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Pharmacokinetics of cefazolin delivery via the cardiopulmonary bypass circuit priming solution in infants and children

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Objectives: Our aim was to describe the pharmacokinetics of cefazolin in paediatric patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) who received cefazolin for peri-operative surgical prophylaxis in addition to having cefazolin added to the CPB circuit priming solution. Secondary aims were to determine the pharmacodynamic exposure associated with the addition of cefazolin to the CPB priming solution and to assess whether a target cefazolin concentration range for the CPB priming solution could be identified.

Methods: A multicentre, prospective, open-label pharmacokinetic study was carried out in children from birth to 16 years of age undergoing cardiac surgery.

Results: Forty-one patients met the inclusion criteria and accounted for 492 samples for analysis. Cefazolin concentrations were best described by a one-compartment model with weight as a covariate on the volume of distribution (V_d) with allometric scaling. The mean ± standard deviation (SD) total body CL for the birth–6 month cohort was 0.009 ± 0.006 mL/min/kg with a mean ± SD V_d of 0.59 ± 0.26 L/kg, the mean ± SD total body CL for the 7 month–3 year cohort was 0.01 ± 0.005 mL/min/kg with a mean ± SD V_d of 0.79 ± 0.15 L/kg, and the mean ± SD total body CL for the 4–16 year cohort was 0.007 ± 0.004 mL/min/kg with a mean ± SD V_d of 3.4 ± 0.94 L/kg. The median cefazolin loss in the CPB circuit ranged from 78% to 95% and the median patient cefazolin concentration after CPB circuit detachment ranged from 92 to 197 mg/L.

Conclusions: These data demonstrate that mixing cefazolin in the CPB circuit priming solution was effective in maintaining cefazolin serum concentrations during surgery. If this practice is utilized, re-dosing of cefazolin during the CPB run and upon CPB circuit detachment is most probably not needed. Larger pharmacokinetic studies are warranted.

Introduction

According to the US CDC, congenital heart defects (CHDs) are the most common type of birth defect, affecting about 1% of births (~40 000 per year in the USA).[1,2] The prevalence of certain mild CHDs is increasing, and the most common defect is a ventricular septal defect.[3,4] Approximately 25% of infants have a critical CHD requiring surgery in the first year of life.[5] About 4.2% of neonatal deaths are due to a CHD and, from 1999 to 2006, there were an estimated 41 000 deaths related to CHD, with 48% of these deaths in children <1 year of age.[6,7] The cost of care for individuals with CHD in the USA was estimated at US$1.4 billion and the cost of care for patients with severe CHDs was about US$511 million, or ~37%, of the overall hospital costs associated with CHDs.[8] The rate of surgical site infections after paediatric cardiac surgery is estimated to be 0.25%–6% and is associated with an increase in hospital costs of about US$136 950 per case and an increased hospital length of stay of 9.5 days per case.[9] As such, the importance of infection prevention measures, including peri-operative antimicrobial management, is crucial.

Cardiopulmonary bypass (CPB) is a form of extracorporeal support for the heart and lungs to maintain circulation and the oxygen content and delivery to organs during cardiac surgery.[10] CPB is used in >18 000 paediatric open heart surgical procedures each year in North America and is known to impact the pharmacokinetics of drugs used during surgery.[11,12] The current recommendation for peri-operative antimicrobial prophylaxis for cardiac surgery with or without CPB is cefazolin in the absence of an allergy.[13]

The alterations in cefazolin pharmacokinetics during CPB have recently been investigated in adults and children.[14–16] These investigations suggest that current peri-operative antimicrobial prophylaxis regimens do not provide an appropriate pharmacodynamic exposure to cefazolin for surgical prophylaxis when a typical intermittent dosing regimen is employed.[14,15] In both of these investigations, the cefazolin was given intravenously directly to the patient. The exact contents of the cardioplegia and CPB priming solutions vary by institution, and drugs such as tranexamic acid and allopurinol have been added to the priming solution for use during the CPB run.[17,18] To date, no investigations have evaluated the pharmacokinetics of cefazolin during CPB when cefazolin is given to the patient in addition to being added to the CPB circuit priming solution. Therefore, the primary aim of this investigation was to describe the pharmacokinetics of cefazolin in paediatric patients undergoing cardiac surgery with CPB who received cefazolin for peri-operative surgical prophylaxis in addition to having cefazolin added to the CPB circuit priming solution. Secondary aims were to determine the pharmacodynamic exposure associated with the addition of cefazolin to the CPB priming solution and to assess whether a target cefazolin concentration range for the CPB priming solution could be identified.

