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Vancomycin prescribing and therapeutic drug monitoring in children with and without acute kidney injury after cardiac arrest

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Abstract

Background: Acute kidney injury (AKI) commonly occurs after cardiac arrest. Those subsequently treated with vancomycin are at additional risk for drug-induced kidney injury.

Objective: We aimed to determine if opportunities exist for improved drug monitoring after cardiac arrest.

Patients and Methods: Retrospective cohort study of children aged 30 days – 17 years treated after cardiac arrest in an intensive care unit from 1/2010–9/2014 who received vancomycin within 24 hours of arrest. Vancomycin dosing and monitoring were compared between those with and without AKI, with AKI defined as pRIFLE Stage 2–3 AKI at day 5 using Schwartz formula-calculated estimated glomerular filtration rate (eGFR).

Results: Sixteen of 43 children (37%) had AKI at day 5. Age, arrest duration, median time to first vancomycin dose, and the number of doses prior to and time to first vancomycin

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COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of Interest: The remaining authors have no financial relationships relevant to this article to disclose.

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concentration measurement were similar between groups. Children with AKI had higher initial vancomycin concentrations than those without AKI (median 16 vs 7mg/L, $p=0.003$). A concentration was not measured before the second dose in 44% of children with AKI. Initial eGFR predicted day 5 AKI. In children with AKI, the initial eGFR was lower in those with vs. without a concentration before the second dose [29 ml/min/1.73m² (IQR 23–47) vs. 52 (IQR 50–57), $p=0.03$], but well below normal in both.

Conclusions: In children with AKI after cardiac arrest, decreased vancomycin clearance was evident early and early monitoring was not performed universally in those with low initial eGFR. Earlier vancomycin therapeutic drug monitoring is indicated in this high-risk population.

1 INTRODUCTION

Cardiac arrest occurs in 16,000 children in the U.S. annually, with an annual incidence of 8–20 per 100,000 children [1]. Acute kidney injury (AKI), an important risk factor for increased mortality and length of mechanical ventilation and hospital stay in all critically ill children [2–4], occurs in 37–64% of children who suffer cardiac arrest [5, 6]. Little data exist to guide post-cardiac arrest drug dosing and therapeutic drug monitoring (TDM) in children with AKI after cardiac arrest.

Infections are suspected in many cases of pediatric cardiac arrest [7], requiring treatment with antibiotics. Vancomycin, commonly prescribed after pediatric cardiac arrest [6], has a narrow therapeutic window and is primarily renally excreted. Dose adjustments based on TDM are made to maximize effectiveness and minimize toxicity. Vancomycin is primarily renally excreted and dose adjustments are made on both TDM and alterations in renal function. It has been previously described that children with decreased renal function or treated with therapeutic hypothermia after cardiac arrest have decreased vancomycin clearance [8].

Children who suffer cardiac arrest undergo intensive monitoring and care in the immediate the post-arrest period. Many develop AKI, and this vulnerable group of children is at high risk of worsening renal dysfunction if dose adjustments for renally cleared medications are not made. We hypothesized that there was substantial variability in vancomycin dosing and monitoring among children after cardiac arrest, providing opportunities for practice improvement and to potentially prevent worsening AKI.

2 METHODS

2.1 Design

We conducted a single-center, retrospective cohort study using an existing de-identified dataset [8] of children treated in an academic, quaternary pediatric intensive care unit after either in-hospital or out-of-hospital cardiac arrest. Patients aged 30 days through 17 years who received at least 2 minutes of cardiopulmonary resuscitation (CPR) between January 1, 2010 and September 30, 2014, achieved return of spontaneous circulation (ROSC), were treated with at least one dose of vancomycin within 24 hours after ROSC, and had at least one vancomycin plasma concentration drawn after ROSC for vancomycin TDM were included (Figure 1). Patients who had a history of chronic kidney disease (CKD), received

extra-corporeal therapies including renal replacement therapy, or had unknown height or CPR duration were excluded. The parent study was approved by the local Institutional Review Board (IRB), and the IRB determined this study was exempt from the need for approval in accordance with the Common Rule as data have since been de-identified.

