

ARTICLE

A physiologically-based pharmacokinetic modeling approach for dosing amiodarone in children on ECMO

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Abstract

Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass device commonly used to treat cardiac arrest in children. The American Heart Association guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care recommend using amiodarone as a first-line agent to treat ventricular arrhythmias in children with cardiac arrest. However, there are no dosing recommendations for amiodarone to treat ventricular arrhythmias in pediatric patients on ECMO. Amiodarone has a high propensity for adsorption to the ECMO components due to its physicochemical properties leading to altered pharmacokinetics (PK) in ECMO patients. The change in amiodarone PK due to interaction with ECMO components may result in a difference in optimal dosing in patients on ECMO when compared with non-ECMO patients. To address this clinical knowledge gap, a physiologically-based pharmacokinetic model of amiodarone was developed in adults and scaled to children, followed by the addition of an ECMO compartment. The pediatric model included ontogeny functions of cytochrome P450 (CYP450) enzyme maturation across various age groups. The ECMO compartment was parameterized using the adsorption data of amiodarone obtained from ex vivo studies. Model predictions captured observed concentrations of amiodarone in pediatric patients with ECMO well with an average fold error between 0.5 and 2. Model simulations support an amiodarone intravenous (i.v.) bolus dose of 22 mg/kg (neonates), 13 mg/kg (infants), 8 mg/kg (children), and 6 mg/kg (adolescents). This PBPK modeling approach can be applied to explore the dosing of other drugs used in children on ECMO.

Study highlights**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**

Amiodarone is widely used in emergency situations to treat ventricular tachyarrhythmias in adult and pediatric patients. Currently, there are no dosing recommendations for amiodarone to treat ventricular tachyarrhythmias in pediatric patients on ECMO.

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WHAT QUESTIONS DID THIS STUDY ADDRESS?

This study utilized a PBPK model parameterized with ex vivo ECMO data to account for the drug interaction with the ECMO components and provide dosing recommendations for amiodarone in pediatric ECMO patients of various age groups.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This approach successfully determined amiodarone dosing in children on ECMO across the pediatric age spectrum.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

This study showed that ex vivo ECMO experiments can be used to parameterize the PBPK model to account for the interaction of drug with ECMO components and predict optimal dosing in the pediatric ECMO population. This approach can be easily adapted to other common forms of extracorporeal techniques such as dialysis.

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass device that supports individuals with refractory heart and lung failure.¹ In pediatrics, ECMO is commonly used to treat cardiac arrest, acute respiratory distress syndrome, and heart and lung transplantations.² Specifically, the use of ECMO in pediatric cardiac arrest patients refractory to CPR is increasing due to better survival rates.³ However, one of the challenges in using ECMO in pediatric cardiac arrest is understanding and compensating for the effect of the extracorporeal circuit on drug pharmacokinetics (PK). Drug PK in ECMO patients can be altered due to the adsorption of drugs to ECMO components, physiological changes associated with ECMO (e.g., inflammation), and organ dysfunction due to the underlying critical illness.^{4–6} This change in drug PK may result in a difference in optimal dosing in this setting when compared with non-ECMO patients.

The American Heart Association (AHA) guidelines for CPR and emergency cardiovascular care (ECC) recommend using amiodarone (5 mg/kg bolus dose, intravenous (i.v.) or intraosseous) as a first-line agent to treat ventricular arrhythmias in children.⁷ However, due to its high lipophilicity ($\text{LogP}=7.58$),⁸ high protein binding (96%),⁹ and high percentage of the ionized fraction at physiological pH (87.3%),⁸ amiodarone has a high propensity for adsorption to the ECMO components leading to altered PK in ECMO patients. In an ex vivo ECMO circuit model, we previously showed that ~78% of the administered amiodarone dose was adsorbed onto the ECMO circuit components within 30 min of administration.¹⁰ Furthermore, Lescroart et al.¹¹ reported a 32% decrease in the area under the curve (AUC)

and 42% decrease in C_{\max} of amiodarone administered to pigs with potassium-induced cardiac arrest and connected to ECMO. These data indicate that amiodarone concentration and PK are significantly altered in ECMO patients, and there is an unmet medical need to develop an optimal dose of amiodarone in pediatric cardiac arrest patients on ECMO.

Physiologically-based pharmacokinetic modeling (PBPK) is a mathematical modeling technique that integrates drug properties (e.g., LogP, protein binding, clearance, etc.) and population information (e.g., organ size and blood flow) to predict the effect of various parameters (e.g., age, genetic variants, disease state etc.) on drug exposure.¹² PBPK models are mechanistic in nature and structured to represent physiologically relevant spaces, with each virtual “organ” parameterized with differential equations describing the disposition of drugs within the compartment.⁴ Using data from ex vivo studies, an ECMO “organ” can be linked and parameterized to the PBPK model.⁴ This ECMO PBPK model can be used to predict the drug PK in ECMO patients and determine the optimal dosing in this vulnerable population. We previously used this approach to determine the optimal dosing of flucnazole in critically ill pediatric patients on ECMO.⁴

In the current study, we developed a PBPK model of amiodarone in adults and extrapolated it to children. The pediatric model was evaluated with opportunistic clinical data. We then added an ECMO compartment to the amiodarone pediatric PBPK model and parameterized the model using the data from ex vivo studies. The final pediatric ECMO PBPK model was verified using amiodarone PK data in pediatric patients on ECMO from two different clinical studies. The verified pediatric ECMO PBPK model

was used to predict the optimal dosing of amiodarone in children on ECMO across the pediatric age spectrum.

