simcyp® (version 19). The hepatic and renal extraction ratio of propofol was then determined in all age groups. Subsequently, dose explorations were conducted under LCO conditions, targeting a 3 µg/mL (80-125%) propofol concentration range. Results: Both hepatic and renal extraction ratios increased from neonates, infants, children to adolescents and adults. The relative change in clearance following CO reductions increased with age, with the least impact of LCO in neonates. The predicted concentration remained within the 3 µg/mL (80-125%) range under normal CO and LCO (up to 30%) conditions in all age groups. When CO was reduced by 40-50%, a dose reduction of 15% is warranted in neonates, infants and children, 25% in adolescents and adults. Conclusions: PBPK driven, the impact of reduced CO on propofol clearance is predicted to be age-dependent, proportionally greater in adults. Consequently, age group specific dose reductions for propofol are required in LCO conditions.

Keywords: physiologically based pharmacokinetic modelling; propofol; low cardiac output; pharmacokinetics; neonate; developmental pharmacology; asphyxia; hypothermia; pediatrics; pharmacokinetics

1. Introduction

Children are not merely small adults as they undergo non-linear developmental changes, impacting pharmacokinetics [1]. These changes include development of organ systems functions, maturation of cardiac output, organ perfusion and permeability, or glomerular filtration rate. Similarly, the ontogeny of cytochrome p450 (CYP) and non-CYP enzymes may result in differences in metabolic clearance [1,2]. Maturational and pathophysiological changes in children often co-exist, and this complicates drug treatment strategies. Though dosing design strategies commonly consider maturational changes occurring with age, there is usually less consideration on the impact of pathophysiology in patients, and their effects on drug disposition [1,2]. Cardiac output (CO) is one of these pathophysiological changes.

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In neonates, asphyxia and therapeutic hypothermia (TH) can reduce CO up to 33%, which is a known example of a disease-related impact on maturational pharmacokinetics [3-5]. Associated with this setting, the hepatic blood flow, intestinal and renal blood flow are affected by CO reduction [6]. The same holds true for children with chronic heart failure, as illustrated for e.g. carvedilol pharmacokinetics [7]. Based on observations in adults, it is therefore reasonable to expect a further decrease in clearance of high extraction drugs, with a pattern in neonates or children, co-modulated by physiology- and pathophysiology-related effects [7].

The clearance of propofol - a high extraction drug - is sensitive to CO changes in adults [8]. It is a fast-acting drug used in general anesthesia for induction and maintenance of sedation in various invasive procedures. It is commonly used in neonates, children and adults. Propofol is administered intravenously, and has a rapid distribution with a large volume of distribution, rapid clearance and high protein binding [9,10]. Uridine 5'-diphospho-glucuronosyltransferase (UGT1A9) is the main metabolic pathway involved in propofol metabolic clearance, accounting for about two-thirds of total clearance. The remaining one-third is by hydroxylation, involving mainly CYP2B6 and a minor contribution of CYP2C9 [10,11]. Propofol clearance also involves significant extra-hepatic metabolic clearance accounting for about 40% of its clearance, mainly driven renally by UGT1A9 [8,10]. The maturation of activity of UGT1A9, CYP2B6 and CYP2C9 evolves over the first weeks of life and beyond [12]. For example, the CYP2B6 activity in infants and in younger children is said to be 1% and 50% of adults levels respectively [13]. The hepatic abundance of UGT1A9 is thought to increase with age as neonates and infants express 3% and 27% of adult UGT1A9 protein abundance levels, and 50% of ugt1a9 adult abundance protein levels reached at 8 years [12,14].

The fact that propofol pharmacokinetics are sensitive to clearance altering parameters such as CO reduction and enzyme ontogeny, necessitates a pragmatic approach to assess the impact of the changes resulting from both pathophysiology and physiology throughout life, including in neonates and infants. Physiologically based pharmacokinetic (PBPK) modelling is a non-invasive and reliable approach that may be used to make such assessments. PBPK models can incorporate both maturational and non-maturational features in pharmacokinetics analysis, enabling assessment of the impact of altered (patho)physiology on drug specific pharmacokinetics [15,16,17]. PBPK models have been successfully used for similar analyses where for example, the non-maturational impact of CYP2B6 genetic polymorphism and drug-drug interaction between efavirenz and lumefantrine alongside maturational changes in children was quantified [18]. More recently, Olusola et al. demonstrated that the reduction in CO, as non-maturational parameter, did not significantly alter the acetaminophen pharmacokinetics in preterm neonates owing to immaturity of acetaminophen clearance pathways in preterms and the inherent low hepatic clearing capacity of acetaminophen [19].