In this dataset, patients were followed for 10 days after ROSC. The dataset included CPR duration, use of therapeutic hypothermia, exposure to nephrotoxic agents (diuretics, aminoglycosides, non-steroid anti-inflammatory drugs, intravenous contrast, antineoplastic agents), serum creatinine measurements, and vancomycin dosing and concentration measurements.

2.2 Study Definitions

AKI was defined as the presence of stage 2 or 3 AKI at day 5 after ROSC (Figure 1) using pRIFLE estimated glomerular filtration rate (eGFR) criteria (stage 1 eGFR decrease by 25%, stage 2 eGFR decrease by 50%, stage 3 eGFR decrease by 75%) [2]. eGFR was calculated using the Schwartz formula [9]. Since patients with CKD were excluded and pre-arrest creatinine values were not in the dataset, baseline eGFR was estimated at 120ml/min/1.73m² [10]. Urine output was not used to define AKI due to the correlation of increased urine output (e.g. forced diuresis) in the setting of therapeutic hypothermia. Patients were classified as having “AKI” if they had stage 2 or 3 AKI that was stable or worsened by day 5 and “no AKI” if they had no AKI, stage 1 AKI, or AKI that improved to stage 1 by day 5.

The institutional standard for initial vancomycin dosing is 10–15mg/kg/dose every 6 hours, and the institutional standard for therapeutic vancomycin trough level is 5–20mg/L.

2.3 Statistical Analysis

Characteristics between groups were compared using Fisher’s exact test for categorical variables and Wilcoxon rank sum test for continuous variables. Unadjusted logistic regression analysis was used to determine the ability of initial eGFR after ROSC to predict AKI. Data time points were anchored to the time of ROSC.

3 RESULTS

3.1 Cohort Characteristics

Of 43 patients with cardiac arrest that received vancomycin as part of clinical care, 16 patients (37%) had AKI at day 5 after cardiac arrest. When evaluating only children over one year of age, the frequency of AKI remained similar at 33% (9/27). All patients had an initial eGFR determination by 9 hours after ROSC, and the median time to initial eGFR was 1.3 hours after ROSC. The initial eGFR was lower in patients with AKI at day 5 (Table 1). The ability of initial eGFR after cardiac arrest to predict day 5 AKI was evaluated using logistic regression analysis. In unadjusted analysis, the initial eGFR was a significant predictor of day 5 AKI: for every decrease of 10ml/min/1.73m² in initial eGFR, the odds of AKI rose by 48% [Odds Ratio (OR) 1.48, 95% CI 1.13–1.94, p=0.005]. In the subset of patients with initial eGFR < 90 ml/min/1.73m², the initial eGFR remained predictive of day 5 AKI (OR 2.03 for every decrease of 10ml/min/1.73m² in initial eGFR, 95% CI 1.23–3.36, p=0.006).

Age, CPR duration, use of therapeutic hypothermia, and nephrotoxin exposures were not associated with AKI (Table 1).

3.2 Vancomycin Dosing

The first vancomycin dose was administered a median of 4 hours (IQR 0.4–8) after ROSC. The median initial vancomycin dosage was 10 (IQR 10–15) mg/kg and the median initial dosing interval was 8 (IQR 6–12) hours. The time to first dose administration, initial weight-based dosage, and initial dosing interval were not statistically different between groups (Table 1). The range of initial dosing intervals was wide in patients with AKI (range 6–40 hours). The initial dosing interval was also not different when comparing patients with an initial eGFR < 90 ml/min/1.73m² to those with an initial eGFR ≥ 90 ml/min/1.73m² [12 hours (IQR 6–16) vs. 9 hours (IQR 6–12), p=0.24].