METHODS

Overview of PBPK model development workflow

We followed the FDA guidance on PBPK model development and workflow in children to build our pediatric PBPK model.¹³ We first developed an adult PBPK model of amiodarone and verified the model prediction using amiodarone PK data from 5 adult PK studies.^{14–18} Model acceptance criteria were defined as: (1) Greater than 80% of observed concentrations captured within the 90% prediction interval of the model simulated concentrations; and (2) Average fold error (AFE) values of simulated concentrations within twofold of observed values.

Once the adult model met the acceptance criteria, we scaled the model to children. In pediatric model, we retained the physicochemical and drug-specific absorption, distribution, metabolism, and elimination (ADME) parameters of amiodarone and replaced the anthropomorphic and physiological information with pediatric values using established age-dependent algorithms in the model software (PK Sim®, Version 9.1, Open Systems Pharmacology Suite, Bayer Technology Services, Leverkusen, Germany). Pediatric model predictions were compared with observed data from a published pediatric amiodarone PK study¹⁹ and evaluated using the same acceptance criteria as for adults.

After confirming that the model acceptance criteria for the pediatric model were met, we added an ECMO compartment to the pediatric PBPK model to form the ECMO PBPK model. The ECMO compartment was parameterized using the adsorption data from our previously published ex vivo study.¹⁰ Model predictions in children on ECMO were evaluated using the data from Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care (POPS) trial¹⁹ and Primary Children's Hospital (PCH) opportunistic PK study.

Software

PBPK modeling was performed in PK Sim® and MoBi® (Version 9.1 Build 2, Open Systems Pharmacology Bayer Technology Services, Leverkusen, Germany). We used R Statistical Software (v4.2.2; R Core Team 2022) for the calculation of amiodarone rate constants using the ex vivo data and GraphPad Prism® (Version 9, GraphPad LLC, CA, USA) for data visualization. Amiodarone PK

parameters area under the curve (AUC_{0-24}) and maximum plasma concentration (C_{max}) in pediatric patients with or without ECMO, were calculated using noncompartmental method using PKanalix® (version 2021R1, Antony, France, Lixoft SAS, 2021. <http://lixoft.com/products/PKanalix/>). The area under the curve was calculated using the Linear Trapezoidal Linear method of PKanalix®. We used the software Plot Digitizer® (version 2.6.8) to extract the concentration versus time data from published PK papers used in model evaluation.

Clinical data

The clinical studies used for the adult PBPK model include two datasets with i.v administration: Cushing et al.¹⁴ – single 150 mg infused over 10 min, Ujhelyi et al.¹⁵ – 5 mg/kg infused over 15 min, and three datasets with oral administration: Meng et al.¹⁶ – 600 mg tablet, Teng et al.¹⁷ – 600 mg tablet, Andreasen et al.¹⁸ – 400 mg tablet. The datasets were selected based on the route of administration, study participant demographics, clinical characteristics, and bioanalytical method used (Table 1). The individual datafiles of each extracted study are provided as Data S1. The PBPK model was verified with oral datasets because our pediatric observed data included patients receiving amiodarone by both i.v and oral routes of administration.

We evaluated the amiodarone pediatric PBPK model using the clinical PK data obtained from the PK samples collected from the Pediatric Trials Network (PTN)-sponsored Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care (POPS) trial.¹⁹ POPS (ClinicalTrials.gov: NCT01431326; protocol-NICHHD-2011-POP01) is a multicenter, prospective, PK, and safety study of understudied drugs administered to children (<21 years old) per standard of care.¹⁹ All dosing was at the discretion of the treating caregiver and samples specifically designated for PK analysis were collected opportunistically at the time of routine lab draws. The completely deidentified PTN PK analysis dataset was accessed through the Eunice Kennedy Shriver Data and Specimen Hub (DASH). The PTN PK analysis dataset was generated and formatted by the EMMES Corporation, MD, USA, the PTN Data Coordinating Center, and Duke Clinical Research Institute, NC, USA. Missing clinical data were imputed using the last value carried forward. For infants and children >120 days old, a gestational age of 40 weeks was imputed.

We evaluated the amiodarone pediatric ECMO PBPK model using two datasets: (1) clinical PK data from children on ECMO in the POPS study and (2) clinical PK data obtained from an opportunistic PK study enrolling

TABLE 1 List of clinical studies used in PBPK model development and qualification.

S.No	Author	Amiodarone dose	Route of administration	Number of participants	Bioanalytical method	References
Datasets used for the model development						
1	Cushing et al.	150 mg	Intravenous infusion at a rate of 10 mL/min for 10 min of 1.5 mg/mL solution	88	LC/MS/MS	14
2	Ujhelyi et al.	5 mg/kg	Intravenous infusion over 15 min	11	HPLC with UV detection	15
Datasets used for the model qualification						
3	Meng et al.	600 mg	Three 200 mg tablets given orally	30	LC/MS/MS	16
4	Andreasen et al.	400 mg	Two 200 mg tablets given orally	7	HPLC with UV detection	18
5	Teng et al.	600 mg	One 600 mg tablet given orally	13	HPLC with UV detection	17

children on ECMO (University of Utah, Institutional Review Board Number: 00138310) that was conducted at PCH, Salt Lake City, UT. This study enrolled children 0–18 years of age who were supported with ECMO and prescribed one of the study drugs of interest per standard of care. Dosing was at the discretion of the treating provider, and PK samples were collected at times of routine lab draws. For patients in both datasets, the ECMO circuit did not include hemofilter.

