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Antithrombin Population Pharmacokinetics in Pediatric Ventricular Assist Device Patients

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Objectives: Describe the pharmacokinetics of antithrombin in pediatric patients undergoing ventricular assist device therapy and provide dosing recommendations for antithrombin in this population.

Design: A retrospective population pharmacokinetic study was designed.

Setting: Large tertiary care children's hospital Subject inclusion criteria consisted of less than 19 years old.

Patients: Subjects less than 19 years old undergoing therapy with a HeartWare ventricular assist device (HeartWare, Framingham, MA) or Berlin EXCOR ventricular assist device (Berlin GmbH, Berlin, Germany), who received a dose of antithrombin with a postdose antithrombin activity level from January 1, 2011, to June 30, 2017.

Interventions: Population pharmacokinetic analysis and simulation using NONMEM v.7.4 (Icon, PLC, Dublin, Ireland).

Measurements and Main Results: A total of 41 patients met study criteria (median age, 5.8 years [interquartile range, 1.6–9.9 yr]), and 53.7% underwent therapy with the pulsatile Berlin EXCOR pediatric ventricular assist device (Berlin Heart GmbH, Berlin, Germany). All patients received unfractionated heparin continuous infusion at a mean ± SD dose of 29 ± 14 U/kg/hr. A total of 181 antithrombin doses (44.1 ± 24.6 U/kg/dose) were included, and baseline antithrombin activity levels were 77 ± 12 U/dL. Antithrombin activity levels were drawn a median 19.9 hours (interquartile range, 8.8–41.6 hr) after antithrombin dose. A one-compartment proportional error model best fit the data, with allometric scaling of fat-free mass providing a better model fit than actual body weight. Unfractionated heparin and baseline antithrombin were identified as significant covariates. A 50 U/kg dose of antithrombin had a simulated half-life 13.2 ± 6.6 hours.

Conclusions: Antithrombin should be dosed on fat-free mass in pediatric ventricular assist device patients. Unfractionated heparin dose and baseline antithrombin activity level should be considered when dosing antithrombin in pediatric ventricular assist device patients. (*Pediatr Crit Care Med* 2019; 20:1157–1163)

Key Words: antithrombin; NONMEM; pediatrics; population pharmacokinetics; ventricular assist device

Anticoagulation management in pediatric patients undergoing therapy with a ventricular assist device (VAD) is challenging and is compounded by the limited data for optimal pharmacotherapy (1–7). A variety of strategies for management of hemostasis and anticoagulation in the VAD population are often used based upon individual patient characteristics, institutional protocols, type of VAD, and overall patient goals (8). Similar to patients treated with extracorporeal membrane oxygenation, the pharmacokinetic disposition of many medications in the pediatric VAD population may be altered due to changes in blood volume, end-organ dysfunction, postoperative inflammation, characteristics of the VAD circuit, and patient circulatory pathophysiology (9).

Use of human-derived antithrombin is a pharmacotherapeutic intervention for patients receiving high dose unfractionated heparin (UFH) therapy who are not achieving anticoagulation goals (10–12). The role of antithrombin in the coagulation cascade involves inactivation of factor IIa (thrombin) and factor Xa in the presence of UFH (13). Antithrombin is an endogenous protein, and high dose UFH can contribute to depletion of antithrombin resulting in diminished efficacy of UFH, undesirable alterations in markers of hemostasis, and potential increase in patient thrombosis risk (14). Alternatively, supplementation of antithrombin is commonly used to improve the efficacy of UFH, resulting in lower UFH doses while maintaining goal anticoagulation markers (15).