Patients and methods

Patient population and study design

This was a prospective, open-label pharmacokinetic study conducted at St Christopher's Hospital for Children and New York University (NYU) Langone Medical Center from 1 January 2015 to 31 December 2016. The study protocol was approved by the Drexel University College of Medicine and NYU Institutional Review Boards. Children from birth to 16 years of age were eligible for inclusion. Patients with known allergies to cefazolin were excluded; however, children with allergies to other β-lactam antibiotics but documented tolerance to cefazolin were included. The age range of birth–16 years of age was chosen to allow for pharmacokinetic variability that may be due to changes in age, weight or other physiological characteristics.

According to institutional protocol, cefazolin 25 mg/kg to a maximum of 2000 mg was given as a bolus over 5 min within 60 min of the first surgical incision and an additional 25 mg/kg dose to a maximum of 1000 mg was added to the CPB priming solution. Prior to connection to the CPB circuit, a single sample for cefazolin determination was obtained from the patient in addition to a single sample from the CPB circuit. Upon connection to the CPB circuit, two cefazolin samples were obtained at each timepoint, with the first sample collected within 5 min after connection and then every 20 min until detachment. One sample was obtained pre-oxygenator and one sample was obtained post-oxygenator. After CPB circuit detachment, a single sample was again taken from the patient and a single sample was obtained from the solution remaining in the CPB circuit.

Blood sampling and pharmacokinetic/pharmacodynamic analysis

A 1 mL aliquot of blood was obtained per sample and subsequently sent to the laboratory for immediate processing. Samples were collected in regular red-top tubes. Upon receipt in the laboratory, samples were centrifuged within 30 min of collection at 3000 rpm for at least 15 min to separate the plasma. Separated plasma was then transferred to a cryovial and stored at −80°C. Couriers transported the specimens on dry ice from the hospital laboratory to the reference laboratory. Upon receipt at the reference laboratory, samples were thawed and analysed. Cefazolin concentrations were determined by LC-MS/MS (US Food and Drug Administration guidelines www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf) at Atlantic Diagnostic Laboratories (Bensalem, PA, USA). The LC-MS/MS method was accurate and precise at a linearity range of 1–500 mg/L with a correlation coefficient (r) of $\geq$0.99 and an inter-day assay variability that was <4% across all control samples.

Cefazolin concentrations were modelled using PMetrics, a non-parametric, pharmacometric modelling and simulation package for R.[19] One- and two-compartment models with zero-order input and first-order elimination were evaluated as the base structural model. Models were differentiated using the Akaike information criterion (AIC), the log likelihood ratio (LLR) test and visual predictive checks of the observed versus predicted concentration plots.[20] Weighting was conducted using the inverse of the assay standard deviation (SD) squared and γ, a multiplicative measure of all environmental noise other than the assay, and was found to be 1.54 for this population model. The mean weighted error of predicted vs observed concentrations was used as the estimate of bias. The bias-adjusted mean weighted squared error was utilized for an estimate of precision.

After identifying a base structural model, covariate analysis was performed using linear regression (SPSS version 22, SPSS Inc., Chicago, IL, USA) to determine a relationship between weight, age and estimated creatinine clearance (estimated glomerular filtration ratio; eGFR) and the pharmacokinetic parameters. Significant covariates were then re-entered into the model using AIC, the LLR test [change in $-2\times$log-likelihood of >6.64 ($P<0.01$ with 1 degree of freedom)] and visual predictive checks to re-assess for model improvement. Linear and allometric scaling techniques were also conducted again using AIC, the LLR test and visual predictive checks to re-assess for model improvement.[21,22] Secondary pharmacokinetic parameters were calculated from the primary parameters for comparison with other studies. Half-life ($t_{1/2}$) was calculated as 0.693/β, where β is the root of the quadratic polynomial.[23] The eGFR was calculated using the updated Schwartz equation.[24]

Extraction ratios were calculated using the cefazolin concentration from the CPB circuit prior to patient connection to the CPB circuit and the cefazolin concentration from the solution remaining in the CPB circuit after patient detachment. For purposes of the pharmacodynamic analysis, two pharmacodynamic targets were utilized for comparison and discussion with the data generated by this investigation: (i) an intra-operative trough and closure serum concentration of $\geq$40 mg/L ($\geq$8 mg/L unbound cefazolin, assuming 80% protein binding); and (ii) presumption of an infection with staphylococci and a worst-case MIC breakpoint of 8 mg/L to evaluate an efficacy exposure of time during which the unbound drug concentration (fT) is above the MIC ($fT_{>MIC}$) for the pathogen defined as 100% $fT_{>MIC}$ during surgery and 50% $fT_{>MIC}$ after surgery.[14,15]

Ethics

This protocol was approved by the Drexel University IRB 4# (paediatric IRB). The IRB ID number is 1408003041 and the initial approval date was 1 February 2015. Written informed consent was obtained from the parent(s) and/or caregiver(s) and assent from those individuals capable of providing assent prior to enrolment.