The plasma concentrations of amiodarone in the POPS study were quantified by the PTN central laboratory (OpAns LLC, Durham, NC) using a validated high-performance liquid chromatography-tandem mass spectrometry (LC–MS/MS) assay. The plasma concentrations of amiodarone in the opportunistic study at PCH were quantified by ARUP Laboratories (ARUP, Salt Lake City, UT) using a validated LC–MS/MS assay. The linearity range was between 5–5000 ng/mL for PTN central laboratory assay and 300–6000 ng/mL for ARUP assay. The lower limit of quantification of 5 ng/mL for amiodarone for PTN central laboratory assay. The method validation parameters related to accuracy and precision were within the limits outlined by FDA guidance.²⁰

Adult PBPK model development

Model development and optimization

We used the standard whole-body 15-organ PBPK model implemented in PK Sim®.^{21,22} The physicochemical parameters and ADME data for amiodarone were collected from the literature (Table 2).^{23–25} For model predictions, we created a virtual adult population ($N=1000$) using the

demographic (sex, age, and weight) distribution reported in the adult PK studies of amiodarone selected from the development and verification datasets. We incorporated a 20% standard deviation based on literature to the fraction of the periportal zone to impart variability in the virtual pediatric populations.²⁶ We also included the inter-individual variability for fluid recirculation flow rates²⁷ and plasma protein scale factor²⁸ in the model based on literature.

For the i.v. amiodarone PBPK model, the cellular permeabilities for the barriers between interstitial and intracellular space for amiodarone were calculated from the physicochemical properties using the PK Sim® standard method.²⁹ Amiodarone is mainly eliminated by hepatic metabolism, which was considered the only elimination mechanism. The total hepatic clearance value of amiodarone was obtained from the literature and added to the model.²⁵ The total hepatic clearance value was partitioned a priori, with 50% of the total clearance attributed to CYP3A4 and 50% attributed to CYP2C8 based on literature-reported enzyme activities.³⁰ We compared the i.v. amiodarone PBPK model predictions with the observed data reported in PK studies by Cushing et al.,¹⁴ and Ujhelyi et al.¹⁵ We optimized the model parameters lipophilicity and unbound fraction of amiodarone using the parameter identification toolkit available in PK Sim®.

We developed the oral amiodarone PBPK model based on the i.v. PBPK model. The physicochemical and physiological parameters for the oral amiodarone PBPK model were retained from the i.v. model. The oral amiodarone PBPK model performance was evaluated by comparing the model predictions with the observed data reported in PK studies by Meng et al.,¹⁶ Teng et al.,¹⁷ and Andreasen et al.¹⁸

Parameter	Literature/ Calculated	Optimized	References
Molecular weight (g/mol)	645.3		23
Compound type	Acid		23
LogP	7.57	7.96	23
pKa	6.56		23
Solubility pH 7 (mg/L)	4.76×10^{-3}		23
Plasma protein	Albumin		23
Fraction unbound	2×10^{-4}	6×10^{-6}	23
Specific Intestinal Permeability (cm/min)	1.68		24
Hepatic clearance (L/min/kg) ^a			
CYP3A4 (50%)	0.13		25
CYP2C8 (50%)			

^aTotal hepatic clearance partitioned between CYP3A4 and CYP2C8.

TABLE 2 Drug-specific parameters used in PBPK model building.

Model evaluation

We evaluated the adult population PBPK model by calculating the AFE of observed amiodarone plasma concentration versus time data to the simulated data. We considered the model final if the mean \pm SD of the simulated data captured >80% of the observed data within 90% prediction interval and the AFE values between observed and predicted plasma concentration were between 0.5 and 2.

Pediatric PBPK model development

Anatomical and physiological parameterization

We used the pre-established age-dependent algorithms in PK Sim® to generate the anatomical and physiological parameters, including body weight, height, organ weights and volumes, blood and lymph flows, cardiac output, total body water, lipid and protein concentrations.^{21,22}

Scaling of hepatic clearance

We obtained the total hepatic clearance of amiodarone from the published adult clinical PK study.²⁵ The total hepatic clearance was partitioned between CYP3A4 and CYP2C8 enzymes. We used the default setting of hepatic CYP3A4 and CYP2C8 ontogeny in PK Sim® for the pediatric population. Enzyme activity of CYP3A4 is, on average, 12% of the adult value at term, increases to 80% by the age of 1.3 years, and reaches adult activity by 5 years.³¹ Enzyme activity of CYP2C8 was observed in early infants

with an approximately 8-fold difference in CYP2C8 levels between individuals less than 35 days postnatal age and >35 days to 18 years.³²

Modification of gastrointestinal parameters in virtual pediatric population

The PK Sim® default values for gastric emptying time (GET) and small intestinal transit time (SITT) were 15 min and 2.1 h, respectively. However, to reflect the actual clinical values in humans, we replaced the PK Sim® default values with reported values of GET and SITT, 3.45 ± 0.5 h (mean \pm SD) and 4.38 ± 1.43 h (mean \pm SD) respectively, in a study involving 215 healthy adult volunteers.³³

Virtual pediatric population for evaluating pediatric PBPK model

A virtual pediatric population ($N=1000$) ranging from neonates to 18 years was created using PK Sim®. Race and gender distributions in the virtual populations were based on those observed in the pediatric POPS PK trial. To evaluate the pediatric amiodarone PBPK model's predictive accuracy, we calculated the number of data points of amiodarone levels from POPS PK trial data that are out of 90% prediction interval and the AFE of observed amiodarone plasma concentration versus time data. We considered the model final if the mean \pm SD of the simulated data captured >80% of the observed data within 90% prediction interval and the AFE values between observed and predicted plasma concentration were between 0.5 and 2.