Since propofol is classified as high extraction drug and clearance is affected by alterations in CO in adults, it serves as a good model compound to explore the impact of both physiology and pathophysiology on its pharmacokinetics across age groups [5,7,20]. The aim of this study was therefore to (*i*) assess the impact of reduced CO in low CO settings, like asphyxia and TH in neonates, on the propofol clearance capacity and (*ii*) how this affects safe and therapeutic concentration attainment across age groups to explore dosing optimization strategies under low CO conditions.

2. Materials and Methods

Simcyp® (Simcyp® Ltd, Certara, Sheffield, UK, Version 19) was used to predict propofol pharmacokinetics. This simulator has pre-validated virtual adult and pediatric population groups based on public health databases such as the US National health and Nutrition Examination Survey [21]. These virtual populations have similar interindividual variability in their demographic and physiological parameters as their real-world

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counterparts, and can thus be used for population simulations. Population sizes for simulations included a 20x10 trial design with 200 subjects.

A previously developed, validated and peer-reviewed propofol model (Michelet et al.) was optimized and further validated [22]. Details of the optimization process and final optimized parameters are provided in the Supplemental Materials (Section 1, including Table S1) [15,22-26]. After optimization, the propofol model was validated with clinical data in adults and children (all age subcategories) retrieved from published literature, also provided in the Supplemental Materials (Table S2) [27-38].

2.1. Hepatic and Renal Extraction Ratio Determination across Age Groups

Following validation of the optimized propofol model, the Morse et al. dosing model [39] was simulated in neonates, infants, children and adolescents, while the Roberts et al. dosing model [40] was implemented in adults to predict the organ clearance, required to determine the extraction ratio of propofol.

The hepatic and renal extraction ratio of propofol were subsequently calculated from the predicted hepatic clearance (CL_H) and metabolic renal clearance (CL_{MR}) respectively and their respective organ blood flows, that is, the hepatic blood flow (Q_H) and the renal blood flow (Q_R) using Equation 1 and 2. A well-stirred model was assumed.

$$Hepatic\ extraction\ ratio\ (E_H) = \frac{CL_H}{Q_H} \quad \textit{Equation 1}$$

$$Renal\ extraction\ ratio\ (E_R) = \frac{CL_{MR}}{Q_R} \quad \textit{Equation 2}$$

2.2. Impact of CO Reduction on Systemic Propofol Clearance across Age Groups

Using the Morse and Robert models, the impact of CO reduction on systemic propofol clearance was determined by calculating the percentage relative change under reduced CO conditions [39,40]. To mimic the potential impact of CO reduction, a 20, 30, 40 and 50% CO reduction was implemented. This was achieved by running the simulations after decreasing the CO input within the simulator by the respectively percentage reductions. The resultant systemic clearance was retrieved. The retrieved clearance under each reduced CO condition and under normal CO condition was used to determine the effect of reduced CO on propofol clearance using Equation 3.

$$Relative\ Clearance\ (CL)\ change\ (\%) = \frac{CL\ under\ normal\ CO - CL\ under\ reduced\ CO}{CL\ under\ normal\ CO} \times 100 \quad \textit{Equation 3}$$

2.3. Impact of Reduced Cardiac Output on Attainment of Propofol Target Concentrations

Morse and Robert models are expected to achieve a target plasma concentration of 3 (80-125%) µg/mL in children [39] and adults [40] respectively. Using these models, concentrations achieved 2 hours after start of dosing under normal CO and 20, 30, 40 and 50% reduced CO conditions were determined [39,40].

2.4. Dose Reduction Exploration to Achieve Target Concentrations in Reduced Cardiac Output Conditions

A dose optimization exploration was conducted under reduced CO conditions. The dosing optimization strategy involved the percentage total dose reduction. The percentage dose reduction was iteratively implemented until the predicted concentrations under reduced CO conditions achieved the target concentration range.

3. Results

3.1. Hepatic and Renal Extraction Ratio across Age Groups

Figure 1 shows that E_H and E_R increase from neonates until adulthood. The E_H was borderline intermediate extraction (0.34) in neonates until adolescence, where E_H increased to high extraction (0.74) (Figure 1). The predicted mean E_R followed the same

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pattern with age, with a low extraction range at 0.02 in neonates until infancy where E_R increases to intermediate extraction at 0.34 until adulthood (0.55) (Figure 1).

