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Are Elevated Vancomycin Serum Trough Concentrations Achieved Within the First 7 Days of Therapy Associated With Acute Kidney Injury in Children?

Chad A. Knoderer, Kristen R. Nichols, Kelsey C. Lyon, Megan M. Veverka, and Amy C.Wilson

Background. In 2008, the empiric vancomycin dosing recommendation in children at our institution was changed from 40 to 60 mg/kg per day. Subsequently, an increased incidence of acute kidney injury (AKI) in patients receiving vancomycin was suspected. The objective of this study was to evaluate AKI in children receiving vancomycin and to determine risk factors for AKI development.

Methods. Medical records of patients aged 30 days through 17 years who received vancomycin for at least 72 hours between January and December 2007 (40 mg/kg per day) and January and December 2010 (60 mg/kg per day) were reviewed. Patients with cystic fibrosis, an elevated baseline serum creatinine, or without a serum creatinine concentration obtained after receipt of vancomycin were excluded. Acute kidney injury was defined using adapted pediatric RIFLE criteria as an increase in serum creatinine from baseline of 50% or more.

Results. Acute kidney injury occurred in 19.4% of the 859 children included, with no difference between the 2007 and 2010 periods (18.8% vs 20%, respectively; $P = .636$). Intensive care unit admission (odds ratio [OR], 1.86; 95% confidence interval [CI], 1.20–2.94) and an initial vancomycin trough concentration ≥15 mg/L (OR, 2.18; 95% CI, 1.21–3.92) were determined to be significantly associated with AKI.

Conclusions. These results suggest an initial vancomycin serum trough concentration of ≥15 mg/L and intensive care unit admission are predictors of AKI in this pediatric population.

BACKGROUND

Vancomycin is commonly used in the pediatric population for empiric or targeted treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections and has been associated with acute kidney injury (AKI) [1].Empiric intravenous (IV) vancomycin in children has traditionally been dosed as 40 mg/kg per day in 4 divided doses to achieve target serum trough concentrations of 5–10 mg/L. Recent evidence and recommendations suggest that such doses are unlikely to achieve the goal serum trough concentrations (10–20 mg/L) that are necessary for the optimal area under the curve (AUC) for plasma concentration relative to the organism minimum inhibitory concentration (MIC) (AUC/MIC) [2-5].

In 2008, the recommendation for empiric vancomycin dosing in children at our institution was changed from 40 to 60 mg/kg per day. Subsequently, an increased AKI incidence in patients receiving vancomycin was suspected. The observed increase was anecdotally attributed to higher vancomycin doses, with acknowledgment that it could be related to other factors.

Adult patients experiencing initial vancomycin serum trough concentrations ≥15 mg/L have a higher incidence of nephrotoxicity, and they may be at higher risk for AKI development [6-10]. Pediatric data are limited to a small series of patients reported by McKamy et al [11], in which children with a mean vancomycin serum trough concentration (throughout the course of therapy) of 15 mg/L or greater were at higher risk for developing nephrotoxicity. There are currently no additional published pediatric data available. The objectives of this study were to evaluate AKI in children receiving vancomycin and to determine factors associated with AKI development.

MATERIALS AND METHODS

Study Design and Population

This was a retrospective, single-center cohort study. Hospital clinical decision support and pharmacy data were used to identify patients aged 30 days through 17 years who received vancomycin for at least 72 hours during the calendar years 2007 and 2010. The selected time frames represent periods before and after the recommended dosing change. Although the pharmacy-recommended dosewas increased, prescribers retained the responsibility for individual vancomycin dosing decisions.

Patients were excluded if they had baseline (before initial vancomycin dose) serum creatinine concentrations (SCr) above institutional age-adjusted normal values, no SCr obtained following vancomycin initiation, or cystic fibrosis. Patients receiving multiple vancomycin courses during the same hospitalization had only data from the first vancomycin course included.
Medical records were reviewed to extract baseline demographic and clinical data, vancomycin dosing information, and history of exposure to other factors known to be associated with higher risk of AKI (ie, intensive care unit [ICU] admission, extracorporeal membrane oxygenation utilization, sepsis). Sepsis was determined by using medical coding information captured by the hospital's information management system. Concurrent nephrotoxins (aminoglycosides, tacrolimus, meropenem, cyclosporine, scheduled nonsteroidal anti-inflammatory drugs, IV acyclovir, amphotericin B deoxycholate, IV contrast dye) were also assessed. Serum creatinine concentrations were collected from before vancomycin initiation and for 7 days after. Patients' initial vancomycin trough serum concentrations were also collected and categorized as described above ($\geq$15 mg/L), or within or below (<15 mg/L) target range.

Outcomes

Acute kidney injury was defined as an increase in serum creatinine by $\geq$50% from baseline, as adapted from pediatric RIFLE (pRIFLE) criteria [12]. The primary outcome analyzed was AKI incidence as determined by pRIFLE criteria. Secondary outcomes included need for renal replacement therapy (RRT), determined by ICD-9 coding for RRT (39.95 and 54.98), and in-hospital mortality.