ECMO PBPK model

The pediatric PBPK model was exported into MoBi[®] where a new compartment representing the ECMO circuit was added. Pulmonary blood was partitioned with 80% allocated to the ECMO compartment and 20% allocated to the lungs to assign the flow in and out of the ECMO compartment. The ECMO compartment was assigned a volume of 400 mL to reflect the standard volume of blood required to prime the ECMO circuit. Based on data from our ex vivo studies, a clearance parameter, rate constant (k) of the amiodarone adsorption by ECMO circuit, was added for the ECMO compartment. The rate constant k was calculated using linear regression from the amiodarone concentration versus time data obtained from the ex vivo ECMO circuit experiments.¹⁰ We used three types of data, concentration versus time, log-concentration versus time, and percentage recovered versus time to calculate the k . The k obtained from the regression line with percentage recovery versus time data was used in the final ECMO PBPK model (Table S1). Sensitivity analysis of all amiodarone ECMO PBPK model parameters was performed on the PK parameter C_{max} to evaluate the influence of model parameters on predictions. The final ECMO PBPK model was evaluated with amiodarone PK data obtained from children on ECMO from the POPS study. Population simulations were performed using the ECMO PBPK model, and the model predictions were compared with observed clinical data. The ECMO PBPK model was then used to simulate various amiodarone dosing regimens to determine the optimal dosing in pediatric patients with different age groups. The various age groups that were simulated are neonates (0 days to 1 month), infants (1 month to 1 year), children (1 year to 12 years), adolescents (13 years through 17 years). For each pediatric ECMO population age group, doses were simulated starting from 5 mg/kg and increasing at 1 mg/kg increments. The simulations were continued for each age group until the AUC_{0-24} targets were achieved. All dosing regimens in simulations were single i.v. bolus doses.

Assessment of dose–exposure relationship

Amiodarone is a class III antiarrhythmic and works primarily by blocking potassium currents that cause repolarization of the heart muscle during the third phase of the cardiac potential.³⁴ Currently, there is no established relationship between drug concentration and therapeutic response for short-term i.v. use of amiodarone.³⁴ Several studies with long-term oral administration suggested a plasma concentration range between 0.5 and 2.5 mg/mL appears to be the most effective.³⁵ Ramusovic et al. in 2013

reported direct evidence of the antiarrhythmic efficacy of amiodarone after i.v. bolus administration to pediatric patients with ventricular fibrillation and ventricular tachycardia. They reported a median maximum serum concentration of 4.7 mg/L after a 5 mg/kg bolus concentration followed by a 10 mg/kg/day maintenance dose.³⁶ Therefore, we considered 4.7 mg/L as the target C_{max} value for amiodarone to show antiarrhythmic efficacy in pediatric patients. In addition to the target C_{max} , we also matched simulated AUC_{0-24} to the median AUC_{0-24} following the AHA-recommended dose of 5 mg/kg; the target median AUC_{0-24} was 661.9 mg/L*min - neonates, 670 mg/L*min - infants, 699.6 mg/L*min - children, and 716 mg/L*min - adolescents. AUC_{0-24} represents the 24 h exposure of amiodarone after the first i.v. bolus dose.

RESULTS

Adult PBPK model evaluation

The adult PBPK model of amiodarone adequately predicted the PK of amiodarone for all dosing regimens and routes of administration. We optimized our adult model using the adult development datasets by changing the parameters lipophilicity (Log P) and fraction unbound. When we compared our optimized model with the development and independent evaluation datasets, the optimized model met our predetermined acceptance criteria (Figure 1, Table 3). We then compared our oral model predictions with the observed data from oral studies, and they met our predetermined acceptance criteria (Figure 2, Table 3). Our model slightly underestimated observed plasma concentrations after i.v. administration (Figure 1) and slightly overestimated observed plasma concentrations after oral administration (Figure 2).

Pediatric PBPK model

To evaluate the pediatric PBPK model's predictive accuracy, we used 99 amiodarone plasma concentrations from 33 participants in the POPS study. Participants received a median of six doses (range 1–18) via oral and i.v. administration at a median dose of 4.8 mg/kg (range 0.03 to 125.5 mg/kg) for amiodarone. The demographic characteristics of the participants in the POPS study are provided in Table S2.

We generated a median and 90% prediction interval of amiodarone plasma concentrations for each individual in the POPS dataset because pediatric participants in the POPS study received different dosing regimens. We observed good model predictability when comparing