Results

During the study period, 41 patients met the inclusion criteria and were enrolled. Demographic, clinical and treatment characteristics are shown in Table 1. The 41 patients yielded a total of 492 cefazolin samples for pharmacokinetic analysis, and all were above the lower limit of detection; therefore, all of the samples were included in the pharmacokinetic analysis.

Cefazolin concentrations were best described by a one-compartment model with first-order elimination (AIC of 1549 and

Table 1. Patient study demographics stratified by age

Patient characteristic	Birth–3 months	4–6 months	7 months–3 years	4–11 years	12–16 years
Number of patients	7	10	12	7	5
Number of females (%)	4 (57)	2 (20)	5 (42)	3 (43)	4 (80)
Weight, kg, median (IQR)	4 (3.5–4.1)	6.4 (5.4–7.2)	8.93 (6.2–10.7)	18 (15.3–22)	64.8 (62–79)
SCr, mg/dL, median (IQR)	0.33 (0.3–0.38)	0.27 (0.22–0.29)	0.28 (0.25–0.3)	0.4 (0.37–0.49)	0.52 (0.5–0.6)
eGFR, mL/min/1.73 m^2, median (IQR)	72.9 (56.8–74.4)	89.5 (82.1–111.4)	114.8 (106.2–136.2)	117.7 (108.7–125.4)	123.9 (108–132.6)
CPB circuit priming volume, mL/kg, median (IQR)	61 (59.2–64.1)	43 (38.2–48.8)	30 (27.2–38.8)	24.8 (22.4–26)	10 (9–14)
CPB time, min, median (IQR)	172 (131.5–217.5)	91.5 (80–104.3)	91 (66.8–98)	103 (66.5–113)	53 (50–93)
Cross clamp time, min, median (IQR)	102 (63–156.5)	52.5 (39–70.5)	49.5 (36.3–71)	60.5 (36.5–75.5)	26 (22.5–94)
Surgery duration, min, median (IQR)	277.5 (208.5–330.5)	155 (139.3–181.5)	166 (152.5–234)	178 (147.5–201)	159 (122–161)
Median no. of cefazolin samples/patient	14	13	12	12	10
Surgical condition/procedure					
ALCAPA	2	–	–	–	–
ASD	–	–	3	–	2
arterial switch	3	–	–	–	–
AV canal	–	1	–	1	–
Fontan	–	–	1	–	–
Glenn	–	2	–	–	–
TAPVR	1	–	–	–	–
TOF	–	3	–	–	–
valve	–	–	1	1	–
VSD	1	4	6	3	1
Warden	–	–	–	1	–
other	–	–	1	1	2

ALCAPA, anomalous left coronary arising from the pulmonary artery; ASD, atrial septal defect; AV, arteriovenous; SCr, serum creatinine; TAPVR, total anomalous pulmonary venous return; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

LLR of 1543) as compared with a two-compartment model with first-order elimination (AIC of 2174 and LLR of 2201), P value <0.05. A statistically significant relationship was identified between weight and age on CL and volume of distribution (V_d) during the linear regression analyses. Linear and allometric scaling models were further explored evaluating weight and age as a covariate on CL and V_d. A one-compartment model was fitted to the data incorporating all patient ages in addition to models stratified by age. Upon age stratification, a one-compartment model with weight as a covariate on V_d with allometric scaling proved to be the superior model, with enhanced visual predictive check and a further reduction in AIC to 658 and LLR of 651 for the birth–6 months cohort, an AIC of 496 and LLR of 489.5 for the 7 month–3 year cohort and an AIC of 352 and LLR of 345 for the 4–16 year cohort. The population pharmacokinetic parameter estimates, stratified by age cohort, are presented in Table 2. The mean $\pm$ SD total body CL for the birth–6 month cohort was 0.009 ± 0.006 mL/min/kg with a mean V_d of 0.598 ± 0.26 L/kg, the mean total body CL for the 7 month–3 year cohort was 0.01 ± 0.005 mL/min/kg with a mean V_d of 0.786 ± 0.15 L/kg and the mean total body CL for the 4–16 year cohort was 0.007 ± 0.004 mL/min/kg with a mean V_d of 3.4 ± 0.94 L/kg. Figure S1 (available as Supplementary data at *JAC* Online) displays the observed versus population-predicted concentrations and the observed versus individual predicted concentrations with their respective R^2, bias and precision values.