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Dr. Moffett disclosed off-label product use of antithrombin in pediatric ventricular assist device patients. Dr. Teruya received funding from STAGO (reagent company for coagulation, Advisory committee), Evaheart, and Octapharma. Dr. Adachi serves as consultant and proctor for Berlin Heart and Medtronic and consultant for Sony-Olympus Medical Solutions. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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UFH is commonly used as an anticoagulation strategy in the pediatric VAD population due to the large substrate for thrombus formation in comparison to patient size and the acuity of the patient population, particularly in the early postoperative period (6, 16–18). Bleeding complications in the VAD population can be frequent and potentially life-threatening, and close management of anticoagulation strategies, including strategies for antithrombin supplementation, is necessary (19–21).

At our institution, antithrombin has been supplemented in pediatric VAD patients undergoing therapy with the HeartWare VAD (HeartWare, Framingham, MA) and the Berlin Heart EXCOR VAD (Berlin Heart GmbH, Berlin, Germany). There are no pharmacokinetic data to support dosing of antithrombin in the pediatric VAD population and the potential for altered disposition of antithrombin in this patient population is significant. The objective of this study is to characterize the pharmacokinetic disposition of antithrombin in the pediatric VAD population and derive dosing recommendations for antithrombin use in the pediatric VAD population.

MATERIALS AND METHODS

The study was approved by the Baylor College of Medicine and Affiliated Institutions Institutional Review Board. A retrospective descriptive population pharmacokinetic study was designed, and patients were identified by querying the hospital electronic medical record system from January 1, 2011, to June 30, 2017, for administration of human-derived antithrombin (Thrombate; Grifols USA, LLC, Clayton, NC). Patients were included in the study if they were less than 19 years old, underwent therapy with a either a pulsatile Berlin Heart EXCOR pediatric VAD (Berlin Heart GmbH) or nonpulsatile HeartWare VAD, received a dose of antithrombin while undergoing VAD therapy, had a baseline antithrombin activity level, and had at least one antithrombin activity level drawn after antithrombin administration while undergoing VAD therapy. Patient data were excluded if they received fresh frozen plasma or cryoprecipitate during antithrombin therapy. The first antithrombin concentration after a dose was included, and subsequent concentrations were included if they were less than or equal to the first postdose concentration.

Data collection included as follows: male (M), patient age in years (AGEYRS), weight (kg), height (cm), type of VAD (pulsatile vs nonpulsatile), UFH dose (U/hr), serum creatinine (mg/dL), urine output over the 12 hours prior to the antithrombin activity (mL), platelets (/mm^3), hematocrit (%), antithrombin dose (U), and antithrombin activity (U/dL). Fat-free mass (FFM) was calculated for each patient as well as body surface area (22, 23) (**Appendix I**, Supplemental Digital Content 1, http://links.lww.com/PCC/B27). The methodology for analysis of antithrombin activity levels at our institution has been previously reported and included the use of the STA-R analyzer using the STA-Rotachrom antithrombin kit (Diagnostica Stago, Asnieres, France) (24).

Descriptive Analysis

Descriptive statistical methods using percentages, mean, SD, median and range, for normally and nonnormally distributed data were used as appropriate, as was data visualization. Statistical analyses were performed using Excel 2013 (Microsoft Corp, Redmond, WA).

Pharmacokinetic Analysis

NONMEM v.7.4 (Icon, PLC, Dublin, Ireland) and PDx-Pop 5.2 (Icon, PLC) using first-order conditional estimation with interaction were used for the population pharmacokinetic analysis. Interindividual variability (IIV) was exponentially modeled. A base model, with no covariates, was initially developed based upon prior literature and graphing antithrombin activity versus time after dose (**Fig. 1**). Baseline activity levels (BASE) were included in the error model to account for endogenous production of antithrombin (25). One and two compartment models, with additive, exponential, proportional, and proportional and additive error structures were evaluated.