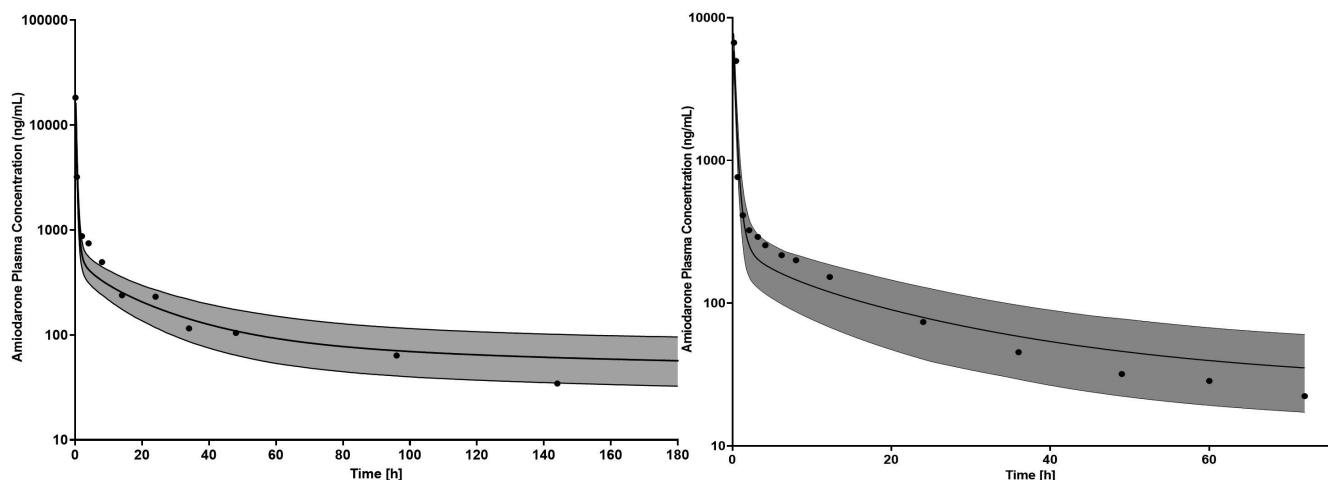


FIGURE 1 Adult optimized model. The physiologically-based pharmacokinetic model concentration-time predictions of amiodarone after intravenous injection doses of 150 mg (left panel) and 5 mg/kg (right panel). Solid black line represents the median predicted concentration; gray shaded area represents the 90% prediction interval; observed data from the adult development datasets^{14,15} are represented by solid circles.

S.No	Study	N	Dose	Average fold error (AFE)
Adult development datasets				
1	Ujhelyi et al.	11	5 mg/kg i.v. infusion	0.97
2	Cushing et al.	88	150 mg i.v. infusion	1.01
Adult verification datasets				
3	Teng et al.	13	600 mg oral	1.66
4	Meng et al.	30	600 mg oral	1.76
5	Andreasen et al.	7	400 mg oral	1.84

TABLE 3 Average fold error (AFE) in concentrations for all amiodarone adult PBPK models.

predicted and observed concentration-time data with only 4% (4/99) of observed data falling outside of the 90% prediction intervals on average for all plasma samples in the dataset. The number of observations and participants in each age group and the number of observations outside the 90% prediction interval are summarized in Table S3. The AFE of observed versus predicted amiodarone plasma concentrations for the pediatric PBPK model without ECMO for all 33 patients is provided in Table S4.

ECMO PBPK model

We added an ECMO compartment to the pediatric PBPK model to account for the loss of drug due to adsorption to the ECMO components. The amiodarone ECMO PBPK model was verified using the data obtained from five children on ECMO from the POPS study and two children from the PCH opportunistic study. The POPS study dataset for children with ECMO consisted of 14 amiodarone plasma concentrations, and the PCH opportunistic

study consisted of two amiodarone plasma concentrations (Table S2). The rate constant “k” was calculated as 3.3 h^{-1} and was included in the pediatric PBPK model with ECMO. The results from sensitivity analysis showed that ECMO-based model parameters ECMO volume, and ECMO rate constant “k” significantly influenced the PK parameter C_{\max} (Figure S1). We used the pediatric ECMO PBPK model to simulate concentration versus time profiles. Greater than 90% of observed data fell within 90% prediction interval, and the AFE value was between 0.5 and 2. The AFE of observed versus predicted amiodarone plasma concentrations for the pediatric PBPK model with ECMO for all seven patients is provided in Table S5. The graph showing the observed and model-predicted amiodarone concentrations of a representative pediatric patient with and without the ECMO compartment added to the model is provided as in Figure 3. The figures of the amiodarone ECMO model-predicted versus observed concentrations for all patients with ECMO from the POPS study are provided as Figure S2. The representative MoBi® file of the pediatric ECMO PBPK model is provided as