Data Analysis

Baseline demographics and clinical characteristics were compared using independent samples t tests, $\chi 2$ analyses, and Mann-Whitney tests for nonparametric data. Logistic regression analysis of pRIFLE AKI was utilized using a forced entry method. Variables were included in the final regression model if they had a P value <.25 after univariate analysis. P values less than .05 were considered to be statistically significant. Statistical analyses were conducted using Statistical Package for Social Sciences version 19.0 (SPSS, Inc, Chicago, IL). The study was approved by the Indiana University institutional review board.

RESULTS

Hospital and pharmacy records initially identified 1480 patient-courses eligible for study inclusion. After exclusions, a total of 859 patients were included in the final analysis. Baseline demographics (gender, age, weight) of patients in the 2007 and 2010 treatment groups were similar. The mean empiric vancomycin dose received was increased in 2010 (43.2 ± 16.6 mg/kg per day) vs 2007 (40.1 ± 14.6 mg/kg per day); P = <.05. The percentage of patients who received a ≥60 mg/kg per day empiric vancomycin dose also increased (31.5% vs 18.3%; P < .05). The median (interquartile range [IQR]) initial vancomycin serum trough concentration (mg/L) was higher in 2010 than in 2007 (8.9 [6.1–12.6] vs 7.7 [5.6–10.8], respectively; P < .05). Although the mg/kg per day dosing difference is not clinically significant, more patients in 2010 (15%) achieved an empiric trough concentration of ≥15 mg/L compared to those in 2007 (8%; P < .05). Acute kidney injury determined by pRIFLE criteria occurred in 19.4% (167 of 859) of all patients. There was no difference in AKI
rate between the 2007 (76 of 405; 18.8%) and 2010 (91 of 454; 20%) groups (P = .636).

Table 1 summarizes characteristics of patients with and without AKI. The mean ± standard deviation empiric vancomycin dose (mg/kg per day) was similar in patients with and without AKI (43.1 ± 15.7 vs 41.6 ± 15.6, respectively; P = .294). Acute kidney injury occurred more frequently in children achieving an initial vancomycin trough concentration of >15 mg/L (33.3% vs 18.6%; P = <.05). There were no differences in rates of exposure to concomitant nephrotoxic medications between patients with and without AKI except for meropenem (21% vs 13.3%; P = <.05). As expected, ICU (neonatal or pediatric) admission occurred significantly more frequently in patients with AKI (57.5% vs 40.8%; P < .05), but no other differences in nephrotoxic factors were observed (Table 1). In multivariate logistic regression analysis, ICU admission (odds ratio [OR], 1.86; 95% confidence interval [CI], 1.20–2.94) and an initial vancomycin trough concentration
of ≥ 15 mg/L (OR, 2.18; 95% CI, 1.21–3.92) were found to be independently associated with AKI development.

Among patients with AKI, serum creatinine increased 50%–877% above baseline, with a 75% (60%–120%) median (IQR) increase. Magnitude of increase in creatinine was similar between AKI patients with and without an initial vancomycin trough concentration of ≥15 mg/L (median [IQR] 95 [65.5–136.5] and 68 [55–106], respectively; P = .077). Renal replacement therapy need was unchanged in patients with initial vancomycin trough concentrations of ≥15 mg/L, although absolute numbers of patients requiring RRT were low (3.2% and 0.6%, respectively; P = .103). All-cause mortality was increased in patients with AKI (9% vs 2.7%; OR, 3.5; 95% CI, 1.7–7) and also in patients with an initial vancomycin trough concentration of ≥15 mg/L (9% vs 2.7%; OR, 3.4; 95% CI, 1.1–10).

Table 1 Characteristics of Patients With and Without AKI

	No AKI (n = 692)	AKI (n = 167)	Value
Patient Characteristics			
Male[a] Age[b] Weight[b] Initial SCr (mg/dL)[b]	384 (55.5) 3(1−9) 14.2 (8.7−28.3) 0.4 (0.3−0.58)	81 (48.5) 2 (1−9) 12.3 (7.3−29) 0.3 (0.2−0.42)	.104 .684 .774 <.05
Vancomycin Information			
Empiric vancomycin dose (mg/kg per day)	41.7 ± 15.6	43.1 ± 15.7	.294
Empiric vancomycin dose >60 mg/kg per day Vancomycin duration (days)[b]	166 (24) 5(4−8.8)	51 (30.5) 6 (4−9)	.08 .149
Trough concentration obtained Initial vancomycin serum trough concentration (mg/L)[b]	439 (63.4) 7.7 (5.8−11.2)	112 (67.1) 9.4 (6.3−13.5)	.380 <.05
Initial vancomycin serum trough concentration ≥15 mg/L	42 (9.6)	21 (18.8)	<.05
Nephrotoxic Factors[a]			
ICU admission	282 (40.8)	96 (57.5)	<.05
Oncologic diagnosis	221 (31.9)	49 (29.3)	.517
Dehydration	50 (7.2)	16 (9.6)	.305
ECMO	47 (6.8)	13 (7.8)	.652
Sepsis	111 (16)	33 (19.8)	.248
Nephrotoxic Medications[a]			
Any concomitant nephrotoxic medication	460 (66.5)	117 (70.1)	.376
Acyclovir (IV)	87 (12.6)	24 (14.4)	.534
Amphotericin	33 (4.8)	12 (7.2)	.208
Aminoglycoside	253 (36.6)	74 (44.3)	.064
Calcineurin inhibitor	66 (9.5)	19 (11.4)	.475
Contrast dye	313 (45.2)	87 (52.1)	.11
Meropenem	92 (13.3)	35 (21)	<.05
NSAID	188 (27.2)	44 (26.3)	.83