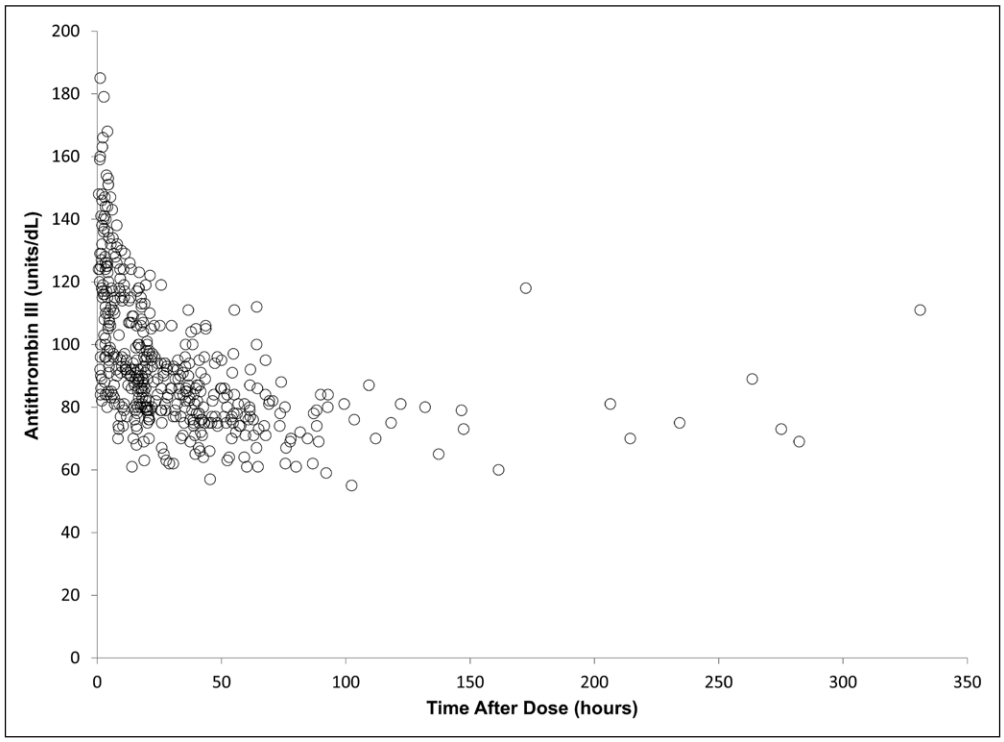

Figure 1. Antithrombin activity (U/dL) versus time after antithrombin administration (hr). A large portion of the antithrombin activity was sampled in the 48 hr after a dose.

TABLE 1. Demographic Variables

Category ($n = 41$)	Value
Male (%)	43.9
Age, yr, median (IQR)	5.8 (1.6–9.9)
Height, cm, median (IQR)	114 (78–132)
Weight, kg, median (IQR)	19.5 (8.6–27.7)
Body surface area, m^2, mean (SD)	0.86 ± 0.54
Fat-free mass, kg, median (IQR)	16.0 (7.0–22.9)
Hematocrit (%), mean (SD)	30.9 ± 3.9
Platelet (count/μL), mean (SD)	244 ± 127
Serum creatinine (mg/dL), mean (SD)	0.42 ± 0.32
Urine output over previous 12 hr (mL), mean (SD)	593 ± 394
Urine output over previous 12 hr (mL/kg/hr), mean (SD)	3.1 ± 2.0

IQR = interquartile range.

Covariates were visually evaluated against pharmacokinetic variables for potential inclusion in the population pharmacokinetic model. After inclusion of a covariate, a reduction of greater than 3.84 in the objective function value (OFV) was considered statistically significant. After individual covariate analysis, a full model, containing all statistically significant covariates, was developed. A covariate was retained for the final model if the OFV increased by greater than 10.83 (a significance level of $p < 0.001$ at one degree of freedom) when an individual covariate was removed from the full model (26). Bootstrap simulations were performed ($n = 1{,}000$) on the final model with calculation of 95% CIs.

Scatter plots of dependent variables versus population predicted (PRED) and individual predicted antithrombin activity levels and conditional weighted residuals versus PRED and time after dose were developed for the final model to evaluate bias and determine goodness of fit (27) (**Figs. 2–5**).