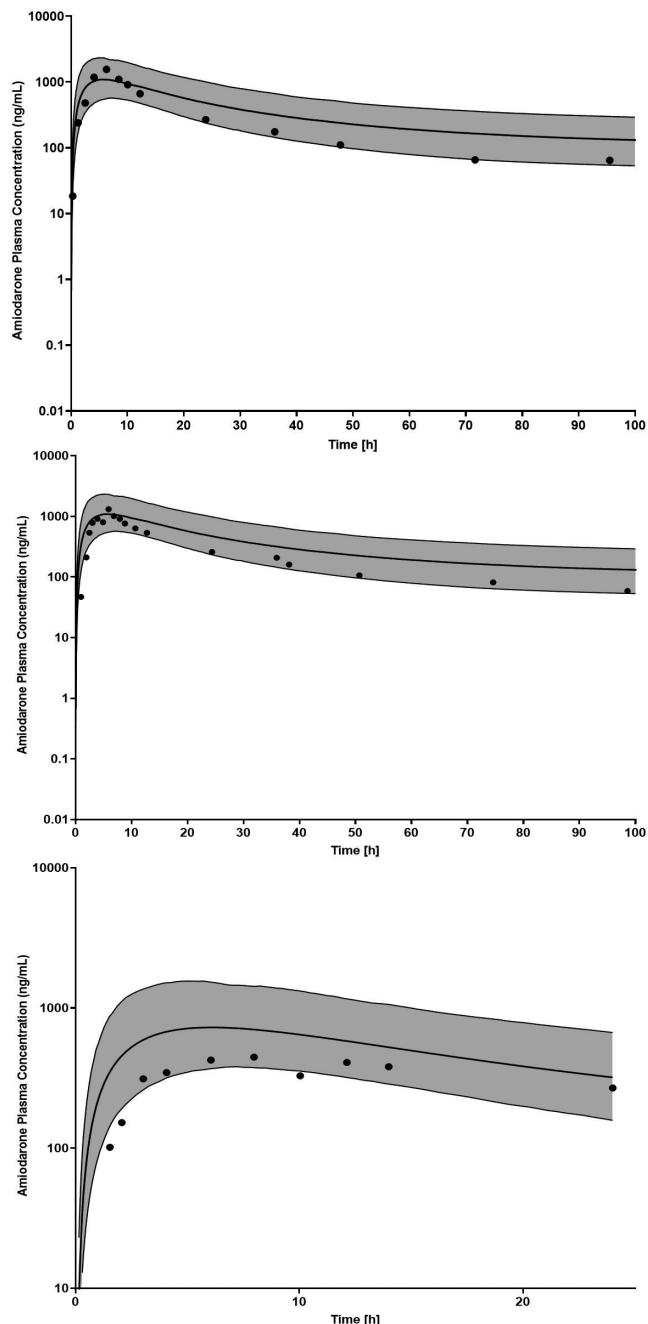


FIGURE 2 Adult verification model. The physiologically-based pharmacokinetic model concentration-time predictions of amiodarone after oral doses of 600 mg (top and middle panels) and 400 mg (bottom panel). Solid black line represents the median predicted concentrations; gray shaded area represents the 90% prediction interval; observed data from the adult verification datasets^{16–18} are represented by solid circles.

Data S2. Compared with the predicted AUC_{0-24} without ECMO, the predicted AUC_{0-24} with ECMO in all pediatric populations with AHA recommended dosing ranged from 22.9%–85.6% (Table S6).

We used the final pediatric amiodarone ECMO PBPK model to simulate dosing regimens that achieved our surrogate efficacy targets of C_{max} 4.7 mg/L and AUC_{0-24}

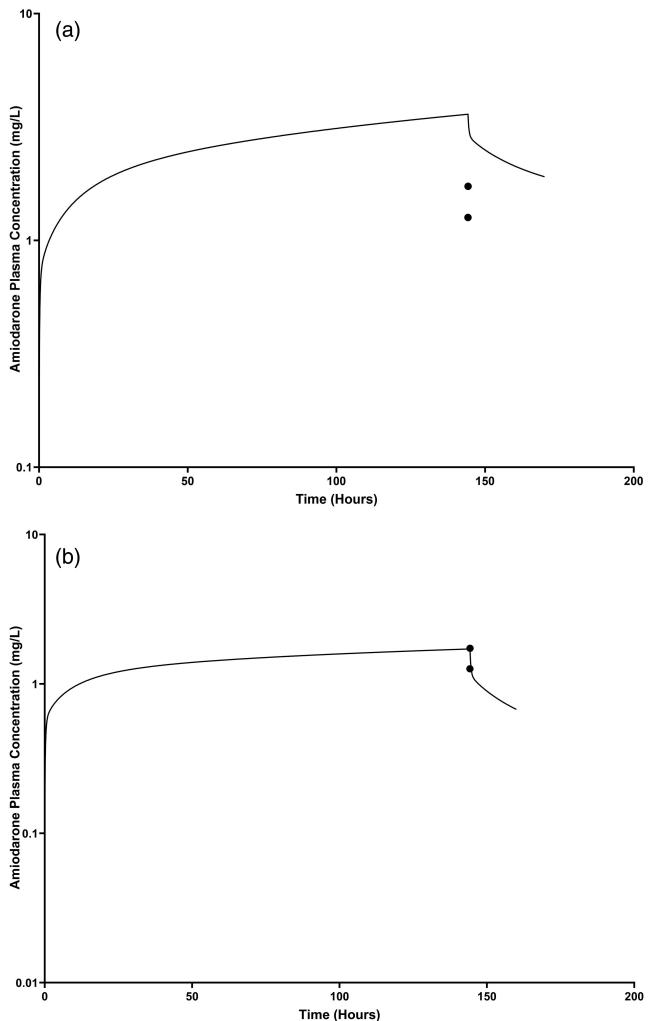


FIGURE 3 Pediatric extracorporeal membrane oxygenation (ECMO) physiologically-based pharmacokinetic model (PBPK) predictions and observed data from pediatric ECMO patients. (a). PBPK model simulation without ECMO compartment, (b). PBPK model simulation with ECMO compartment added. The representative pediatric patient received a 125.51 mg/kg dose of amiodarone as intravenous infusion for a duration of 144.27 h. Solid black line is median predicted concentration; observed data are represented by dark circles.

of 670 mg/L*min. Figure 4 compares, by age group, the predicted AUC_{0-24} after receiving the AHA-recommended 5 mg/kg loading dose versus the loading dose optimized to attain target exposure. The boxplots showing the C_{max} of amiodarone with AHA and optimized dose in children with ECMO are provided in Figure S3. The simulations suggest that the i.v. loading doses of amiodarone necessary to attain target exposure of AUC_{0-24} in pediatric patients on ECMO are as follows: neonates – 22 mg/kg, infants – 13 mg/kg, children – 8 mg/kg, and adolescents – 6 mg/kg. The simulated median C_{max} and AUC_{0-24} of amiodarone in pediatric ECMO populations of various age groups at all doses is provided in Table S7.

