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A Pharmacokinetic Model for Amiodarone in Infants Developed from an Opportunistic Sampling Trial and Published Literature Data

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Abstract

Amiodarone is a first-line antiarrhythmic for life-threatening ventricular fibrillation or ventricular tachycardia in children, yet little is known about its pharmacokinetics (PK) in this population. We developed a population PK (PopPK) model using samples collected via an opportunistic study design of children receiving amiodarone per standard of care supplemented by amiodarone PK data from the literature. Both study data and literature data were predominantly from infants <2 years old, so our analysis was restricted to this group. The final combined dataset consisted of 266 plasma drug concentrations in 45 subjects with a median (interquartile range) postnatal age of 40.1 (11.0–120.4) days and weight of 3.9 (3.1–5.1) kg. Since the median sampling time after the first dose was short (study: 95 hours; literature: 72 hours) relative to the terminal half-life estimated in adult PopPK studies, values of the deep compartment volume and flow were fixed to literature values. A 3-compartment model best described the data and was validated by visual predictive checks and non-parametric bootstrap analysis. The final model included body weight as a covariate on all volumes and on both inter-compartmental and elimination clearances. The empiric Bayesian estimates for clearance (CL), volume of distribution at steady state, and terminal half-life were 0.25 (90% CL: 0.14–0.36) L/kg/h, 93 (68–174) L/kg, and 266 (197–477) h, respectively. These studies will provide useful information for future PopPK studies of amiodarone in infants and children that could improve dosage regimens.

Keywords

amiodarone; population pharmacokinetics; pediatrics; cardiac arrhythmias

INTRODUCTION

Seventeen percent of children with in-hospital cardiac arrest experience ventricular fibrillation or ventricular tachycardia, and the reported rate of survival to hospital discharge following these tachyarrhythmias is only 11% [1, 2]. The American Heart Association recommends amiodarone as the first-line antiarrhythmic for these rhythm abnormalities in children, but it is not approved by the U.S. Food and Drug Administration for the treatment of pediatric life-threatening ventricular fibrillation or ventricular tachycardia [3]. In a multicenter review of pediatric tachyarrhythmias on mechanical support, all patients treated with multiple agents received amiodarone in conjunction with other agents, and 81% of patients treated with a single agent received amiodarone [4]. Side effects associated with amiodarone in children are similar to those seen in adults: hypotension, QTc prolongation, and elevated liver enzymes are most commonly reported [5, 6].

Amiodarone undergoes hepatic metabolism, primarily by cytochrome P450 (CYP) 3A4, but also CYP2C8, CYP1A1, and CYP2D6 [7]. The major active metabolite, desethylamiodarone, has shown antiarrhythmic effects in animals but has not been well studied in humans. Amiodarone is lipophilic, binding avidly to lipoproteins and albumin (96–99%) with extensive uptake into tissue [8–18]. In 4 adult population PK studies, clearance (CL) estimates varied from 0.06–0.22 L/kg/hr, volume of distribution at steady state (Vss) varied from 10.3–87 L/kg [8, 11, 13, 16], and elimination half-life estimates varied from 20–120 days [19]. As a result, onset of action for oral administration may take 1

to 3 weeks, and months may be required to reach equilibrium between plasma and tissues concentrations.

Although there are many reports of amiodarone administration to infants and children [5, 20–38], little is known about amiodarone pharmacokinetics (PK) in this population, and no pediatric studies report PK model analysis. PK studies are critical to designing effective dosage strategies, improving drug efficacy, and avoiding toxicity. In children, PK studies are often limited due in part to the challenges associated with conducting trials in this population. However, the expansion of opportunistic study designs capitalize on standard medical procedures performed in children already receiving a drug per standard of care [39]. This design decreases study costs, increases consent rates, and minimizes study-related risk to the patient. Accordingly, we developed a population PK model for amiodarone in children using an opportunistic clinical trial design. Information from previously published population PK studies in children and adults were used to enhance, interpret, and refine the pediatric model.

METHODS

Patient population

PK samples were collected from the Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care (POPS) trial. POPS (ClinicalTrials.gov NCT01431326; protocol NICHD-2011-POP01) was a multicenter, prospective, PK and safety study of understudied drugs administered to children (<21 years old) per standard of care. Children who were administered intravenous (IV) or enteral amiodarone per standard of care by their treating caregiver were eligible for enrollment. Exclusion criteria included failure to obtain consent/assent or a known pregnancy as determined by interview or testing, if available.

In order to improve the PK analysis, additional data from amiodarone administration to children were obtained from the report of Ramusovic et al [34], which included 20 patients administered a loading dose of amiodarone followed by continuous infusion for incessant supraventricular tachycardia, junctional ectopic tachycardia, or ventricular tachycardia. Patients with amiodarone exposure 4 weeks prior to study initiation or with co-morbidities precluding blood sampling were excluded. Treatment efficacy and associated hypotension or bradycardia were evaluated.

In both the POPS and Ramusovic datasets, few subjects were >2 years old, and of those subjects, many had complicating factors (extracorporeal membrane oxygenation [ECMO], obesity). Consequently, we focused our modeling on data from the children <2 years old.

Drug dosing and sample collection

POPS, which is ongoing, uses an opportunistic study design. Dosing information was collected for up to 8 doses prior to the sampling dose (last dose prior to first biological sample collection). Blood samples for the determination of plasma amiodarone concentrations were collected at the time of blood sampling for other laboratory tests as a component of each patient's prescribed care or, with parental consent, at alternate times from standard of care collections. No new laboratory tests were performed as part of this

study design, but the results of laboratory tests were recorded if performed as part of routine care (e.g., basic metabolic panel, comprehensive metabolic panel, etc.) and collected within 72 hours of a sampling dose of the drug. Gestational age (GA) was recorded in infants <120 days postnatal age (PNA). Subjects were enrolled in the study for up to 90 days. The Pediatric Trials Network (PTN) PK analysis dataset—including clinical, dosing, and drug concentration information—was generated and formatted by The EMMES Corporation, the PTN Data Coordinating Center. Missing clinical data were imputed using the last value carried forward. For infants and children >120 days old, a GA of 40 weeks was imputed.