Based upon the final model, a simulation was performed with 10,000 replications to derive dosing recommendations. A virtual patient for the simulation was developed from mean covariate values in the dataset based upon the included covariates in the final model. A dose of 50 U/kg infused over 15 minutes was simulated, based upon previously published data, and antithrombin activity levels were simulated at 1-hour post-infusion, 6 hours, 12 hours, and 24 hours (28). Simulated clearance, volume of distribution (VD), and half-life were calculated from the simulation dataset to help provide dosing and monitoring recommendations.

RESULTS

Demographics

A total of 41 patients met study criteria and 53.7% ($n = 22$) underwent therapy with the Berlin EXCOR VAD (pulsatile), the rest with the HeartWare VAD (nonpulsatile). Demographic information was summarized (**Table 1**). All patients received UFH continuous infusion at a mean dose of 29 ± 14 U/kg/hr. Patients received a total of 181 doses of antithrombin infused over 15 minutes at a mean dose of 798 ± 720 U (44.1 ± 24.6 U/kg/dose). Baseline antithrombin activity levels were a mean 77 ± 12 U/dL prior to an antithrombin dose. In total, 475 post-dose antithrombin activity levels (median 6 [interquartile range (IQR) 3–14] per patient) were sampled at a median 19.9 hours (IQR, 8.8–41.6 hr) after an antithrombin dose and were a median 89 U/dL (IQR, 79–106 U/dL) (Fig. 1).

Pharmacokinetic Modeling

Initial noncompartmental pharmacokinetic investigations into the data elucidated estimates of VD to be median 2.67 dL/kg (IQR, 1.1–5.9 dL/kg) and clearance of median 2.35 dL/hr (IQR, 0.62–6.89 dL/hr). Population pharmacokinetic modeling identified a one-compartment proportional error model fit the data (had the lowest OFV) with IIV modeled exponentially. Weight and FFM were added to the base model with allometric scaling on clearance (exponent 0.75) and VD (exponent 1), and the model with FFM had the lowest OFV (**Supplemental Table 1**, Supplemental Digital Content 2, http://links.lww.com/PCC/B28). The model with FFM was then used for further analysis of individual covariates.

Covariates which resulted in a significant (> 3.84) decrease in OFV on clearance included UFH and BASE antithrombin activity level, while AGEYRS and the use of the Berlin Heart EXCOR (pulsatile) resulted in significant changes in the OFV when evaluating VD. During the backward stepwise removal of covariates, only UFH and BASE remained statistically significant (change in OFV > 10.83), and remained the only two covariates (other than FFM) in the final model (**Table 2**).

TABLE 2. Final Pharmacokinetic Model

Model ($n = 41$)	Interindividual Variability (%)	Residual Variability (%)
$CL = 2.75 \times \left(\frac{FFM}{70}\right)^{0.75} \times \left(\frac{BASE}{76}\right)^{2.88} \times \left(\frac{UFH+1}{400}\right)^{0.11}$	42.7	11.4
$VD = 71.5 \times \left(\frac{FFM}{70}\right)$	21.1	

BASE = baseline antithrombin activity (U/dL), CL = clearance (dL/hr), FFM = fat-free mass (kg), UFH = unfractionated heparin (U/hr), VD = volume of distribution (dL).