3.3 Vancomycin Monitoring

All patients in the cohort had a vancomycin concentration measured within three days of the first administered dose of vancomycin. The median number of vancomycin doses prior to the first concentration and median time to first vancomycin concentration measurement did not differ in those with and without AKI (Table 1). The first vancomycin concentration was higher in those who developed AKI (Table 1). Similar results were seen when the analysis was limited to children over one year of age (data not shown).

A vancomycin concentration was measured before the second dose in 56% (9/16) of patients who had day 5 AKI (0% patients with stage 2 AKI and 82% with stage 3 AKI). A vancomycin level was measured before the second dose in only 43% (13/30) of patients with an initial eGFR < 90 ml/min/1.73m². Across the entire cohort, the initial eGFR was lower in those with a vancomycin concentration obtained before the second dose than in those without [47 (IQR 29–72) vs. 85 (IQR 54–128) ml/min/1.73m², p=0.01]. Similarly, in the subset of patients who had AKI at day 5, the initial eGFR was lower in those with a vancomycin concentration obtained before the second dose than in those without [29 (IQR 23–47) vs. 52 (IQR 50–57) ml/min/1.73m², p=0.03]. However, in both groups within this subset the median eGFR was <60 ml/min/1.73m², thus identifying an at-risk patient population with low initial eGFR without early vancomycin TDM who developed persistent AKI. Age, CPR duration, and use of therapeutic hypothermia were not different between patients with and without measurements before the second dose. Patients without vancomycin concentrations before the second dose received more doses of vancomycin in the first 24 hours of therapy than those with concentrations before the second dose in all patients [median 3 (IQR 3–4) vs. 2 (IQR 1–2), p<0.001] and in those with AKI [median 4 (IQR 2–4) vs. 1 (IQR 1–2), p=0.002].

4 DISCUSSION

AKI was common in this cohort of children after cardiac arrest. Differences in creatinine and vancomycin clearance were evident within hours of ROSC in those with AKI at day 5, providing a potential opportunity to identify patients at high risk for persistent AKI early after cardiac arrest, implement early personalized TDM for vancomycin therapy to ensure

efficacy and limit toxicity, and possibly mitigate further AKI in this high-risk patient population. Therapeutic vancomycin concentrations should be achieved in a timely manner for optimal efficacy, and supra-therapeutic concentrations should be avoided to limit drug-associated toxicity. Based on our results, we advocate for earlier vancomycin TDM in all children after cardiac arrest, with first vancomycin concentration measurement prior to the second dose of vancomycin.

Variability in both initial vancomycin prescription and individual monitoring was present in this cohort. Initial eGFR was the only identified characteristic associated with the decision to perform early TDM. Many patients with initially low eGFR who subsequently were classified as having AKI did not have vancomycin concentrations measured before the second vancomycin dose administration, and these patients received more doses of vancomycin in the first 24 hours of vancomycin therapy than those with concentrations measured before the second dose. This implies that knowledge of a high trough after the first dose could lead to prescription modifications resulting in decreased dosing in patients at highest risk of AKI. A trough measurement is used clinically as a surrogate for vancomycin area under the curve (AUC), the main driver of the antibiotic's effect and toxicity. Troughs are unreliable predictors of AUC in critically ill children, especially those with renal dysfunction. Furthermore, children may need lower trough levels to achieve AUC goals for vancomycin [11]. Thus, more frequent TDM may be necessary to adequately estimate AUC in the vulnerable patients.

We have identified possible opportunities to implement strategies to mitigate further AKI in this high-risk patient population through earlier TDM and more standardized vancomycin prescription in those with an initial eGFR <60 ml/min/1.73m². Initial eGFR after cardiac arrest is an important predictor of persistent AKI after pediatric cardiac arrest, and carries significant value for determining subsequent vancomycin dosing and other aspects of clinical patient care, and may be a valuable factor for potential research study selection. Vancomycin troughs may also predict persistent AKI after pediatric cardiac arrest, and future study using a systematic analysis with timed vancomycin sampling could answer this question.