In the Ramusovic study, multiple blood samples were obtained for determination of amiodarone concentrations following bolus administration and throughout IV infusions. Individual subject demographics and dosing information extracted from Table 1 in the Ramusovic report included patient age; weight; time and dose of IV bolus; time, dose, and duration of continuous IV infusions. Data from each subject's concentration time profiles were digitized from Figure 1 in the Ramusovic report, using GetData Graph Digitizer v. 2.26 (<http://www.getdata-graph-digitizer.com/>).

Analytical methods

Amiodarone plasma concentrations from patients 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 assay. The calibration range of quality-control parameters was between 5–5000 ng/mL using a 10 L sample volume. During method validation, accuracy and precision of all sample runs were within 11%. The lower limit of quantification for amiodarone was 5 ng/mL.

In the Ramusovic study, amiodarone concentrations were determined by high-performance liquid chromatography with ultraviolet detection. Accuracy and intra- and inter-assay precision for samples were all reported to be 5%. The lower limit of quantification for amiodarone was 0.1 g/mL.

Population PK analysis

Amiodarone plasma PK data were analyzed with a nonlinear mixed effects modeling approach using Phoenix NLME (Certara, Princeton, NJ, USA, v 7.0). The first-order conditional estimation method with extended least squares was used for all model runs. Visual predictive checks (VPCs) and bootstrap methods were performed using Phoenix NLME. Data manipulation and visualization was performed using R (R Foundation for Statistical Computing, Vienna, Austria, v 3.3.1) and RStudio (Boston, MA, USA, v 0.99.489) with the packages lattice and ggplot2.

Based on visual inspection of the PK data and a review of the primary literature, 1-, 2- and 3-compartment PK models were evaluated. Between-subject variability was assessed for PK model parameters using an exponential relationship (Equation 1):

$$P_{ij} = \theta_{Pop,j} * \exp(\eta_{ij}) \quad (1)$$

where P_{ij} denotes the estimate of parameter j in the i th individual; $\theta_{Pop,j}$ is the population value for parameter j ; and η_{ij} denotes the deviation from the average population value for parameter j in the i th individual. The random variable η is assumed to be normally distributed with a mean zero and variance ω^2 . Proportional, combined (proportional plus additive), and exponential residual error models were evaluated.

In analyses using 2 separate datasets, the expected difference in residual error between these data sources was accounted for by modeling the residual error as follows (Equation 2):

$$C_{obs,ij} = C_{pred,ij} * (1 + \varepsilon_{prop,ij} * \exp(PTN * \theta_{(8)})) \quad (2)$$

where PTN is a binary variable, the value of which reflects the dataset of origin.

The potential effects of clinical covariates on PK parameters were evaluated if a relationship was suggested by visual inspection of scatter and box plots (continuous and categorical variables, respectively) of the individual deviations from the population-typical value PK parameters (ETAs) against covariates. The following covariates were explored: body weight (WT), PNA, and dataset of origin.

WT was assumed to be a significant covariate for CL and volume of distribution (V) and was included in the base model prior to assessment of other covariates. The relationship between WT and PK parameters was characterized using a linear-scale for volume parameters and an estimated exponent for CL parameters (Equations 3–6) [40]. Scaling was based on a population median WT as shown below.

$$CL_i = tvCL * \left(\frac{WT_i}{median\ WT} \right)^{dCLdWT} \quad (3)$$

$$V_{ci} = tvV_c * \left(\frac{WT_i}{median\ WT} \right)^1 \quad (4)$$

$$Q_{pi} = tvQ_p * \left(\frac{WT_i}{median\ WT} \right)^{dCLdWT} \quad (5)$$

$$V_{pi} = tvV_p * \left(\frac{WT_i}{median\ WT} \right)^1 \quad (6)$$

$$Q_{di} = tvQ_d * \left(\frac{WT_i}{median\ WT} \right)^{0.75} \quad (7)$$

$$V_{di} = tvV_c * \left(\frac{WT_i}{median\ WT} \right)^1 \quad (8)$$

In Equations 3–8, WT_i denotes the weight of an individual subject; CL , V_c , Q_p , V_p , Q_d and V_d are the typical value (tv) estimates for a subject of the median weight of the population; and CL_i , V_{ci} , Q_{pi} , V_{pi} , Q_{di} and V_{di} are the estimates for each subject. (Note: while these equations are appropriate for a 3-compartment model, analogous equations were used to evaluate 1- and 2-compartment models). A saturable model of CL (Michaelis-Menton) was also evaluated. Before finalizing the forms of equations, several variations were modeled and evaluated by the change in objective function value (OFV): the exponential terms of CLs were estimated separately, fixed to the allometric value of 0.75, or fixed to the value of 1 [41]. Models were also generated normalizing WT to 70 kg and 1 kg. While these latter exploratory models made no difference in the OFVs or the empirical Bayesian estimates (EBEs) for parameters, normalizing to median WT was chosen as the best representation of the population of infants in the final model. Selection of the final model also considered the computed estimates model parameter precision and validation of the model (see below).

Patient age and the dataset of origin were the other potential covariates available for PK parameters. Dataset of origin was tested as a categorical variable and as a factor for the residual error, as outlined above. Age was tested as a potential power covariate for all PK parameters, as illustrated for WT above. The relationship between age and CL was also explored using a power model and as a sigmoidal maximum effect (E_{MAX}) maturation function as shown in Equation 9 [42]:

$$F_{Age} = \frac{Age^{HILL}}{TM_{50}^{HILL} + Age^{HILL}} \quad (9)$$

where F_{Age} denotes the fraction of the mature clearance value, TM_{50} represents the value of age (weeks) when 50% mature clearance is reached, and HILL is a slope parameter for the sigmoidal maturation model.