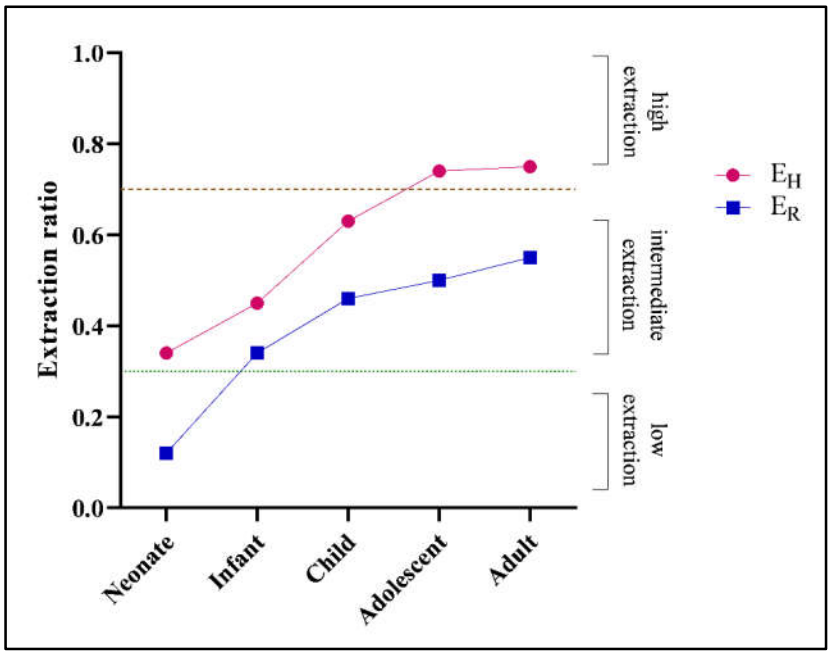

Figure 1. Predicted changes in hepatic extraction ratio (E_H) and renal extraction ratio, (E_R) with age. Red circle and line: E_H; blue circle and line: E_R; green broken line: low extraction ratio target (0.3); brown broken line: high extraction ratio target (0.7).

3.2. The Impact of Reduced Cardiac Output on Systemic Propofol Clearance across Age Groups

In Figure 2, the relative change in clearance following CO reductions increased with age with the least impact of CO reduction in neonates across all CO reduction scenarios. The greatest magnitude of change occurred between neonates and infants, suggesting the greatest developmental changes impacting propofol clearance in the first year of life. Figure 2 shows that higher percentage CO reductions resulted in greater relative percentage reductions. The impact of CO reductions across age groups was greatest when CO was reduced by 50% with relatively lower percentage clearance reduction across age group when CO reduction was limited to 20%.

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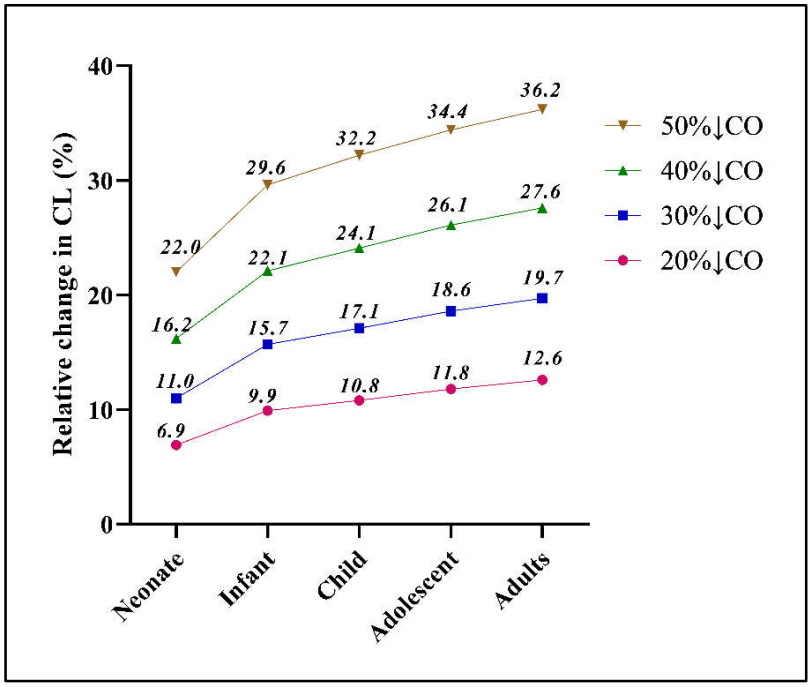

Figure 2. Relative percentage change in systemic clearance of propofol under reduced cardiac output condition across age groups.