This study is limited by a single-center, retrospective design. It is challenging to retrospectively determine if drug concentrations were drawn as trough levels, potentially confounding comparisons across groups. Due to the exclusion of infants under 30 days of age, our findings may not be generalizable to this group of patients who are at risk for cardiac arrest. The small sample size decreases power to determine differences between groups. Baseline eGFR values prior to arrest were not available in the dataset, leading to potential misclassification bias and limiting our ability to determine if AKI was related to cardiac arrest or vancomycin toxicity. However, our objective was not to study vancomycin toxicity, and our conclusions about earlier TDM still apply whether the decrement in renal function was present prior to or subsequent to cardiac arrest. Despite the small sample size, differences in creatinine clearance were evident early after arrest, and we found areas where TDM could be improved. Future directions of study should include evaluation of how incorporating biomarkers of kidney function into TDM could further improve our vancomycin, and other medication, prescribing and monitoring practices.

5 CONCLUSION

Earlier personalized monitoring and dosing of vancomycin may be indicated in children treated with vancomycin after cardiac arrest. We recommend consideration of instituting TDM for vancomycin even earlier, e.g. after the first dose, in all patients receiving vancomycin after cardiac arrest. Early TDM may be especially important in those with an initial eGFR <60 ml/min/1.73m².

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Key points

- Children who suffer cardiac arrest are at high risk of developing persistent acute kidney injury
- Vancomycin concentrations are frequently not monitored before the second dose of vancomycin is administered in this population despite early signs of decreased kidney function
- After cardiac arrest, children without vancomycin concentration measurements before the second dose have higher vancomycin exposure in the first 24 hours of vancomycin therapy

Fig. 1.

Study flowchart. The flowchart shows patient inclusion and exclusion criteria, and classification scheme for acute kidney injury

Table 1:

Patient Characteristics

Characteristic	No AKI ^a N=27	AKI ^a N=16	P value
Age in months, median (IQR)	26 (7–110)	12 (4–69)	0.21
Initial measured eGFR ^b , median (IQR)	88 (72–128)	49 (29–54)	<0.001
Hours to first eGFR ^b , median (IQR)	1.3 (0.1–2.8)	1.4 (0–3.0)	0.88
Minutes of CPR ^c , median (IQR)	14 (4–22)	13.5 (6–30)	0.49
Therapeutic hypothermia, n (%)	7 (26)	1 (6)	0.22
Diuretic exposure, n (%)	17 (63)	11 (69)	0.75
Aminoglycoside exposure, n (%)	3 (11)	1 (6)	1.00
NSAID ^d exposure, n (%)	6 (22)	0 (0)	0.07
Contrast exposure, n (%)	7 (26)	2 (13)	0.45
Antineoplastic agent exposure, n (%)	0 (0)	1 (6)	0.37
Number of nephrotoxins, median (IQR)	2 (2–3)	2 (2–2)	0.42
Vancomycin Dosing			
Hours to first dose, median (IQR)	4 (2–10)	5 (0–8)	0.43
First dose in mg/kg, median (IQR)	10 (10–15)	10 (10–13)	0.24
Initial dosing interval in hours, median (IQR)	7.5 (6.0–11.5)	13 (6.0–20.5)	0.11
Vancomycin Monitoring			
Hours to first concentration, median (IQR)	19 (9–24)	17 (13–25)	0.74
Number of doses before concentration, median (IQR)	2 (1–3)	1 (1–3.5)	0.45
First concentration in mg/L, median (IQR)	6.8 (4.3–18.0)	15.8 (9.6–21.0)	0.003
Concentration measured prior to second dose, n (%)	8 (30)	9 (56)	0.11
Maximum concentration in mg/L, median (IQR)	8.6 (5.7–18.0)	19.6 (15.0–24.4)	<0.001
Any concentration >20mg/L, n (%)	3 (11)	7 (44)	0.02

^a AKI: Acute Kidney Injury on day 5

^b eGFR: estimated Glomerular Filtration Rate calculated by Schwartz formula

^c CPR: Cardiopulmonary resuscitation

^d NSAID: Nonsteroidal anti-inflammatory drug