Table 2. Mean cefazolin population pharmacokinetic parameter estimates

Age cohort	CL (mL/min/kg)	V_d (L/kg)
Birth–6 months	0.009 (0.006)	0.598 (0.26)
7 months–3 years	0.01 (0.005)	0.786 (0.15)
4–16 years	0.007 (0.004)	3.4 (0.94)

The values in parentheses are the SD. V_d, volume of distribution.

Table 3 shows the median cefazolin concentrations in the CPB circuit prior to the start of surgery, the median patient cefazolin concentration at the time of CPB circuit separation and the cefazolin CPB circuit extraction ratio, all stratified by age.

Discussion

This is, to the best of our knowledge, the first description of cefazolin pharmacokinetics during CPB when cefazolin is mixed in the CPB circuit priming solution in addition to the patient receiving perioperative dosing of cefazolin. To date, Calic *et al.*[14] and De Cock *et al.*[15] have described the pharmacokinetics of cefazolin in children and adults undergoing CPB. The pharmacokinetic parameters of CL and V_d in this investigation are different from those in either of these reports as a result of mixing cefazolin into the CPB circuit

Table 3. Cefazolin cardiopulmonary bypass circuit and patient concentrations (mg/L) with extraction ratios

Age cohort	Cefazolin concentration in CPB circuit	Patient cefazolin concentration off bypass	Percentage cefazolin circuit loss
Birth–3 months	2520 (1614–2708)	92.6 (73.5–101.5)	95.9 (91.5–97.2)
4 months–6 months	1251 (823–1524)	138.5 (117–160.8)	85.1 (82.8–87.7)
7 months–3 years	1069.5 (682–2386.5)	141 (118.8–181.8)	88.1 (77.6–94.6)
4–11 years	716 (522–1104.5)	197 (137.5–272)	78.2 (69.2–81.4)
12–16 years	1560 (1295–1755.5)	147.5 (93.4–168)	91.5 (84.6–94)

Values shown are median (IQR).

priming solution, most notably resulting in a slower CL. The practice of mixing cefazolin in the CPB priming solution essentially facilitated a continuous infusion of cefazolin to the patient during the surgical procedure.

The investigations of De Cock *et al*.[15] and Calic *et al*.[14] demonstrated that current dosing recommendations for peri-operative prophylaxis with cefazolin do not result in an appropriate pharmacodynamic exposure. Calic *et al*.[14] used a pharmacodynamic target of an intra-operative trough and closure serum concentration of ≥40 mg/L (≥8 mg/L unbound cefazolin, assuming 80% protein binding) and De Cock *et al*.[15] used an infection with staphylococci and a worst-case MIC breakpoint of 8 mg/L to evaluate an $fT_{>MIC}$ for the pathogen defined as $fT_{>MIC}$=100% during surgery and $fT_{>MIC}$=50% after surgery. Interestingly, there is no specific pharmacodynamic target suggested in the current guidelines for serum or tissue concentrations during surgery, at the time of skin closure or post-surgery for paediatric or adult cardiac surgery patients.[13]

The summary of evidence listed in the guidelines for cefazolin concentrations centre around a study of 38 adult patients undergoing Roux-en-Y gastric bypass surgery demonstrating that tissue cefazolin concentrations were lower than a targeted concentration of 8 mg/L in all patients.[13] The 8 mg/L 'target' is the resistance breakpoint for cefazolin and appears to be a reasonable target; however, the amount of time the concentration remains above the breakpoint and the actual concentration multiple above the breakpoint of 8 mg/L are unknown for prophylaxis, even though one target often evaluated for β-lactams is a free drug concentration 4–6×MIC at the site of infection for treatment of serious infections in critically ill patients.[13,25] If the range of 4–6×MIC is chosen, then a cefazolin serum concentration range of 160–240 mg/L would be needed to produce a free cefazolin concentration in the range of 32–48 mg/L using the 8 mg/L resistance breakpoint. The cefazolin penetration ratio into tissues and interstitial fluid is reported to range from 85% to 100%; however, cefazolin penetration into soft tissue during cardiac surgery from a 7 patient adult pharmacokinetic study found that the maximum cefazolin concentration in subcutaneous interstitial fluid was 22.6% of the maximum plasma level, and a 12 patient paediatric pharmacokinetic study found a median cefazolin tissue penetration ratio of 28.6%.[16,26–28] The 22.6% ratio suggests that a serum level range of 142–212 mg/L would be needed to provide tissue (i.e. free) cefazolin concentrations in the range of 32–48 mg/L. Considering the fact that the guidelines state that paediatric dosing recommendations are extrapolated from adult studies for efficacy, more research needs to be conducted to determine an appropriate cefazolin dosing regimen for paediatric cardiac surgery when CPB is utilized in addition to a pharmacodynamic target or target range for prophylaxis.[13]