Brown inverted triangles and line; green triangles and line; blue squares and line; red circles and line represent relative change in clearance with 50%; 40%; 30%; 20% cardiac reduction respectively. Numbers are calculated percentage change (decrease) in mean clearance (CL) following corresponding reduced cardiac output (CO) as described in Supplemental Materials, Section 2) [27-38].

3.3. Impact of Reduced Cardiac Output on Attainment of Propofol Target Concentrations

Under normal CO conditions, predictions fell within the target concentration at 2 hours of infusion to safely maintain anesthesia (3, 2.4 - 3.75 μg/mL) [39]. All reduced CO conditions resulted in raised plasma concentrations at 2 hours after infusion in all age groups, however, under 20 and 30% reduced CO conditions, the predicted mean plasma concentrations remained within 80 and 125%, but raised above the upper limit (125%) under 40 and 30% reduced CO conditions in all age groups (Figure 3).

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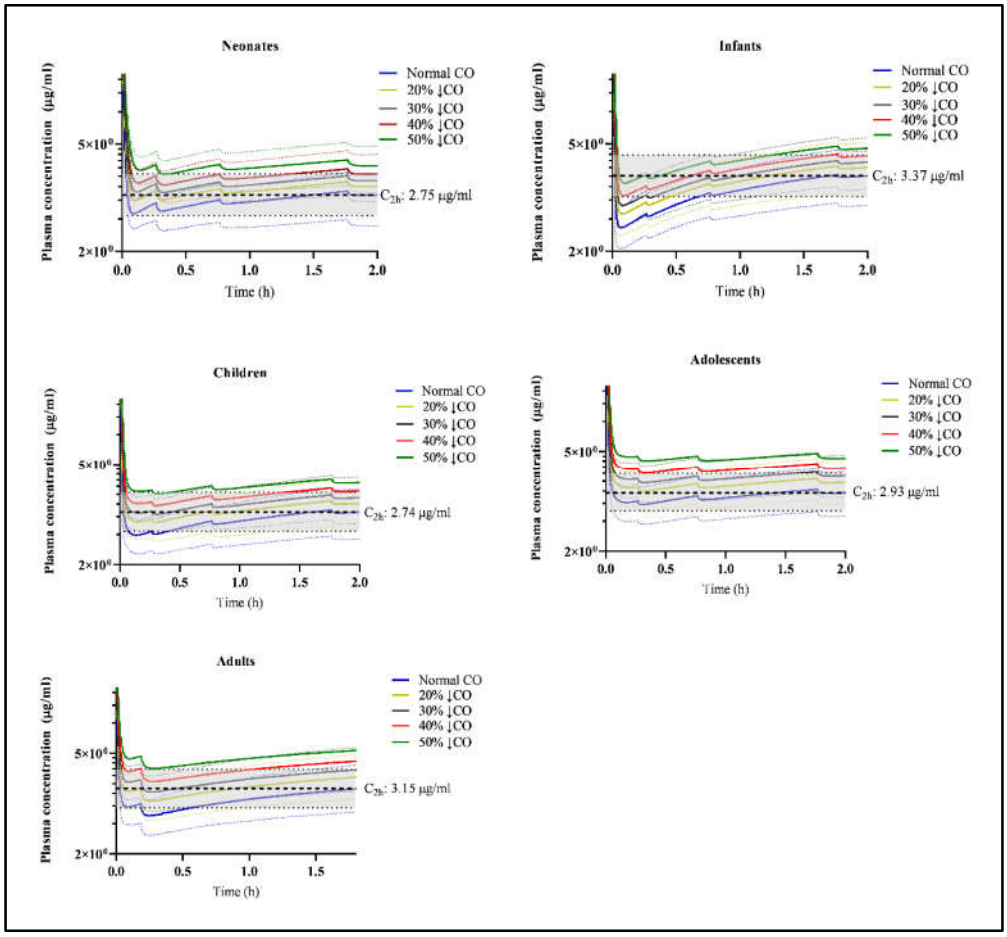

Figure 3. Simulated propofol plasma concentration under various cardiac output conditions.

