Are children undergoing cardiac surgery receiving antibiotics at subtherapeutic levels?

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Objectives: Perioperative antibiotics have decreased—but not eradicated—postoperative infections. In patients undergoing cardiac surgery with cardiopulmonary bypass, the dilutional effect of the priming and any additional volume given during the procedure may lead to subtherapeutic antibiotic levels. Our aim was to determine if children undergoing cardiac surgery with cardiopulmonary bypass receive perioperative antibiotics at subtherapeutic levels.

Methods: Using published pharmacokinetic data on cefuroxime, we developed a computer simulation model to generate a nomogram predicting patients at risk for subtherapeutic cefuroxime levels based on time from initial dosing and additional volume given.

Results: A computer-generated 1-compartment pharmacokinetic model was created to predict cefuroxime plasma levels over time for patients of all weights and additional volumes given for both a 25- and 50-mg/kg intravenous dose. For example, following a 25-mg/kg dose, a patient receiving an additional volume of 275 mL/kg is predicted to be subtherapeutic (<16 mg/L = $4 \times$ minimum inhibitory concentration) at 4 hours. Our nomogram predicts all patients will be subtherapeutic at 8 hours, consistent with general pediatrics dosing schemes. Following a 50-mg/kg dose, levels are predicted to be subtherapeutic after an additional volume of 315 mL/kg at 5.5 hours.

Conclusions: Our model predicts which patients undergoing cardiac surgery with cardiopulmonary will have subtherapeutic cefuroxime levels. This nomogram enables providers to determine when to administer additional antibiotics in patients receiving large additional volumes during cardiac surgeries. This rational approach to perioperative antibiotic dosing may result in a reduction in postoperative infection in this vulnerable patient population. (*J Thorac Cardiovasc Surg* 2014;148:1591-6)

Postoperative wound infections in pediatric patients undergoing cardiothoracic surgery occurs in 2.3% to 8% of patients.¹ This complication results in increased morbidity, longer hospitalizations, and increased cost—with more than \$1.6 billion annually in extra hospital charges reported.² In particular, the financial burden is becoming a more urgent concern for our field as insurance reforms limiting the reimbursement for these preventable complications become more common. Within the United States in 2007, Medicare began refusing reimbursement for postoperative mediastinitis in patients who have undergone coronary artery bypass grafting.³ One major strategy in

limiting postoperative surgical site infections has been the use of perioperative antibiotics to reduce primarily gram-positive skin flora that colonizes the skin and can potentially infect an open wound.⁴⁻⁷ Since the days of Lister's introduction of carbolic acid spray in the 1860s and Burke's demonstration of the efficacy of perioperative antibiotics in guinea pigs in the 1960s,⁸ postoperative wound infections have decreased dramatically. This strategy is used across surgical subspecialties and the dosage is the same for patients regardless of the employment of cardiopulmonary bypass (CPB).

CPB machines require priming with a certain volume that is determined by the length and diameter of tubing, size of reservoir, and specific oxygenator. The priming volume consists of variety of different fluids that varies between institutions, including but not limited to electrolyte solutions, albumin, sodium bicarbonate, and blood. For smaller patients, the priming volume may exceed their total circulating volume. In a neonate or small infant with a circulating volume of approximately 270 mL, the bypass priming volume could easily exceed 300 mL using various commonly used oxygenators and cardioplegia setups.

We know that the antibiotic levels can be subtherapeutic in a percentage of adult patients undergoing cardiac surgery using CPB.^{6,7} Although a previous small study in pediatric

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Abbreviations and Acronyms

%fT	= percent of dosing interval
$C_{\max}$	= maximum total plasma concentration
CPB	= cardiopulmonary bypass
IV	= intravenous
MIC	= minimal inhibitory concentration
PK	= pharmacokinetics
V_D	= volume of distribution

patients showed average cefuroxime concentrations to be therapeutic after CPB,⁸ it is unknown what percentage of individual patients were subtherapeutic. In addition, it is unknown if a difference in ages and weights was demonstrated because the sample size was perhaps too small to demonstrate a significant difference. Antibiotic levels may vary with age and weight given the variation in proportion of priming volume to circulating volume in patients of different sizes. Given this risk, some investigators have advocated the administration of an additional dose of antibiotics with the priming volume.^{9,10} Although cefuroxime, in particular, is a safe medication with minimal risk associated with supratherapeutic levels, further evidence is needed to justify adoption of a widespread change in published guidelines.