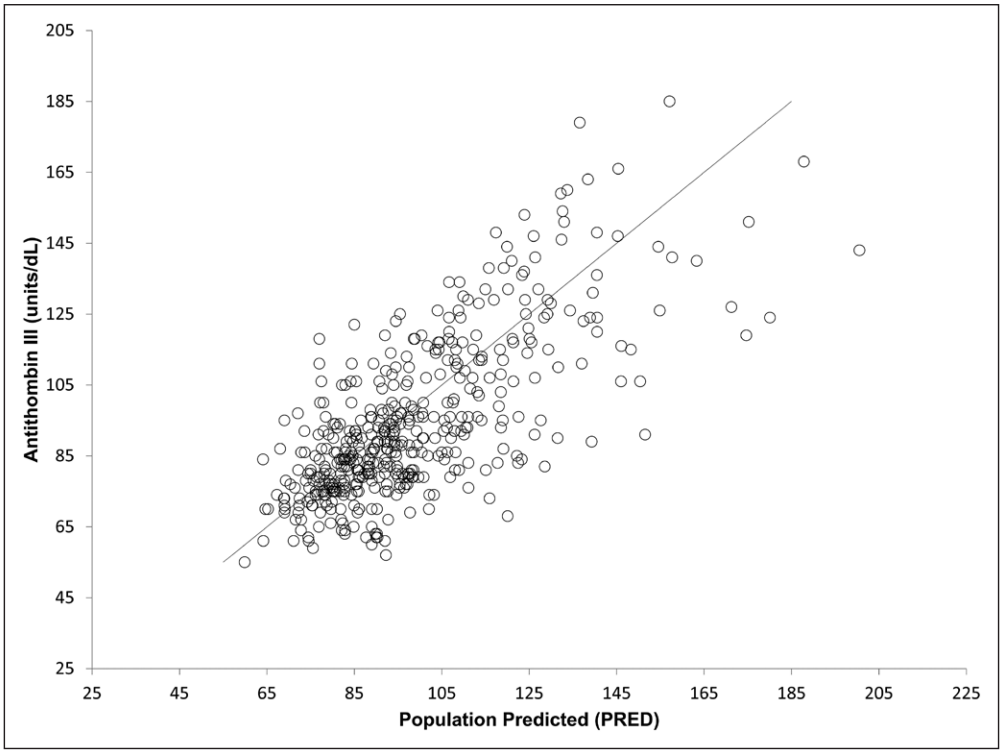

Figure 2. Dependent variables versus population predicted. There is good agreement around the line of unity demonstrating model fit.