Solid blue, yellow, black, red and green lines represent the predicted mean plasma propofol concentration under normal cardiac output (CO); 20%; 30%; 40% and 50% reduced CO respectively. Dotted blue, yellow, black, red and green lines represent the predicted 5th and 95th percentile of the corresponding mean predicted propofol plasma concentration. Bold black dashed line is plasma concentration achieved at 2 hours, the grey shaded area bordered by thin black dashed line is ± 20% of plasma concentration achieved at 2 hours.

3.4. Dose Reduction Exploration to Achieve Target Concentrations in Reduced Cardiac Output Conditions.

Figure 4 shows that dose reduction of 40 and 50% reduced CO conditions resulted in predicted plasma concentrations within the target range in all age groups. A 15% reduction of total dose administered (Table 1) was sufficient to result in target attainment in neonates, infants, and children, whereas - in adolescents and adults - a 25% dose reduction (Table 1) was required to achieve similar target concentrations (Figure 4).

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Table 1. Dosing models and optimized dosing strategy under reduced cardiac output conditions [39,40].

Population	Model used	Dose (mg/kg/h)	Duration (min)	Optimized dose (mg/kg/h)	% Dose Reduction
Neonates	Morse [39]	2*	induction	1.7*	15%
		9	15	7.7	
		7	30	6.0	
		6	60	5.1	
		5	120	4.3	
Infants	Morse [39]	2.5*	induction	2.1*	15%
		11	15	9.4	
		10	30	8.5	
		9	60	7.7	
		8	120	6.8	
Children	Morse [39]	2.5*	induction	2.1*	15%
		13	15	11	
		12	30	10	
		11	60	9.4	
		10	120	8.5	
Adolescents**	Morse [39]	2.5*	induction	1.9*	25%
		13	15	9.8	
		12	30	9.0	
		11	60	8.3	
		10	120	7.5	
Adults	Robert [40]	1*	induction	0.8*	25%
		10	10	7.5	
		8	10	6	
		6	2	4.5	

**: unit in mg/kg; **: dosing strategy in children implemented. The optimized doses are under 40 and 50% CO reduced conditions*

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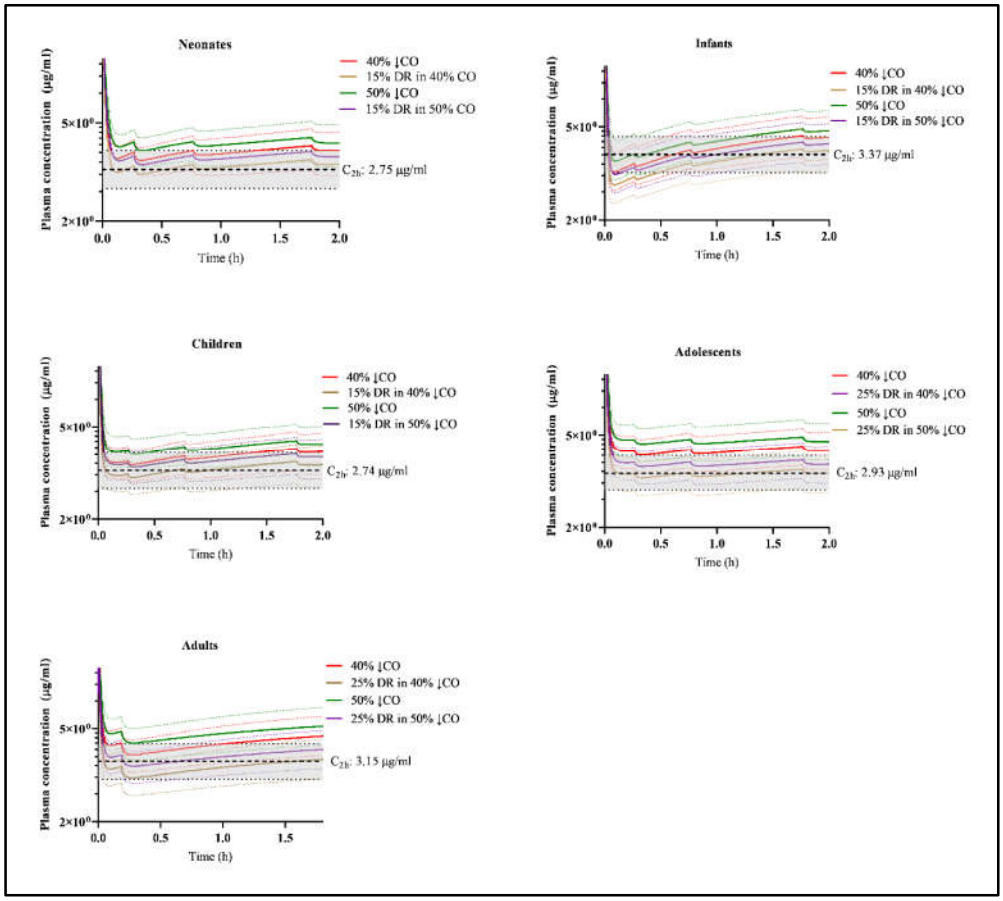