A forward inclusion ($p < 0.05$ and $OFV > 3.8$) and backward elimination ($p < 0.001$ and $OFV > 10.8$) approach was used to evaluate statistical significance of relevant covariates.

Population PK model evaluation and validation

To assess model appropriateness during the population PK model-building process, successful minimization, diagnostic plots, plausibility and precision of parameter estimates,

as well as objective function and shrinkage values were all considered. Diagnostic plots generated included: individual predictions (IPRED) and population predictions (PRED) vs. observations; conditional weighted residuals (CWRES) vs. PRED and time; and individual weighted residuals (IWRES) vs. IPRED.

To explore the final model, new model generation was performed using each dataset (PTN and Ramusovic) separately. The initial parameter estimates for these sub-model parameter values were parameter values of the final model. Parameter values and their distributions from these 2 sub-models were compared with those of the final model.

Parameter precision for the final population PK model was evaluated using non-parametric bootstrapping (1000 replicates) to generate the 95% confidence intervals for parameter estimates. Phoenix 7.0 utilizes the unconstrained Broyden-Fletcher-Goldfarb-Shanno quasi-Newton UNCMIN optimizer presented as pseudo-code in Dennis and Schnabel [43]. VPCs were performed whereby the base and final models were used to generate 1000 Monte Carlo simulation replicates per time point of amiodarone exposure, and simulated results were compared with those observed in the study. The dosing and covariate values used to generate the simulations in the VPC were the same as those used in the study population.

RESULTS

Subject demographics

PTN dataset—A total of 38 subjects with 68 plasma samples were enrolled from 12 participating PTN sites in this study. Of them, 29 (76%) were <2 years old (Table 1). The median (interquartile range [IQR]) PNA of the subjects <2 years old was 40 (20–171) days, and the median (IQR) WT was 3.9 (3.1–6.0) kg. Of the 38 total subjects, 24 were male, 22 were white, and 10 were black. Beyond these characteristics, there was either very little variability in values of potential covariates (e.g., serum creatinine) or few subjects with recorded values (e.g., bilirubin, aspartate transaminase, albumin, concomitant medications). Subjects received multiple IV bolus doses, continuous IV infusions, multiple enteral doses, and various combinations of these dosage methods. Individual fits of observed serum amiodarone concentrations over time with model-predicted concentration-time curves are illustrated in Supplemental Figure 2.

Ramusovic dataset—A total of 20 subjects with 247 plasma samples were collected from the Ramusovic dataset. Similar to the PTN dataset, the majority of subjects (n=16) were <2 years old (Table 1). The median (IQR) PNA of the subjects <2 years old was 49.5 (15.5–112.5) days, and median (IQR) WT was 4.0 (3.6–4.6) kg. Sex and race data were not published, and the study did not provide values for potential covariates (e.g., laboratory tests, concomitant medications). The administration of amiodarone in the Ramusovic study was 5 mg/kg IV bolus followed by 0.42 mg/kg/h continuous IV infusion.

Combined dataset—Among the infants <2 years old, there was a somewhat wider distribution of ages and WTs in the PTN dataset, although the distribution in both datasets was weighted toward smaller, younger infants. The median (IQR) PNA of the combined dataset was 40.1 (11.0–120.4) days with a median (IQR) WT of 3.9 (3.1–5.1) kg. The

comparison in amiodarone administration between the PTN, Ramusovic, and combined datasets is provided in Table 2.

Population PK model development and evaluation

Among the base PK structural models evaluated, based on model-selection criteria, a 3-compartment model fit the data best (Table 3, Steps 1–4). WT was assumed to be a significant covariate for CL parameters and V parameters and was included in the base model using linear scaling for V parameters (exponent=1) and an allometric exponent for CL, Q_p , and Q_d . Modeling for a saturation CL did not improve the model fit, while a model including a maturation function on CL did not converge. The addition of a separate term that accounted for differing residual errors in the 2 datasets resulted in further reduction in the OFV (Step 5).

Poor precision in the estimates of model parameter values led to further modeling efforts. Estimation of the scaling exponent on CL and Q_p (Step 6), fixing values of V_d and Q_d to extrapolated literature-based values [8] without ETA estimates (Step 7), fixing both the values of V_d and Q_d and the exponent on CL and Q_p but estimating ETA values (Step 8), and fixing V_d and Q_d but estimating ETA values (Step 9) did not improve the OFV but progressively improved parameter precision. The scaling exponent on CL and Q_p Bootstrap analysis of Steps 6 and 9 validated parametric variable estimates for Step 9 but not Step 6. Step 9 was therefore adopted as the final model.

Standard goodness-of-fit (Figure 1) plots of the final model indicated reasonable performance at all amiodarone concentrations and times after the initial doses.

Scatter plots of ETAs for PK parameters were examined as a function of PNA. The absence of a trend in the plot of age vs. ETA-CL was consistent with the failure of the model to improve with the addition of age as a covariate on CL, either linearly or modeled through a HILL equation.

Residual variability was modeled to acknowledge that the 2 separate datasets had inherently different sources of error, as described above in Equation 2, where PTN represented the dataset (0 = Ramusovic, 1 = PTN). The standard deviation of was 0.74. Correspondingly, the proportional residual error was estimated at 0.74 in the Ramusovic dataset and 0.21 in the PTN dataset.

The estimated values for the population PK parameters for the final model, along with the standard error of these estimates, are listed in Table 4. ETA shrinkage is reported for all parameters where ETA was estimated. The epsilon shrinkage in the final model is 0.13.