This risk of subtherapeutic antibiotic levels is not limited to cardiac surgery and, in fact, may be broadly applied to many other surgical fields such as trauma, orthopedics, and any surgeries requiring administration of large volumes of fluid, particularly in the pediatric population. Our aim was to determine the volume of additional fluid administration that would put a surgical patient at risk for subtherapeutic antibiotic levels and, thereby, postoperative wound infection.

MATERIALS AND METHODS**Data Sources and Selection**

We performed a systematic search using PubMed (1970–March 2013) using combinations of the following search terms: *pediatric*, *children*, *infant*, *neonate*, *cefuroxime*, *CPB*, and *pharmacokinetics*. We then searched reference lists for additional relevant articles. In a meta-analysis of studies describing cefuroxime pharmacokinetics (PK) and pharmacodynamics in pediatric patients, 8 articles were reviewed to identify PK parameters^{9,16} and the mean or median of reported values are listed in Table 1. Although a 2-compartment model would give a more accurate representation of cefuroxime plasma concentration-time curves, reliable and reproducible PK parameters for a 2-compartment model have not been published. One study reported 2-compartment parameters that were not consistent with individual parameters published in the other reports.¹⁰

PK Simulations

A computer model was designed using a median or mean of PK data obtained in the studies found above. Nascimento and colleagues¹⁴ reported a volume of distribution (V_D) of 0.19, 0.25, and 0.22 L/kg (mean, 0.22 L/kg), which matched the V_D of 0.21 L/kg (range, 0.081–0.423 L/kg) reported by Knoderer and colleagues.¹² Powell and colleagues¹⁷ reported a half-life of 1.9, 1.4, and 1.9 hours (mean, 1.75 hours), which was similar to the half-life of 1.8 hours reported by del Rio and colleagues.¹⁶ Therefore, a

1-compartment PK model with first-order elimination was used. An elimination coefficient of 0.693/1.75 hours or 0.396/hour was used for in silico plasma concentration-time simulations following intravenous (IV) cefuroxime 25 mg/kg and 50 mg/kg doses. The V_D range of 0.081 to 0.423 L/kg reported by Knoderer and colleagues¹² was used to simulate priming volumes, where 0.08 represented a priming volume of 0 mL/kg and the upper range of 0.43 L/kg represented a priming volume of 350 mL/kg (0.43–0.08 L/kg = 0.35 L/kg or 350 mL/kg). Simulations were run using Phoenix WinNonLin 6.2.1.51 (Sunnyvale, Calif).

Pharmacodynamic Simulations

A minimum inhibitory concentration (MIC) for cefuroxime of 4 mg/L was used.¹⁴ According to standard clinical antibiotic dosing goals, a minimum total (bound and free drug) cefuroxime concentration of 4 times the MIC (4×4 mg/L = 16 mg/L) was chosen as a target concentration for drug efficacy.^{14,15} The maximum total plasma concentration ($C_{\max}$) was multiplied by the fraction unbound in the plasma (0.5) to determine unbound drug concentration ($C_{\max, \text{free}}$). Free drug concentrations were used to determine the time that free drug concentrations (percent of dosing interval [%fT]) were above the MIC of 4 mg/L during a dosing interval of 8 hours (%fT > MIC = $[\ln(C_{\max, \text{free}}/\text{MIC})]/\text{partition coefficient of cefuroxime} \times 100$). A %fT > MIC of 50% for cefuroxime, which reflects 4 hours for an 8-hour dosing interval, was chosen for bactericidal effect.¹⁸

RESULTS

Table 2 and Figure 1 show the additional volumes at which concentrations fall below 16 mg/L (which equals the target of $4 \times \text{MIC}$ for cefuroxime) for cefuroxime at 25 mg/kg and 50 mg/kg IV doses. The therapeutic target of $4 \times \text{MIC}$ is the widely accepted goal in antibiotics dosing schemes. After a cefuroxime 25 mg/kg IV dose, total cefuroxime plasma concentrations at 0.5 hours ($C_{\max}$) and at 2 hours remain therapeutic (>16 mg/L) for an additional volume of up to 250 mL/kg. The threshold for additional volume resulting in subtherapeutic concentrations decreases as the time from cefuroxime administration increases. Thus at 8 hours—consistent with the established dosing scheme of 8-hour dosing intervals—any additional volume would result in subtherapeutic concentrations. For example, following a 25-mg/kg dose, a patient receiving an additional volume of 275 mL/kg is predicted to be subtherapeutic at 4 hours. Our algorithm predicts all patients will be subtherapeutic at 8 hours, consistent with general pediatrics dosing schemes.