Figure 4. Simulated plasma propofol concentrations under various cardiac output conditions. Solid red and green lines represent the predicted mean plasma concentration of propofol at 40% and 50% reduced cardiac output (CO). Solid brown and purple line represent the predicted mean plasma concentration of propofol at 40% and 50% reduced CO following 15% or 25% dose reduction. Dotted red, green, brown and purple lines represent the predicted 5th and 95th percentile of corresponding predicted plasma concentration of propofol. Bold dashed broken line is plasma concentration achieved at 2 hours, the grey shaded area bordered by thin black dashed line is ± 20% of plasma concentration achieved at 2 hours. CO: cardiac output; DR: dose reduction.

4. Discussion

PBPK models become increasingly important to assess pharmacokinetics in special populations with complex pathophysiological conditions [15-17]. This is particularly important in pediatrics, whose immature physiology may already imply altered pharmacokinetic properties compared to adults. Treatment strategies may be further complicated by pathophysiologic events, like low CO [16]. Clinically, children are exposed to propofol in low CO conditions, such as neonatal asphyxia and TH, after cardiac surgery, or heart failure [5,6,7]. The effect of reduced CO on propofol pharmacokinetics has been described in adults [20], while the combined effect of age and low CO was not yet well explored.

The propofol models used in this analysis were optimized from a published model (Michelet et al.) [22], and satisfactorily recovered pharmacokinetic profiles and estimated clearance parameters reported for children and adults (Supplementary Materials, Figure S1 and Table S3) [27-38]. In adults, total propofol clearance has been reported with some variability with a clearance of 1.54, 2.2 or 2.64 L/min [20,41,42]. These are greater than hepatic perfusion (0.8-1.2 L/min) [43], and similar to the model predicted clearance in this analysis, implementing the Robert et al. model [40] (1.66 ± 0.45 L/min; Supplementary Materials, Table S4). In children, applying the Morse et al. model [39], the model predicted systemic clearance ranged from 0.048 ± 0.02 to 1.58 ± 0.5 L/min between neonatal life to

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adolescence (Supplementary Materials, Table S5), similar to literature-reported values across pediatric age group (0.034 to 1.1 L/min) [32-35].

The E_H and E_R ratio of propofol was reported to be 0.87 ± 0.09 and 0.7 ± 0.13 respectively in adults [6]. It was predicted to be 0.75 ± 0.2 and 0.55 ± 0.22 in adults in the current study (Figure 1). As the renal pathway constitutes a significant portion of propofol clearance, it is also important to consider the impact of low CO on renal extraction of propofol [8].]The effect of age on the E_H of drugs has been previously reported when Salem et al. showed that the E_H may increase with age [44]. This age-dependent alteration was attributed to the disproportionate maturation of E_H-impacting physiological and biochemical parameters occurring after birth, such as maturation of the fraction of unbound drug, intrinsic clearance of unbound drug, or hepatic blood flow [44]. A similar principle can be expected to impact the metabolic clearance occurring in the kidneys and therefore the propofol E_R. The extent to which either of these parameters impact the extraction rate depends on the susceptibility of the drug clearance to alteration of given parameters. For example, Takizawa et al. showed that - despite high protein binding of propofol - hypoalbuminemia did not significantly alter its E_H [45]. In contrast, CO is documented to affect propofol clearance in adults [3,6,10].