The median (and 90% confidence intervals) of the empirical Bayesian post-hoc PK parameter estimates for all children aged zero to 2 years old were as follows: CL: 0.25 (0.14–0.36) L/h/kg; V_{ss} (calculated as the sum of V_c , V_p , and V_d): 93 (68–174) L/kg; half-life alpha: 0.09 (0.06–0.18) h; half-life beta 10.4 (4.40–27.9) h; and half-life gamma 497 (297–1161) h [44]. EBE values were examined as a function of PNA and dataset of origin and appeared similar among 3 age groups (Table 5) and between the 2 datasets.

Of bootstrap replicates, 100% successfully converged; 77% of replicates converged with the absolute and relative change of the OFV below the predetermined absolute and relative thresholds of 10^{-6} .

The VPC, which is based on 1000 simulations of the final population PK model, showed that the model adequately described the data; 10.7% of observed concentrations were outside the 90% prediction interval in a binned analysis. The proportion of outliers appeared slightly higher in the PTN dataset compared with observations in the Ramusovic dataset. The relationship between observed and predicted concentrations, as analyzed in the VPC, is illustrated as a function of time after the first dose in Figure 2. Two panels are presented, illustrating performance in the 2 datasets separately.

Data from patients >2 years old in the PTN dataset (n=9) and the Ramusovic study (n=4) were excluded from model development, as outlined above, but re-examined after model development. The median age of this combined group was 6.0 (range: 2.08–16.6) years, and the median WT was 18.0 (range: 11.0–110) kg. Of these subjects, 4 were obese and 3 were on ECMO. The data from these subjects (drug dosages, times of administration, plasma amiodarone concentrations, and WT) were analyzed using the final model to determine whether major differences are to be expected in future trials of older children. As illustrated in Figure 3, there was general agreement between observed concentrations and the amiodarone concentrations individually predicted from the model developed with data from children <2 years old.

DISCUSSION

A 3-compartment model appropriately described the data from children <2 years old and was validated by bootstrapping and VPC. The EBEs for CL and Vss (calculated as the sum of V_c , V_p , and V_d) were 0.25 L/kg/h and 93 L/kg, respectively. This model varied somewhat from currently published 1-, 2-, and 4-compartment adult models (Table 6) [8, 11, 13, 16]. CL values were comparable to those reported in Korth-Bradley, but higher than the other 3 studies. Vss values were similar to those described in Pollak, but higher than the other adult studies. Mean residence time (MRT) values were similar to the Vadie and Araki studies, but quite different from the Korth-Bradley study (Table 6). Several factors commonly are associated with higher drug CL values in infants and children compared with those from adults. Some drug-metabolizing enzymes are more abundant and influential early in life and subsequently decline in activity toward adolescence and adulthood [45]. More commonly, it is likely that expressing CL on a weight-normalized basis leads to higher CL values because of the relatively higher ratio of liver weight to total body weight found in infants and young children [46]. However, among the studies listed in Table 6, including the present study, differences in sampling strategies were likely to be the most important factor compounding the interpretation of differences in CL estimates. Notably, mean plasma sampling times were the longest in the studies reporting the lowest CL and longest MRT values. In retrospect, mean plasma sampling times of <1000 hours could not be expected to define the complete deep compartment volume and elimination PK characteristics of a drug with an MRT of 515–1426 hours. Defining the deep compartment is important for characterizing drug accumulation and understanding the long elimination half-life.

Both the PTN and Ramusovic studies were too limited in sampling duration to definitively characterize the deep tissue compartment. The furthest sample collection from the initial amiodarone dose was in the Ramusovic study at 244 hours (approximately 10 days). Despite our inability to accurately characterize the volume of the deep compartment, we must assume its presence to accurately characterize the pediatric data [19, 47]. To demonstrate the clinical impact of the deep tissue compartment, we simulated a conventional IV dosing regimen for both a 2-compartment and 3-compartment model (Figure 4). The 2-compartment model predicts a rapid accumulation to a steady state concentration of about 1 mg/L. The 3-compartment model predicts accumulation to a median concentration of about 2 mg/L in our population that is not quite complete at 200 days. Notably, inclusion of the large, deep compartment in the model is important to the determination of CL. Correspondingly, the concentration at steady state, time to reach steady state, and persistence of drug after dosing are all impacted. Use of extrapolated adult values to characterize the deep compartment is validated by improvement in the OFV and by the standard goodness-of-fit plots of the final model. Further, the final model showed agreement in a plot of observed and individually predicted concentrations for the 13 children aged >2 years in our dataset.

A limitation of this study is the lack of covariate data. Amiodarone undergoes hepatic metabolism, primarily by CYP3A4 but also CYP2C8, CYP1A1, and CYP2D6 [7]. Thus, baseline liver metabolic function and genetic variability of CYP isoforms are likely to influence amiodarone metabolism and elimination. Activity of CYP3A4 and CYP2D6 is limited over the first months to years of life, but these isoenzymes are 2 of the greatest contributors to drug metabolism in children and adults [48]. Liver enzymes were not available in most study patients and were not considered in the model. Hepatic metabolism is correlated more closely with age than WT; however, the effect of other age-based covariate information (i.e., postmenstrual age) on PK parameters could not be analyzed. The drug's intense protein binding and lipophilicity present additional factors that may contribute to differences in drug distribution between patients and should also be considered in future studies. Further, the small number of subjects >2 years old without complicating covariates (ECMO, obesity) prevented a meaningful analysis in these older age groups.