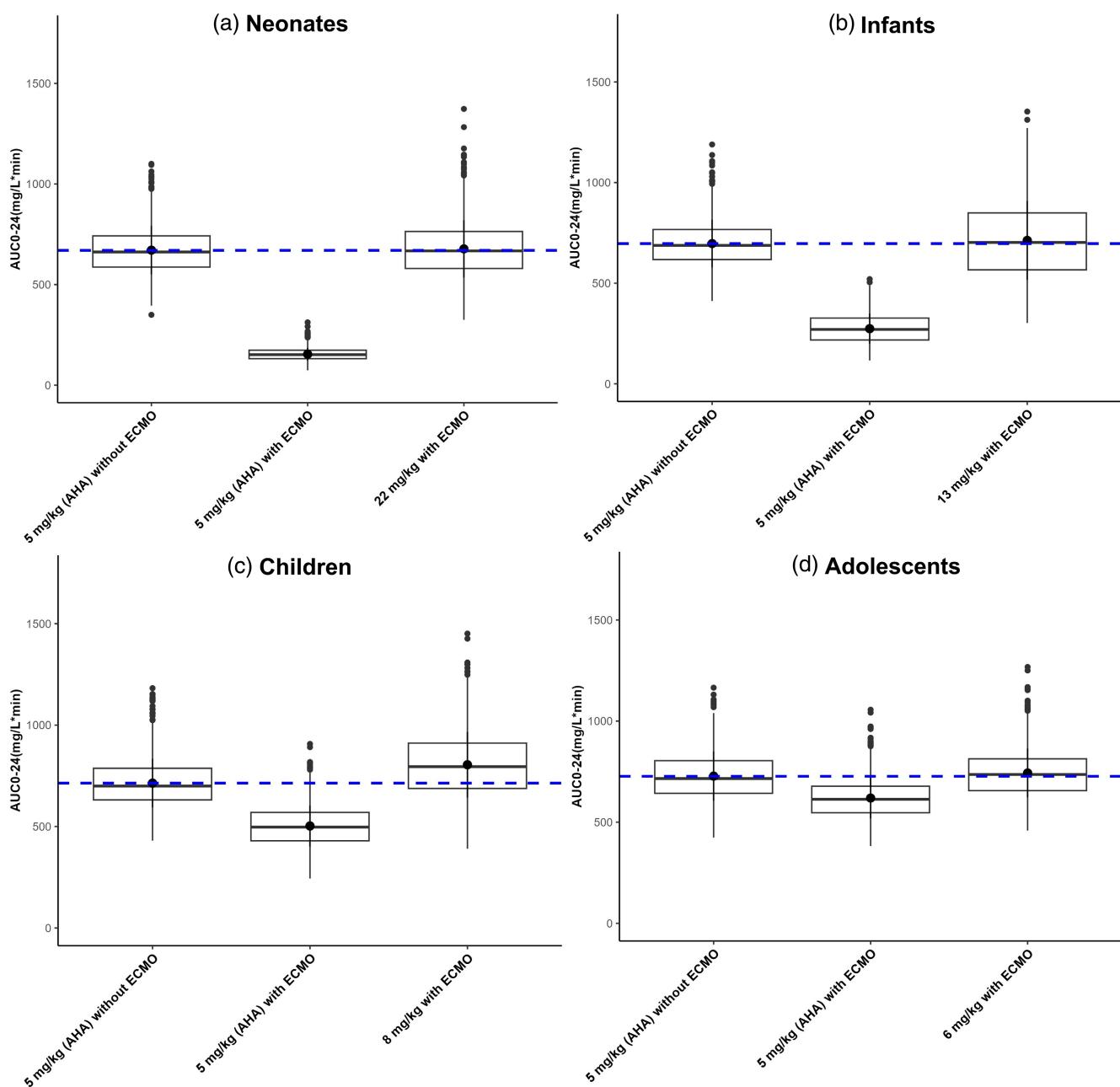


FIGURE 4 The extracorporeal membrane oxygenation (ECMO) physiologically-based pharmacokinetic model (PBPK)-predicted optimized amiodarone dosing and exposure in children on ECMO across the pediatric age spectrum. Solid line represents the median, box represents interquartile range, and whiskers represent 90% prediction interval. The solid circles represent the outliers in the data. Dosing achieved the median target area under the concentration-time curve (AUC_{0-24}) (blue dashed line) in simulated children on ECMO in the first 24 h of therapy. In each individual box plot, the boxplots refer to the following from left to right: AHA recommended dose of 5 mg/kg in pediatric patients without ECMO, AHA recommended dose of 5 mg/kg in pediatric patients with ECMO, and optimized dosing in the same population. (a) Neonates (0 days to 1 month). (b) Infants (1 month to 1 year). (c) Children (1 year to 12 years). (d) Adolescents (13 to 17 years).

DISCUSSION

Amiodarone is a life-saving medication to treat ventricular arrhythmias and supraventricular tachyarrhythmias such as atrial fibrillation in high-risk pediatric and adult patients.³⁷ AHA guidelines for CPR and ECC recommend using amiodarone (5 mg/kg i.v. bolus) as a first-line agent

to treat ventricular arrhythmias in children.⁷ However, there are no dosing recommendations for amiodarone to treat ventricular arrhythmias in children supported with ECMO. Children on extracorporeal support require special attention for dose selection due to the interaction of amiodarone with ECMO components. PBPK modeling is a viable alternative to traditional PK modeling approaches

for dose selection of drugs for children on ECMO. We developed a robust amiodarone PBPK model in adults and extrapolated it to the pediatric population. The extrapolated pediatric model performed well in children of all age groups. After adding the ECMO compartment, our model was able to predict the optimal dosing of amiodarone in children on ECMO.