As expected, cefuroxime plasma levels were higher for the 50-mg/kg dose of cefuroxime. Total cefuroxime plasma concentrations are therapeutic up to 5.5 hours with the administration of up to 325 mL/kg of volume. Before dosing again at 8 hours, as little as 75 mL/kg of volume administered would result in subtherapeutic levels. For example, following a 50-mg/kg dose, levels are predicted to be subtherapeutic after an additional volume of 255 mL/kg at 6 hours after cefuroxime administration.

A secondary therapeutic goal in clinical antibiotic dosing schemes is unbound or free drug concentrations above the MIC for 50% of the dosing interval (which is 8 hours for cefuroxime). For cefuroxime 25 mg/kg IV, the time that free drug concentrations are above an MIC of 4 mg/L range

TABLE 1. Published demographics and cefuroxime pharmacokinetic parameters in selected articles

Demographic or parameter	Mean or median ± standard deviation (range) reported in the Results section	Mean or median ± standard deviation (range) reported in the Abstract
Age (mo)	14.2 ± 8.65 (3-33.6)	
Weight (kg)	9.36 ± 2.83 (4.5-15.4)	
Distribution clearance	43.9 ± 40.2 mL/min/kg	
Systemic clearance	11.8 ± 4.79 mL/min/kg Or 0.708 ± 0.287 L/h/kg	0.050 (0.041-0.058) L/h/kg
Volume of distribution in the peripheral compartment	8.08 ± 4.49 L/kg	
Volume of distribution in the central compartment	8.53 ± 3.72 L/kg	0.081 (0.046-0.162) L/kg
Volume of distribution at steady state	0.2104 ± 0.0605 L/kg	0.213 (0.0181-0.423) L/kg
Half-life (h)	1.91 ± 3.51	3.76 (1.03-6.81)*
Beta	0.037 ± 0.006 1/h	
Maximum concentration	328 ± 102 mg/L	

*Reference 12.

from 100% to 60% of an 8-hour dosing interval (or 8 to 4.8 hours) for priming volumes ranging from 0 to 350 mL/kg. For cefuroxime 50 mg/kg IV, the time that free drug concentrations are above an MIC of 4 mg/L range from 100% to 80% of an 8-hour dosing interval (or 8 to 6.5 hours) for priming volumes ranging from 0 to 350 mL/kg.

DISCUSSION

Along with cefazolin, which follows similar PK, cefuroxime is 1 of the most commonly used antibiotics in perioperative antibiotic prophylaxis across surgical subspecialties⁴ and is 1 of the first-line agents for antibiotic prophylaxis recommended by the Society of Thoracic Surgeons.⁵ However, despite its long history of use, its efficacy may be insufficient in the setting of dilution from large volumes used in certain surgical fields. Particularly in pediatrics, intraoperative volumes, including priming volume in CPB surgeries, blood products, drugs, and other fluids may have an even more deleterious dilution effect on perioperative antibiotic levels. In our model we focused on cefuroxime, although it can also be applied to cefazolin given the similar PK, including comparable half-lives (1.68 ± 0.55 hours for cefazolin vs 1.75 hours

for cefuroxime).¹⁹ Using our computer-generated model, we created a nomogram that enables determination of what additional volume and at what time postdose patients are at risk for subtherapeutic cefuroxime levels during CPB procedures. One clinical measure of antibiotic efficacy—the percent of dosing interval that plasma levels are above the MIC—is sufficient. However, the plasma concentration falls below the goal of 4 times the MIC for a wide range of commonly administered volumes given during the recommended 8-hour dosing interval. Subtherapeutic levels were predicted for both 25 mg/kg and 50 mg/kg doses currently recommended by the Society of Thoracic Surgeons.⁴ It is clear with this nomogram that many patients, especially smaller patients undergoing longer bypass procedures, are at high risk for subtherapeutic perioperative antibiotic prophylaxis and may also be at high risk for postoperative infection.