An additional limitation is the study's reliance on the literature for key data. The PTN dataset alone was too limited for a robust analysis; and thus, we added data from Ramusovic et al. Outliers in the data (Figure 1) were almost exclusively from the Ramusovic dataset and correspond to higher residual error in that study. We speculate this residual error may originate from both the poorer sensitivity of the analytical assay in that study and inadvertent error in digitizing the Ramusovic data. Despite these outliers, the bootstrap analysis and visual predictive checks support the validity of the final model. Further, the sampling duration in the PTN and Ramusovic studies was too short, necessitating the extrapolation of deep compartment characteristics from adult literature. The large, deep compartment has important implications for prolonged administration of amiodarone, and the long gamma half-life of this drug (Table 5) presents a challenge in future clinical trial design intended to define PK and propose dosing regimens. Ignoring the deep compartment will produce substantial errors.

We combined data from 2 sources to propose the best-possible model for PK analysis of a life-saving drug in children. Our findings have important implications for the design of future PK studies in infants and children that may improve on the precision and accuracy of the current study. Short-term studies (drug administration for a few days or weeks) may be possible but will require many weeks of follow-up plasma drug concentration sampling and a highly sensitive analytical drug assay to define all compartments and clearances. Studies performed with longer term drug administration (e.g. greater than 3 months) will not require a drug assay of such high sensitivity and will provide better data for the estimation of PK parameters and their sources of variability.

CONCLUSION

Use of an opportunistic study design was an efficient approach that resulted in the development of a population PK model characterizing amiodarone disposition in children. The findings reported here should be useful to investigators who seek to devise improved dosage regimens, perform pharmacodynamic studies, and explore the value of therapeutic monitoring of this drug.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Nadkarni VM, Larkin GL, Peberdy MA, Carey SM, Kaye W, Mancini ME, Nichol G, Lane-Truitt T, Potts J, Ornato JP, Berg RA. National Registry of Cardiopulmonary Resuscitation Investigators. First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. *JAMA*. 2006; 295:50–57. [PubMed: 16391216]
2. Samson RA, Nadkarni VM, Meaney PA, Carey SM, Berg MD, Berg RA. American Heart Association National Registry of CPR Investigators. Outcomes of In-Hospital Ventricular Fibrillation in Children. *N Engl J Med*. 2006; 354:2328–2339. [PubMed: 16738269]
3. Kleinman ME, Chameides L, Schexnayder SM, Samson RA, Hazinski MF, Atkins DL, Berg MD, de Caen AR, Fink EL, Freid EB, Hickey RW, Marino BS, Nadkarni VM, Proctor LT, Qureshi FA, Sartorelli K, Topjian A, van der Jagt EW, Zaritsky AL. Part 14: pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010; 122:S876–S908. [PubMed: 20956230]
4. Silva JN, Erickson CC, Carter CD, Greene EA, Kantoch M, Collins KK, Miyake CY, Carboni MP, Rhee EK, Papez A, Anand V, Bowman TM, Van Hare GF. Participating Members of Pediatric and Congenital Electrophysiology Society (PACES). Management of pediatric tachyarrhythmias on mechanical support. *Circ Arrhythm Electrophysiol*. 2014; 7:658–663. [PubMed: 24987047]
5. Etheridge SP, Craig JE, Compton SJ. Amiodarone is safe and highly effective therapy for supraventricular tachycardia in infants. *Am Heart J*. 2001; 141:105–110. [PubMed: 11136494]
6. Burri S, Hug MI, Bauersfeld U. Efficacy and safety of intravenous amiodarone for incessant tachycardias in infants. *Eur J Pediatr*. 2003; 162:880–884. [PubMed: 14508682]