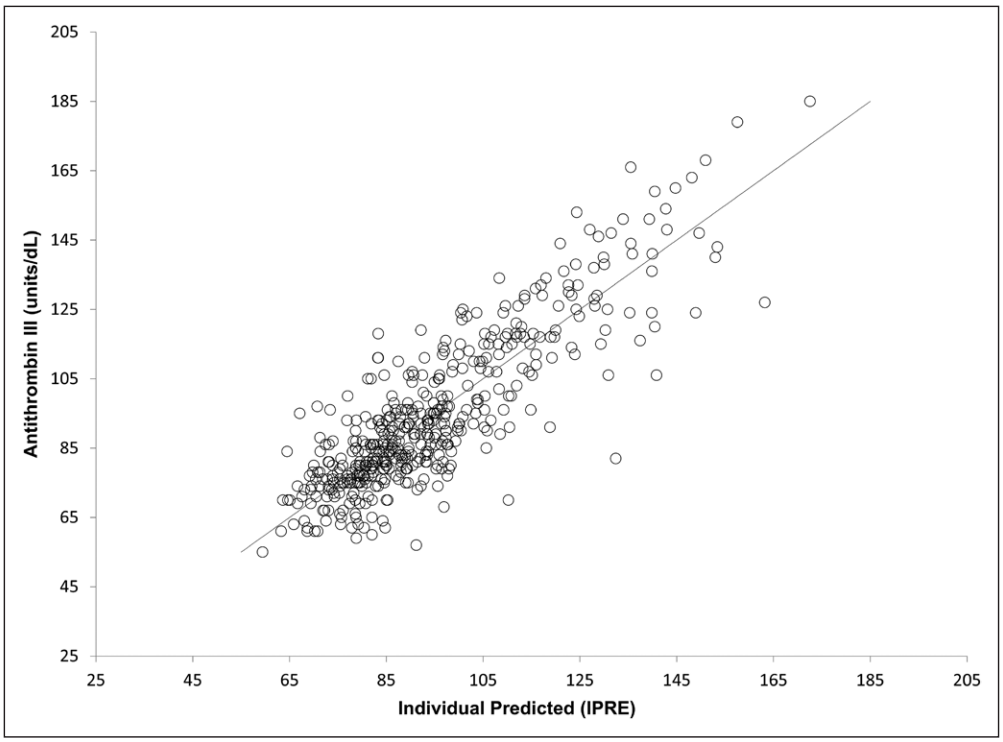

Figure 3. Dependent variables versus individual predicted. There is good agreement around the line of unity demonstrating model fit.

Diagnostic plots demonstrated good fit around lines of unity and no apparent bias (Figs. 2–5). Bootstrap analysis was performed on the final model with a 95.2% success rate (**Supplemental Table 2**, Supplemental Digital Content 3, http://links.lww.com/PCC/B29).

Simulation

A virtual patient was developed from the mean covariate values in the dataset (weight = 19.5, FFM = 16 kg, BASE (baseline antithrombin activity) = 77 U/dL, UFH = 29 U/kg/hr) who received a 50 U/kg bolus (based on FFM). The resultant simulated concentrations at 1, 6, 12, and 24 hours after the dose were 124 ± 11, 111 ± 9, 101 ± 9, and 89 ± 8 U/dL, respectively. Simulated pharmacokinetic values were as follows: clearance was 0.05 ± 0.02 dL/kg/hr, VD was 0.85 ± 0.18 dL/kg, and half-life was calculated to be 13.2 ± 6.6 hours.

DISCUSSION

This is the first evaluation of antithrombin population pharmacokinetics in the pediatric VAD population. Insights into the pharmacokinetic profile include the lack of effect of VAD type on antithrombin pharmacokinetics and the use of FFM to more accurately describe clearance and VD. The use of FFM in this patient population is significant as the presence of obesity in the pediatric patient population approaches 20% of 2–18 year olds (29). The use of FFM to dose medications in this patient population can potentially be extrapolated to other medications used in pediatric VAD patients, such UFH, which require lower doses per body weight in obese patients as compared with nonobese patients (30, 31). FFM should be used to dose antithrombin in the pediatric VAD population.

We have identified two additional covariates, baseline antithrombin activity level (BASE) and dose of UFH, which affect the clearance of antithrombin. The clearance of antithrombin in the pediatric VAD population is greater than what has been previously reported in adult and pediatric patients