Age-dependent alterations in propofol E_H and E_R were not yet explored. The current study demonstrates that both E_H and E_R increase with age: neonates have a EH within the intermediate extraction range (0.34 ± 0.18) to evolve to high extraction (0.75 ± 0.2) in adults. Related to E_R, neonates have a low extraction range (0.12 ± 0.06) to evolve to intermediate extraction (0.55 ± 0.2) in adults (Figure 2). This confirms the midazolam pattern, with an E_H low extraction (0.02) pattern at birth and intermediate extraction (6.0) during adulthood [44].

Non-maturational parameters can also impact clearance and extraction ratios. For instance, CO changes and the resultant reduction in organ perfusion may influence the extraction capacity of such organs if the drug behaves as a high extraction compound. The impact of various degrees of CO reduction observed in this current study showed that the proportional impact of CO on clearance depends on age, with a lower impact in neonates and young infants compared to adults (Figure 3). This re-illustrates the fact that a neonate is not a small adult [1]. Furthermore, an age-dependent proportional impact of the severity in CO reduction on propofol clearance was observed (Figure 3). This is consistent with the fact that propofol possess some level of extraction capacity in early life, and this capacity becomes greater with age (Figure 1).

The pathophysiological effect of low CO as observed in clinical conditions such neonatal asphyxia undergoing TH or pediatric patients with heart failure on propofol clearance requires considerations on how this impacts propofol dosing. In neonates, propofol is an intermediate extraction drug and reduced CO alters clearance, though the extent of change increases with age. Being aware that several dosing models are available, such as the Eleveld [46] and McFarlan [47] models, the Morse model was applied in this current study, and targets propofol plasma concentration of 3 (80-125%) µg/mL [39]. Applying this target, CO reduction (up to 30%) did not result in mean plasma concentrations outside of this target range across all age groups (Figure 3).

However, further reduced CO (by 40 or 50%) resulted in mean plasma concentrations above the upper limit of the target concentration (Figure 3), which increases the risk of side effects associated with raised propofol concentrations such as hypotension [39]. This is consistent with Leslie et al., which reported that in hypothermic (34°C) subjects, the propofol concentrations were significantly raised compared to normothermic (37°C) subjects [3]. However, as this study did not measure the CO in the hypothermic subjects, it is difficult to link the reduced CO to propofol clearance [3].

The impact of up to 50% CO reduction on the achieved plasma concentration is particularly crucial in neonates undergoing TH as right and left ventricular output in asphyxiated TH cases are 108 (-51%) and 107 (-52%) significantly lower when compared to normative (224 and 222 mL/kg/min) values [48]. Along the same line, a 33% CO reduction has been documented in TH patients in a paired study design (169 versus 254 mL/kg/min) [5].

A 15% dose reduction in neonates, infants and children under 40% and 50% reduced CO conditions was sufficient to result in mean plasma concentrations within the target range (Figure 4). In adolescents and adults, a 25% dose reduction was required to achieve similar exposure. The greater amount of dose reduction in adults and adolescents compared to the younger age groups reflects the higher magnitude of the effect of CO on clearance in adults and adolescents.

While the result from this study provides valuable insight into the impact of reduced CO on clearance and dosing strategies of propofol across age groups, a limitation of the study was the inability to validate the model in patients with reduced CO. Though there are published studies showing the impact of reduced CO on propofol pharmacokinetics, the dosing methods used in these studies were target concentrated based making it impossible to simulate a particular dosing strategy as one would expect for manual infusions [20,49]. However, it does support the practices to be much more cautious and vigilant on propofol in low CO patients, making the collection of pharmacokinetic samples in pediatric studies even more challenging.

In conclusion, we have shown that - using a PBPK modelling approach - that the hepatic and renal extraction of propofol is predicted to change with age and the impact of reduced CO on propofol clearance is age-dependent with the greater impact in adults. Also, age group specific dosing optimizations are required in low CO conditions.

Supplementary Materials: section 1: methodology for optimization and validation of the Michelet propofol model; section 2: optimization of the propofol model in adults and children; Supplemental Figure 1; Supplemental Tables S1, S2, S3, S4 and S4

Author Contributions:, K.A., M.Y.A and O.O.; methodology, M.Y.A., R.M, O.O.; data curation, K.A., R.M., O.O.; writing—original draft preparation, M.Y.A. and O.O.; writing—review and editing, K.A., R.M.; supervision, K.A. and O.O. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement: Ethical review and approval were waived for this study as this was an additional analysis of previously published data.

Data Availability Statement: The data are available upon reasonable request by an e-mail to the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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