7. Elsherbiny ME, El-Kadi AO, Brocks DR. The metabolism of amiodarone by various CYP isoenzymes of human and rat, and the inhibitory influence of ketoconazole. *J Pharm Pharm Sci*. 2008; 11:147–159. [PubMed: 18445370]
8. Pollak PT, Bouillon T, Shafer SL. Population pharmacokinetics of long-term oral amiodarone therapy. *Clin Pharmacol Ther*. 2000; 67:642–652. [PubMed: 10872646]
9. Chow MS. Intravenous amiodarone: pharmacology, pharmacokinetics, and clinical use. *Ann Pharmacother*. 1996; 30:637–643. [PubMed: 8792951]
10. Freedman MD, Somberg JC. Pharmacology and pharmacokinetics of amiodarone. *J Clin Pharmacol*. 1991; 31:1061–1069. [PubMed: 1753010]
11. Araki R, Yukawa E, Nakashima MN, Fukuchi H, Sasaki H, Yano K, Nakashima M. Population pharmacokinetic investigation for optimization of amiodarone therapy in Japanese patients. *Ther Drug Monit*. 2011; 33:750–756. [PubMed: 22105593]
12. Kannan R, Miller S, Singh BN. Tissue uptake and metabolism of amiodarone after chronic administration in rabbits. *Drug Metab Dispos*. 1985; 13:646–650. [PubMed: 2867865]
13. Korth-Bradley JM, Rose GM, de Vane PJ, Peters J, Chiang ST. Population pharmacokinetics of intravenous amiodarone in patients with refractory ventricular tachycardia/fibrillation. *J Clin Pharmacol*. 1996; 36:715–719. [PubMed: 8877675]
14. Plomp TA, van Rossum JM, Robles de Medina EO, van Lier T, Maes RA. Pharmacokinetics and body distribution of amiodarone in man. *Arzneimittelforschung*. 1984; 34:513–520. [PubMed: 6540111]
15. Riva E, Gerna M, Latini R, Giani P, Volpi A, Maggioni A. Pharmacokinetics of amiodarone in man. *J Cardiovasc Pharmacol*. 1982; 4:264–269. [PubMed: 6175810]
16. Vadieli K, Troy S, Korth-Bradley J, Chiang ST, Zimmerman JJ. Population pharmacokinetics of intravenous amiodarone and comparison with two-stage pharmacokinetic analysis. *J Clin Pharmacol*. 1997; 37:610–617. [PubMed: 9243354]
17. Veronese ME, McLean S, Hendriks R. Plasma protein binding of amiodarone in a patient population: measurement by erythrocyte partitioning and a novel glass-binding method. *Br J Clin Pharmacol*. 1988; 26:721–731. [PubMed: 3242577]
18. Wyss PA, Moor MJ, Bickel MH. Single-dose kinetics of tissue distribution, excretion and metabolism of amiodarone in rats. *J Pharmacol Exp Ther*. 1990; 254:502–507. [PubMed: 2384884]
19. Kowey PR, Marinchak RA, Rials SJ, Bharucha D. Pharmacologic and pharmacokinetic profile of class III antiarrhythmic drugs. *Am J Cardiol*. 1997; 80:16g–23g. [PubMed: 9205013]
20. Chang PM, Silka MJ, Moromisato DY, Bar-Cohen Y. Amiodarone versus procainamide for the acute treatment of recurrent supraventricular tachycardia in pediatric patients. *Circ Arrhythm Electrophysiol*. 2010; 3:134–140. [PubMed: 20194798]
21. Dick M, Scott WA. Amiodarone in pediatric patients. *Clinical Progress in Electrophysiology and Pacing*. 1986; 4:522–527.
22. Dieks JK, Klehs S, Müller MJ, Paul T, Krause U. Adjunctive ivabradine in combination with amiodarone: A novel therapy for pediatric congenital junctional ectopic tachycardia. *Heart Rhythm*. 2016; 13:1297–1302. [PubMed: 27216242]
23. Dubin AM, Van Hare GF, Collins KK, Bernstein D, Rosenthal DN. Survey of current practices in use of amiodarone and implantable cardioverter defibrillators in pediatric patients with end-stage heart failure. *Am J Cardiol*. 2001; 88:809–810. [PubMed: 11589857]
24. Fishberger SB, Hannan RL, Welch EM, Rossi AF. Amiodarone for pediatric resuscitation: a word of caution. *Pediatr Cardiol*. 2009; 30:1006–1008. [PubMed: 19495851]
25. Haas NA, Camphausen CK. Impact of early and standardized treatment with amiodarone on therapeutic success and outcome in pediatric patients with postoperative tachyarrhythmia. *J Thorac Cardiovasc Surg*. 2008; 136:1215–1222. [PubMed: 19026806]
26. Hasegawa T, Oshima Y, Maruo A, Matsuhisa H, Kadowaki T, Noda R. Landiolol for junctional ectopic tachycardia refractory to amiodarone after pediatric cardiac surgery. *Gen Thorac Cardiovasc Surg*. 2013; 61:350–352. [PubMed: 22893321]

27. Hatib NA, Lee JH, Loh LE, Mok YH, Menon AP, Loh TF, Tan TH. Accidental Intra-Arterial Infusion of Amiodarone in a Pediatric Patient With Atrial Ectopic Tachycardia. *Crit Care Med*. 2016; 44:e1013–e1014.
28. Perry JC, Fenrich AL, Hulse JE, Triedman JK, Friedman RA, Lamberti JJ. Pediatric Use of Intravenous Amiodarone: Efficacy and Safety in Critically Ill Patients From a Multicenter Protocol. *J Am Coll Cardiol*. 1996; 27:1246–1250. [PubMed: 8609351]
29. Mazic U, Berden P, Podnar T. Repetitive paroxysms of supraventricular tachyarrhythmias triggered during pediatric cardiac interventions: suppression after short infusion of amiodarone. *Pediatr Cardiol*. 2004; 25:684–685. [PubMed: 14743306]
30. Moffett BS, Valdes SO, Kim JJ. Amiodarone monitoring practices in pediatric hospitals in the United States. *Pediatr Cardiol*. 2013; 34:1762–1766. [PubMed: 23640245]
31. Nalli N, Stewart-Teixeira L, Dipchand AI. Amiodarone-sirolimus/tacrolimus interaction in a pediatric heart transplant patient. *Pediatr Transplant*. 2006; 10:736–739. [PubMed: 16911499]
32. Paul T, Guccione P. New antiarrhythmic drugs in pediatric use: amiodarone. *Pediatr Cardiol*. 1994; 15:132–138. [PubMed: 8047495]
33. Perry JC, Fenrich AL, Hulse JE, Triedman JK, Friedman RA, Lamberti JJ. Pediatric use of intravenous amiodarone: efficacy and safety in critically ill patients from a multicenter protocol. *J Am Coll Cardiol*. 1996; 27:1246–1250. [PubMed: 8609351]
34. Ramusovic S, Ler S, Meibohm B, Lagler FB, Paul T. Pharmacokinetics of intravenous amiodarone in children. *Arch Dis Child*. 2013; 98:989–993. [PubMed: 24051016]
35. Saharan S, Balaji S. Cardiovascular collapse during amiodarone infusion in a hemodynamically compromised child with refractory supraventricular tachycardia. *Ann Pediatr Cardiol*. 2015; 8:50–52. [PubMed: 25684888]
36. Saul JP, Scott WA, Brown S, Marantz P, Acevedo V, Etheridge SP, Perry JC, Triedman JK, Burriss SW, Cargo P, Graepel J, Koskelo EK, Wang R. Intravenous Amiodarone Pediatric Investigators. Intravenous amiodarone for incessant tachyarrhythmias in children: a randomized, double-blind, antiarrhythmic drug trial. *Circulation*. 2005; 112:3470–3477. [PubMed: 16316969]
37. Tsuda E, Matsuo M, Sakaguchi H, Hayashi T, Hosoda K, Miyazaki A. Combined amiodarone and low-dose carvedilol treatment for severe heart failure in childhood. *Pediatr Int*. 2010; 52:e39–e42. [PubMed: 20158646]
38. Valdes SO, Donoghue AJ, Hoyme DB, Hammond R, Berg MD, Berg RA, Samson RA. American Heart Association Get With The Guidelines-Resuscitation Investigators. Outcomes associated with amiodarone and lidocaine in the treatment of in-hospital pediatric cardiac arrest with pulseless ventricular tachycardia or ventricular fibrillation. *Resuscitation*. 2014; 85:381–386. [PubMed: 24361455]
39. Gonzalez D, Melloni C, Yogev R, Poindexter BB, Mendley SR, Delmore P, Sullivan JE, Autmizguine J, Lewandowski A, Harper B, Watt KM, Lewis KC, Capparelli EV, Benjamin DK Jr, Cohen-Wolkowicz M. Best Pharmaceuticals for Children Act – Pediatric Trials Network Administrative Core Committee. Use of opportunistic clinical data and a population pharmacokinetic model to support dosing of clindamycin for premature infants to adolescents. *Clin Pharmacol Ther*. 2014; 96:429–437. [PubMed: 24949994]
40. Holford N, Heo Y, Anderson B. A pharmacokinetic standard for babies and adults. *J Pharm Sci*. 2013; 102:2941–2952. [PubMed: 23650116]
41. Weibel ER. Physiology: the pitfalls of power laws. *Nature*. 2002; 417:131–132. [PubMed: 12000943]
42. Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. *Annu Rev Pharmacol Toxicol*. 2008; 48:303–332. [PubMed: 17914927]
43. Dennis, J., Schnabel, RB. Numerical Methods for Unconstrained Optimization and Nonlinear Equations. 1996. Available at: <https://doi.org/10.1137/1.9781611971200>
44. Upton RN. Calculating the hybrid (macro) rate constants of a three-compartment mamillary pharmacokinetic model from known micro-rate constants. *J Pharmacol Toxicol Methods*. 2004; 49:65–8. [PubMed: 14670695]