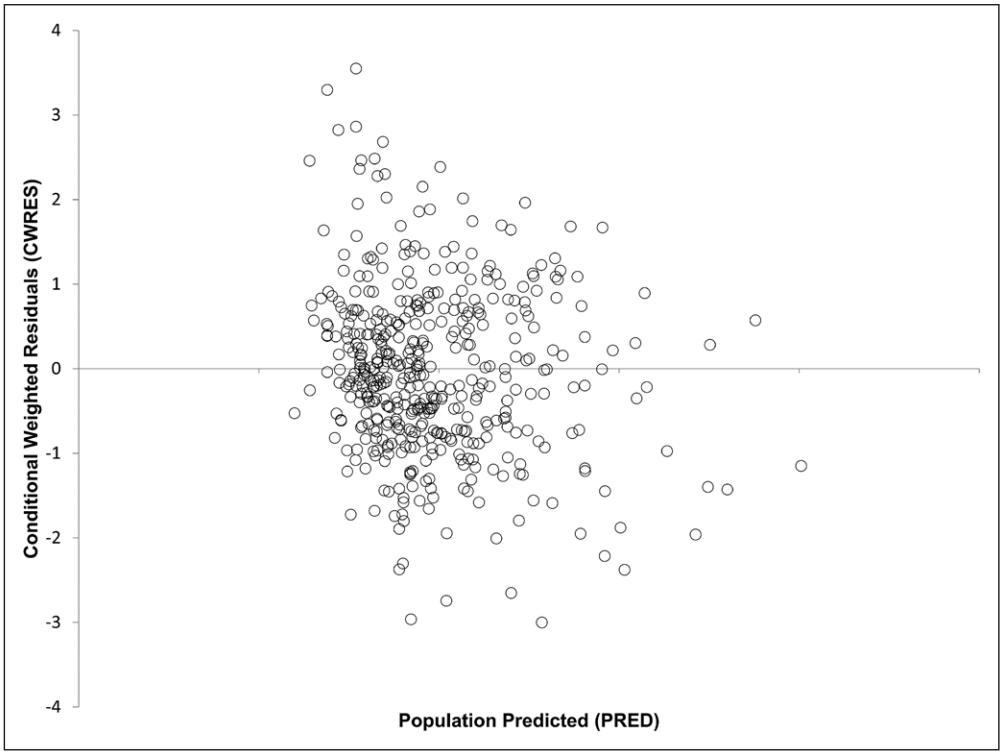

Figure 4. Conditional weighted residuals versus population predicted concentrations. No apparent bias is noted in the figure demonstrating model fit.

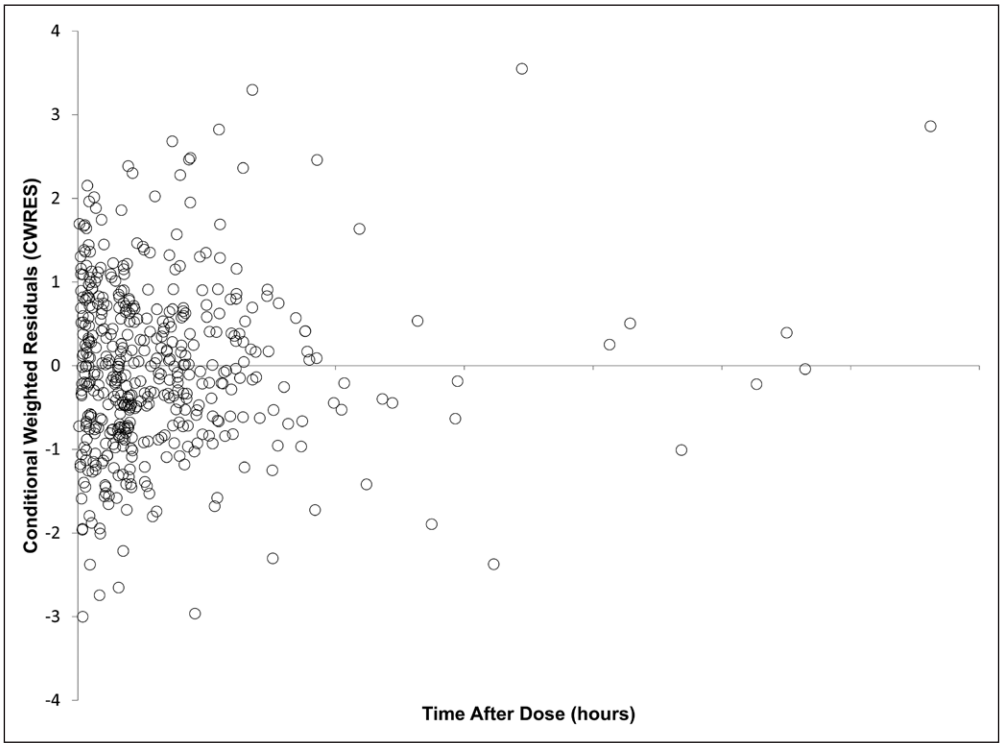

Figure 5. Conditional weighted residuals versus time after antithrombin administration (hr). No apparent bias is noted in the figure demonstrating model fit.