Our finding is particularly interesting because the incidence of sternal wound infections has been shown to be greater in neonates compared with older children (5.5% vs 0.5%).²⁰ Although this incidence has decreased significantly since the introduction of perioperative antibiotics, there has not been a dramatic reduction in postoperative infection rates in recent years, which should prompt reevaluation by our subspecialty. Unfortunately, this preventable complication is a major contributor to morbidity, mortality, longer hospital stays, increased costs, and scrutiny of congenital cardiac surgery programs in today’s closely monitored medical environment.

Beyond cardiac surgery, our findings can be generalized to other surgical fields, including orthopedics and trauma involving massive blood loss and in which large volumes of blood product and fluids are administered. In orthopedics in particular, postoperative infections can be devastating, especially in the setting of implanted devices. In fact, in any pediatric surgery, there is increased risk of dilution effects resulting in subtherapeutic antibiotic levels given the relatively small circulating volume in children.

There are limitations to our computer-simulated approach that uses published PK parameters for general

TABLE 2. Minimum additional volumes resulting in cefuroxime concentrations ≤16 mg/L at given times after administration

Time after administration (h)	Additional volume (mL/kg) following 25 mg/kg IV cefuroxime dose	Additional volume (mL/kg) following 50 mg/kg IV cefuroxime dose
4	≥275	—
4.5	≥225	—
5	≥170	—
5.5	≥125	≥325
6	≥90	≥255
6.5	≥60	≥195
7	≥35	≥145
7.5	≥15	≥105
8	0	≥75

IV, Intravenous.

FIGURE 1. A, Simulated plasma decay curves for concentration of cefuroxime after 25 mg/kg dose given intravenously (IV) with different additional volumes administered. Each curve shows concentration at different hours after administration. The solid line indicates the goal plasma concentration of 4 times the mean inhibitory concentration (MIC) and the points at which the dotted lines intersect the solid line represent the additional volumes that would result in subtherapeutic levels at given times after administration. B, Matching simulated plasma decay curves for concentration of cefuroxime after 50 mg/kg dose.

pediatric patients. Despite being a widely used antibiotic with 2-compartment PK, there is not sufficient published data for cefuroxime to create a 2-compartment model simulation. However, although using a 2-compartment model would improve accuracy in the initial immediate distribution in tissues after administration, it has little effect on predicting the later concentrations more likely to be subtherapeutic and on which we focus in our study. In fact, using a 1-compartment model may overestimate the additional volume and thereby underestimate the risk for a child to have subtherapeutic cefuroxime levels, because the initial distribution to organs such as the kidneys accelerates drug clearance before equilibrium,²¹ resulting in lower

connective tissue levels that we target for prevention of wound infection.

Other factors unique to our patient population undergoing CPB are multiple and include altered protein-binding; loss of blood containing antibiotics; and potentially decreased drug metabolism with cooling, hypotension, hemodilution, and peribypass renal injury. At least in adults, we know that CPB alters cefuroxime hemodynamics.^{22,23} The altered protein-binding and/or the decreased metabolism may explain the long cefuroxime half-life reported by Knoderer and colleagues¹² that is nearly twice the half-life reported in all other pediatric studies. The addition of protein-rich volume such as the priming volume and blood

FIGURE 2. A, Simulated decay curves for unbound cefuroxime concentration after 25 mg/kg dose given intravenously (IV). The dotted lines represent concentrations after different additional volumes administered. The horizontal solid line depicts the mean inhibitory concentration (MIC) of 4 mg/mL and the vertical solid line depicts the goal time of 4 hours (50% of the dosing interval of 8 hours) that unbound concentrations are above the MIC. B, Matching simulated decay curves for unbound cefuroxime concentration after 50 mg/kg dose. %fT, Time of free drug concentrations.

products, increase the substrate for protein-binding and thereby lower the free fraction concentration and tissue level of cefuroxime—which is ultimately the most accurate reflection of the level of protection from postoperative infection. This is particularly relevant because previous studies measuring only plasma levels may have overestimated tissue levels in patients undergoing CPB.²⁴ Therefore, further studies that include free fraction and tissue levels performed in pediatric patients undergoing cardiac surgeries with CPB are necessary to validate our computer-generated model and to determine if our current perioperative antibiotic strategies are appropriate.

Our nomogram provides a rational approach to perioperative antibiotic dosing that may result in a substantial

reduction in postoperative infection in populations of children—especially small children—undergoing cardiac surgery. Beyond cardiac surgery, this nomogram may also be translated to other surgeries such as trauma and orthopedic surgeries involving massive blood loss and/or the administration of large volumes of fluids.

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