45. Fernandez E, Perez R, Hernandez A, Tejada P, Arteta M, Ramos JT. Factors and mechanisms for pharmacokinetic differences between pediatric population and adults. *Pharmaceutics*. 2011; 3:53–72. [PubMed: 24310425]
46. Batchelor HK, Marriott JF. Paediatric pharmacokinetics: key considerations. *Br J Clin Pharmacol*. 2015; 79:395–404. [PubMed: 25855821]
47. Holt DW, Tucker GT, Jackson PR, Storey GC. Amiodarone pharmacokinetics. *Am Heart J*. 1983; 106:840–847. [PubMed: 6613830]
48. Hines RN. Developmental expression of drug metabolizing enzymes: impact on disposition in neonates and young children. *Int J Pharm*. 2013; 452:3–7. [PubMed: 22766445]

Fig. 1. Standard goodness-of-fit plots of the final model. Observed versus population (A) and individual (B) predictions for the amiodarone model (note log-log scale). The line of identity is indicated by a solid line, the smooth fit to the data by the dashed line. Conditional weighted residuals (CWRES) versus time after dose (C) and population predictions (D) for the base amiodarone PK model.

Fig. 2.

Visual predictive check of the amiodarone population PK model displays observations and prediction intervals for the PTN (A) and Ramusovic (B) datasets. Solid lines and surrounding shaded areas represent, from top to bottom, 5th, 50th and 95th percentile of model predictions, each with their respective ± 1 SD. Top and bottom dashed lines are the 95th and 5th percentiles for the observed data; middle dashed line is the median. Circles represent the observed data collected across all subjects.

Fig. 3. Observed and predicted amiodarone concentrations determined in 13 patients over 2 years of age

Fig. 4. Mean values ($\pm$ SD) from simulation to illustrate impact of third, deep compartment on expected amiodarone concentration accumulation and decay with chronic dosing (open circles = 3-compartment model with large, deep compartment – final model; filled circles = 2-compartment model)

Table 1

Demographic data for subjects <2 years old

	PTN (n=29)	Ramusovic (n=16)
Postnatal age, days	40.0 (20.0–171.0)	49.5 (15.5–112.5)
Weight, kg	3.9 (3.1–6.0)	4.0 (3.6–4.6)
Male sex	18 (62%)	Not available
White race	15 (52%)	Not available

Continuous variables expressed as median (interquartile range); categorical variables expressed as n (%).

PTN, Pediatric Trials Network.

Table 2

Comparison of amiodarone administration in subjects <2 years old in PTN, Ramusovic, and combined datasets

Group	PTN	Ramusovic	Combined
Total subjects	29	16	45
Patients receiving IV only	13	16	29
Patients receiving enteral only	10	0	10
Patients receiving both IV and enteral	6	0	6
IV bolus doses, mg/kg, mean $\pm$ SD	3.1 $\pm$ 2.4 N = 16	5.0 N = 33	4.4 $\pm$ 1.6 N = 49
IV infusions, mg/kg/h, mean $\pm$ SD	0.7 $\pm$ 0.7 N = 64	0.4 N = 16	0.6 $\pm$ 0.7 N = 80
Infusion duration, h, mean $\pm$ SD	39.9 $\pm$ 59.5	94.6 $\pm$ 68.8	50.8 $\pm$ 64.9
Enteral doses, mg/kg, mean $\pm$ SD	4.3 $\pm$ 2.4 N = 110	– N = 0	4.3 $\pm$ 2.4 N = 110
Number of plasma drug concentrations	52	214	266

IV, intravenous; PTN, Pediatric Trials Network; SD, standard deviation.