and is approximately three times higher than those we have previously identified in the pediatric non-VAD population (2.75 dL/hr vs 0.917 dL/hr) (24). We can speculate that the VAD circuit, and the associated coagulopathies that have been identified with VAD patients, resulted in the higher clearance values. Also, the model developed from the prior investigation demonstrated an additive effect of the use of UFH on clearance, while the model we have developed in the present study has a multiplicative effect of UFH on clearance (24). The relationship between UFH and antithrombin is complex, as increased doses of UFH can increase the clearance of antithrombin, yet supplementation of antithrombin has been shown to decrease UFH requirements while maintaining goal markers of anticoagulation, such as the activated partial thromboplastin time (11, 12, 32, 33). We did not incorporate anticoagulation endpoints into our analysis; however, it is evident that evaluation of UFH dose prior to antithrombin dosing and monitoring in the pediatric VAD population is necessary.

Estimates for VD were remarkably similar in this analysis of the pediatric VAD population (71.5 dL) as compared with the pediatric non-VAD population (67.9 dL) (24). Both of these values are somewhat higher than the estimates reported from a noncompartmental pharmacokinetic analysis of antithrombin in the adult population (45 dL) (34). The difference in VD is likely due to changes in body habitus associated with maturation of pediatric patients (35). It is clear from our analysis that the pediatric VAD population has altered antithrombin pharmacokinetic values, particularly on clearance, compared with adult or pediatric non-VAD patient populations.

We simulated a dose of 50 U/kg, which has been previously reported as an empiric dose in the pediatric patient population (28). We had previously estimated a dose of approximately 60 U/kg in the pediatric non-VAD population to attain an

antithrombin activity level of 120% in patients with a baseline of 60 U/dL and receiving 34 U/kg/hr of UFH (24). We present the data from the simulation as a guide to antithrombin dosing in this patient population, as individual patient cases will undoubtedly require alterations in dosing and monitoring strategies. The goal of antithrombin activity levels in pediatric VAD patients are not absolutely defined, and the normal values of antithrombin activity in pediatric patients are often considered 85–130% (36). Due to the complexity involved in VAD anticoagulation, recommendations for specific dosing and monitoring regimens would be outside the scope of this article. However, the dose of 50 U/kg appears to be a reasonable empiric dose to achieve antithrombin activity levels that have been recognized as therapeutic. Monitoring and re-dosing strategies can be evaluated based upon the half-life values generated and the dose of UFH concomitantly administered. The dose to be used for a patient should encompass overall patient goals and the analysis we have provided should serve as a basis for monitoring and dosing of antithrombin.

This is a retrospective review of data, and the limitations associated with this type of study should temper the conclusions and applications of these data. The data collected were clinical data, and data such as fluid intake, were unable to be captured. The indications for antithrombin, such as baseline antithrombin activity, and frequency of monitoring, were under the purview of the clinician. Prospective analysis, with a defined sampling strategy, would likely improve the characterization of the pharmacokinetic estimates we have derived. Prospective validation of the developed model would also be necessary to evaluate the recommendations we have provided.

We would like to note that the patient population we evaluated consisted of the HeartWare or Berlin Heart EXCOR patients (the only VAD patients who received antithrombin at our institution) and that extrapolation to other VAD types should only occur with considerable caution. We were unable to evaluate any patient outcomes with antithrombin supplementation. To fully evaluate the effect of antithrombin in the pediatric VAD population, outcomes such as bleeding, thrombosis, and circuit life will have to be evaluated.

CONCLUSIONS

This study provides the first insight into the pharmacokinetics of antithrombin in children with end-stage heart failure supported with VADs. Antithrombin pharmacokinetics appear to be altered by UFH and the baseline antithrombin activity levels in pediatric patients undergoing VAD therapy. FFM appears to be superior to actual body weight for characterization of antithrombin pharmacokinetics and should be used for replacement dosing. Finally, the characteristics of the VAD flow pattern and support do not seem to affect antithrombin pharmacokinetics.

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