Adsorption of drugs to the ECMO components such as tubing and cannulas, pump, and oxygenator is a major reason for the decrease in drug exposure in patients on ECMO.³⁸ For the treatment of acute conditions such as ventricular arrhythmias in children, this decrease in drug exposure can be life-threatening. Numerous ex vivo studies suggested that high lipophilicity, degree of ionization, and high protein binding are significant factors resulting in the adsorption of drugs to ECMO components.^{10,11} Amiodarone has a high potential for adsorption to ECMO components as it is highly lipophilic ($\text{LogP}=7.58$), has high protein binding (96%), and has a high percentage of the ionized fraction at physiological pH (87.3%).⁸ Specifically, as amiodarone exists in highly ionized fraction (87.3%) with positive surface charge at physiological pH, it can electrostatically bind to the negative surfaces of the materials of ECMO components such as polyvinyl chloride (tubings and cannulas),³⁹ polycarbonate, polypropylene, and silicone (oxygenator).⁴⁰ However, the degree of amiodarone extraction can be affected by the brand/type of ECMO components of the circuit used. To obtain accurate predictions using the ECMO PBPK model, the adsorption data from the ex vivo studies that used the same brand/type of ECMO circuit components that will be used in the clinic is recommended.

Our ex vivo study of amiodarone adsorption to ECMO circuit components confirmed that amiodarone is rapidly adsorbed onto ECMO circuit, and that saturation is not achieved after administration of 6 doses.¹⁰ The data from our study suggests that all three components (the hemofilter, oxygenator, and tubing) contributed to the extraction of amiodarone. This confirms our theory that positively charged amiodarone can electrostatically bind to the negatively charged surfaces of ECMO components.¹⁰ In another *in vitro* study, Lescroart et al.¹¹ also reported rapid adsorption of amiodarone onto ECMO circuit within the first 2 h of injection into the circuit.

Despite the wide use of short-term i.v. amiodarone, there is no established relationship between drug concentration and therapeutic response for short-term i.v. use of amiodarone.³⁴ Our pediatric ECMO PBPK model simulations with the AHA recommended loading dose of 5 mg/kg showed that compared with children not supported with ECMO, children supported with ECMO had a significantly lower median C_{\max} ($p < 0.05$). The percent decrease in C_{\max} was highest in the neonatal population

(53.6%) and lowest in the adolescent population (9.4%). The simulations also showed that the median C_{\max} in pediatric patients in all age groups with ECMO receiving the AHA recommended loading dose of 5 mg/kg was greater than the literature reported target C_{\max} 4.7 mg/L.³⁶ The recommended optimal doses of amiodarone that reached target AUC_{0-24} in pediatric patients with ECMO were: 22 mg/kg for neonates, 13 mg/kg for infants, 8 mg/kg for children, and 6 mg/kg for adolescents. It is important to note that our recommended dose in neonates (22 mg/kg) would achieve a C_{\max} of >20 mg/L in more than 75% of the population, which is significantly greater than the C_{\max} reported in the majority of patients in reported pediatric amiodarone PK/PD study.³⁶ This high C_{\max} may result in adverse effects of amiodarone in neonates, and caution must be exercised before administering the model recommended dose to neonates. However, further validation of our model with prospective PK data in children is needed to support our predictions.

The dosing recommendation of 22 mg/kg in neonates, which is based on our amiodarone ECMO PBPK is significantly higher (4.4 times) than the current recommended dose of 5 mg/kg. Due to the potential for amiodarone toxicity, clinicians must exercise caution before using our recommended dose in the clinic. As is the case for all models, the model predictions must be further validated with future clinical studies and/or data before applying them in the clinic. Specifically, in our study, data from only one neonate with ECMO was included in our final validation dataset, an inherent limitation of using our dosing recommendation in neonates with ECMO. Furthermore, due to the variability of amiodarone PK/PD and the potential for toxicity in neonates, a dose titration regimen from low to high doses with appropriate efficacy and toxicity endpoints must be used in this population.

Despite its satisfactory performance, our model has limitations. An important limitation is that our model can only be used to inform the optimal dosing of amiodarone after the IV bolus loading dose. Our model cannot be applied to inform optimal dosing for infusion maintenance dosing of amiodarone. This is due to the anomalous PK of amiodarone after long-term therapy, as it accumulates mainly in fat, skeletal muscle, and liver. To accurately predict amiodarone PK after maintenance dosing in children on ECMO, the current model must be modified to include a nonexponential tissue trapping component that controls the transport of molecules back to the plasma from adipose tissue.⁴¹ Future studies will involve updating our current model and validating it with prospective clinical trial data to allow prediction of both loading and maintenance doses of amiodarone in children on ECMO. The other limitations of the model include the sparsity of opportunistic data and the assumption of physiological

scaling that pediatric clearance pathways are the same as adults and the ontogeny functions of albumin, CYP3A4, and CYP2C8. Also, due to a lack of data on amiodarone efficacy and toxicity targets in children on ECMO, we used exposure matching with AUC_{0-24} as our target. However, a more relevant target that directly correlates with amiodarone efficacy and/or toxicity in children with ECMO must be used in the future for dose optimization. More robust pediatric PK studies are warranted to optimize the PBPK model further.

In conclusion, the ECMO PBPK model parameterized with the data from ex vivo ECMO studies described in this manuscript provides i.v. loading dosing recommendations for amiodarone in children supported with ECMO. This approach can also be applied to predict the drug PK in a specific population undergoing other forms of extracorporeal support (e.g., hemodialysis). Furthermore, when new extracorporeal technology is introduced, we can reparametrize the extracorporeal compartment of our ECMO PBPK model using ex vivo experiments and derive new model-based dosing recommendations.

AUTHOR CONTRIBUTIONS

V.K.Y. and K.W. wrote the manuscript. V.K.Y., K.W. designed the research. V.K.Y., K.W., J.P.H., D.J.G., A.M., and A.W. performed the research. V.K.Y. and K.M.W. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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