Table 3

Summary of model-building process for amiodarone

Step	Structural model Compartment	CL, Q scaling by WT ^a	Residual error model	N parameters	OFV	OFV	Condition number
1	1 CPT	$CL_i = \theta_{(2)} * \left(\frac{WT_i}{median\ WT} \right)^1$	Proportional	9	685		99
2	2 CPT	$CL_i = \theta_{(2)} * \left(\frac{WT_i}{median\ WT} \right)^1$	Proportional	13	615	-70	288
3	2 CPT	$CL_i = \theta_{(2)} * \left(\frac{WT_i}{median\ WT} \right)^{0.75}$	Proportional	13	614	-71	361
4	3 CPT (V _d , Q _d , ETAs estimated)	$CL_i = \theta_{(2)} * \left(\frac{WT_i}{median\ WT} \right)^{0.75}$	Proportional	17	595	-90	355
5	3 CPT (V _d , Q _d , ETAs estimated)	$CL_i = \theta_{(2)} * \left(\frac{WT_i}{median\ WT} \right)^{0.75}$	Proportional ^b	16	573	-112	1701
6	3 CPT (V _d , Q _d , ETAs estimated)	$CL_i = \theta_{(2)} * \left(\frac{WT_i}{median\ WT} \right)^{\theta_{(7)}}$	Proportional ^b	17	574	-111	454
7	3 CPT (fixed V _d , Q _d , ETAs not estimated)	$CL_i = \theta_{(2)} * \left(\frac{WT_i}{median\ WT} \right)^{\theta_{(7)}}$	Proportional ^b	13	598	-87	189
8	3 CPT (fixed V _d , Q _d , ETAs estimated)	$CL_i = \theta_{(2)} * \left(\frac{WT_i}{median\ WT} \right)^{0.75}$	Proportional ^b	14	575	-110	154
9	3 CPT (fixed V _d , Q _d , ETAs estimated)	$CL_i = \theta_{(2)} * \left(\frac{WT_i}{median\ WT} \right)^{\theta_{(7)}}$	Proportional ^b	15	575	-110	171

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θ Analogous expressions used for CL_j and Q_j with identical exponents.

η Proportional residual error model was used with modification to account for differences in residual error between PTN and Ramusovic datasets (Equation 2).

CL, clearance; CPT, compartment; ETAs, individual deviations from the population-typical value pharmacokinetic parameters; OFV, objective function value; Q, intercompartmental clearance; V_d, volume of distribution, WT, weight.

Table 4

Parameter estimates for the final population PK model for amiodarone

Parameter	Estimate	RSE, %	2.5%	Bootstrap ^a Median	97.5%	Shrinkage, fraction
Structural Model^a						
K_A, h^{-1}	0.18	25	0.04	0.17	0.28	
$CL_{median}, L/h$	1.03	18	0.62	1.03	1.49	
V_{median}, L	2.59	33	1.20	2.66	5.29	
$Q_{pmedian}, L/h$	14.7	21	7.10	13.2	21.2	
$V_{pmedian}, L$	30.0	22	16.0	28.6	45.8	
$Q_b, L/h^b$	1.32					
V_b, L^b	326					
F, fraction	0.53	14	0.40	0.56	0.78	
WTG on CL and Q ^c	0.69	28	0	0.61	1.48	
Inter-individual Variability, CV%						
CL	49	12	31	44	67	0.55
V_c	121	55	96	115	165	0.63
Q	90	32	65	79	126	0.59
V_p	101	29	83	96	126	0.45
Q_d	125	56	104	121	266	0.34
V_d	84	40	46	76	489	0.67
Residual Error						
Proportional error, %	74	10	58	73	88	0.13
Exponential of PTN on residual error ^d	-1.26	17	-2.04	-1.28	-0.82	

^aPK parameters normalized to median weight in kg.

^bPK parameters fixed to literature values (see text).

^cThe estimated body weight scaling exponent for CL and Q.

^dThe modifying factor for residual variability in the PTN dataset (see Equation 2).

CL, clearance; CV, coefficient of variation; F, bioavailability; K_A, absorption rate constant; Q, intercompartmental clearance; RSE, relative standard error; V, volume of distribution.

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Table 5

Comparison of empirical Bayesian estimates of PK parameters by age groups in the combined datasets

Age Group	N	CL, L/h/kg	Vss, L/kg	Half-life alpha, h	Half-life beta, h	Half-life gamma, h
0–2 months	27	0.27 (0.16–0.38)	99.4 (63.5–173)	0.09 (0.06–0.18)	9.29 (4.11–24.0)	420 (277–926)
2 months – 1 year	4	0.23 (0.14–0.28)	89 (86–107)	0.11 (0.06–0.28)	11.7 (6.91–47.9)	515 (349–1180)
1–2 years	14	0.20 (0.14–0.24)	101 (87–167)	0.13 (0.08–0.16)	12.7 (60.2–20.6)	637 (522–1099)
Combined age groups	42	0.25 (0.14–0.36)	93 (68–174)	0.09 (0.06–0.18)	10.4 (4.40–27.9)	497 (297–1161)

Values are median (90% confidence intervals).

CL, clearance; Vss, volume of distribution at steady state; Half-lives alpha, beta, and gamma from each phase of the tri-phasic decline in serum concentrations.

Table 6

Mean population PK parameter values in the current study compared with published adult values

Study	Population	CL, L/kg/h	V _{ss} , L/kg	MRT, h	Mean plasma sampling, h	# Model compartments
Korth-Bradley et al (1996) [13]	Adults	0.22	10.3	47	151	2
Vadiei et al (1997) [16]	Adults	0.113	58.2	515	1824	4
Pollak et al (2000) [8]	Adults	0.061	87	1426	17452	2
Araki et al (2011) [11]	Adults	0.06	39.2	653	28896	1
Current study	<2 years	0.25	93	346	NA ^a	3

^aThe mean plasma sampling from the current study was 76 hours, but it is not comparable to sampling times from other studies because values of deep compartment parameters were fixed rather than estimated.

CL, clearance; MRT, mean residence time; V_{ss}, volume of distribution at steady state.