Mixing cefazolin in the CPB priming solution for delivery during surgery resulted in serum concentrations that would have met the pharmacodynamic targets suggested by De Cock *et al*.[15] and Calic *et al*.[14] As such, this practice appears to be rather promising to ensure 'target' serum, and presumably tissue, concentrations. As shown in Table 3, adding 25 mg/kg, to a maximum of 1000 mg, of cefazolin to the priming solution resulted in robust starting concentrations in the CPB circuit. Considering that the priming volume of the circuit is a known volume, the amount of cefazolin added to the priming solution could be tailored based on each institution's desired target concentration in conjunction with institutional pathogen MICs and the cefazolin extraction ratios in Table 3. Owing to the concern regarding cefazolin loss within the CPB circuit during surgery, our institutional protocol is to re-dose patients with an additional 25 mg/kg dose of cefazolin upon CPB circuit detachment. With the ability to customize the cefazolin concentration in the CPB circuit priming solution for delivery during surgery, the practice of re-dosing during surgery based on the antimicrobial half-life and blood loss and re-dosing with detachment from CPB could most probably be eliminated, as evidenced by the median patient cefazolin concentrations immediately off bypass prior to re-dosing. If the 'more aggressive' cefazolin serum concentration of ≥40 mg/L (≥8 mg/L unbound, assuming 80% protein binding) is chosen and utilizing the range of 80%–90% cefazolin loss in the CPB circuit, based on our data a cefazolin concentration of 200–400 mg/L in the CPB circuit priming solution could be utilized to achieve this target, which would result in something similar to a cefazolin continuous infusion during surgery as advocated by some as a viable option.[16]

This investigation has several limitations. First, the analysis of cefazolin concentrations was of total cefazolin concentrations and not unbound cefazolin concentrations. Second, tissue concentrations were not measured in our study. As suggested previously, serum concentrations do not always reliably result in anticipated tissue concentrations.[16] Third, similar to other studies, cefazolin concentrations were evaluated against pharmacodynamic targets based on MICs for potential pathogens utilized for the treatment of infections as opposed to those needed for prophylaxis of infections. The pharmacodynamic targets are relatively unknown and could be different, requiring less cefazolin than is needed for treatment of an infection. This limitation is indicative of the paucity of pharmacokinetic/pharmacodynamic research in the area of peri-operative prophylaxis for cardiac surgery in adults and children.

Despite these limitations, the technique of mixing cefazolin, or any antimicrobial, into the CPB circuit priming solution appears to be a rather promising and practical opportunity.

Conclusions

These data demonstrate that mixing cefazolin in the CPB circuit priming solution was effective in maintaining cefazolin serum concentrations during surgery. If this practice is utilized, re-dosing of cefazolin during the CPB run and upon CPB circuit detachment is most probably not needed. Additional larger pharmacokinetic studies evaluating this dosing technique are warranted.

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Author contributions

J. J. C. conceived the idea for this study, wrote the protocol, achieved IRB approval, obtained consent for patient inclusion, collected and processed specimens, conducted the pharmacokinetic analysis, wrote and edited the manuscript and serves as the guarantor for the manuscript. W. S. M. II helped achieve IRB approval, and wrote and edited the manuscript. J. P. obtained consent for patient inclusion, collected and processed specimens, and wrote and edited the manuscript. R. S. obtained consent for patient inclusion, collected and processed specimens, and edited the manuscript. Y. A.-Q. achieved IRB approval, obtained consent for patient inclusion, collected and processed specimens, and edited the manuscript. A. E. conducted LC-MS/MS analysis for cefazolin concentration determination. A. C. wrote the protocol, and wrote and edited the manuscript.

Supplementary data

Figure S1 is available as Supplementary data at *JAC* Online.

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