Abbreviations: AKI, acute kidney injury; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; SCr, serum creatinine concentrations.
[a]Data reported as n (%).
[b]Data reported as median (interquartile range).

DISCUSSION

The need for increased empiric vancomycin doses relates directly to the drug's pharmacokinetic/pharmacodynamics (PK/PD) parameters and increasing MRSA resistance incidence [3]. Clinical efficacy with vancomycin is most likely optimized in adult patients when an AUC/MIC ratio of at least 400:1 is attained. The vancomycin serum trough concentration is an appropriate surrogate, and values of 15–20 mg/L in adult patients correlate with AUC/MIC of at least 400:1 for MRSA isolates with MIC values of ≥ 1 mg/L to vancomycin [3]. Recent pediatric data suggest that AUC/MIC of 400:1 correspond with vancomycin trough concentrations of 7–10 mg/L. Targeting a trough concentration of 15–20 mg/L in children may actually lead to vancomycin overexposure and increase the potential for toxicity [13, 14]. Decreasing susceptibility of MRSA to vancomycin in the adult population has resulted in the utilization of increased empiric vancomycin doses to target initial trough concentrations of 15–20 mg/L. Although there is limited but similar data in children, it is important to evaluate recent pediatric PK/PD data along with bacterial resistance trends when considering dosing strategy changes.

Vancomycin has long been considered nephrotoxic, but more recent literature has firmly established an association
between vancomycin exposure and kidney injury. Adult patients experiencing initial vancomycin serum trough concentrations of ≥15 mg/L have been shown to have a higher incidence of nephrotoxicity, and these patients may be at higher AKI risk [6-10]. Vancomycin serum trough concentrations ≥14 mg/L and therapy durations ≥ 7 days have been shown to be independent predictors of vancomycin-associated AKI in hospitalized adults [8]. Duration of vancomycin exposure was similar in our non-AKI and AKI patients. Hidayat et al [7] demonstrated

significantly higher vancomycin associated nephrotoxicity incidence in adults with MRSA infections when those patients had serum trough concentrations of 15–20 mg/L and were receiving concomitant nephrotoxic medications. A 2011 prospective study revealed that adults with MRSA infections have a greater risk of AKI with vancomycin serum trough concentrations of ≥15 mg/L (OR, 3.6; 95% CI, 1.75–7.59) [9]. Likewise, adults with MRSA pneumonia have been shown to be at a 3–5 times greater risk for developing AKI with vancomycin serum trough concentrations of ≥15 mg/L [6, 10].

Overall, we found a 19% (167 of 859) AKI incidence in children receiving at least 72 hours of vancomycin therapy, with no difference in incidence after increasing the empiric vancomycin dosing strategy in children at our institution. The empiric vancomycin dose was statistically similar in patients with and without AKI, although the median initial vancomycin trough was significantly higher in the AKI group. The reason for this discrepancy is unclear, but it could be related to an unobserved, underlying renal insufficiency before vancomycin initiation. It could also be that the AKI patients were sicker, compared to non-AKI patients, due to factors that were not considered in this study.

Our findings are similar to the 14% (24 of 167) vancomycin-associated nephrotoxicity incidence in children shown by McKamy et al [11], who evaluated 167 patients. In that retrospective study, 28% of children with a high vancomycin serum trough concentration (≥15 mg/L) were determined to have nephrotoxicity compared to 7% of children with a low trough concentration (<15 mg/L). Likewise, AKI incidence was increased in our study in children with an initial vancomycin trough concentration ≥15 mg/L. Similar to adults, empiric vancomycin doses in children necessary to attain higher trough concentrations are associated with AKI.

McKamy et al [11] averaged serum trough concentrations obtained through the course of therapy to categorize patients into the high vs low trough group. We evaluated only the initial vancomycin serum trough concentration, and we found that a concentration of ≥15 mg/L and ICU admission were predictors for AKI within the first 7 days of therapy. Others have evaluated average vancomycin trough concentrations and the association with AKI throughout the vancomycin course, but they have not specifically assessed the relationship between initial vancomycin concentrations and early AKI development. Our finding that children with an initial vancomycin trough concentration of ≥15 mg/L are twice as likely to develop early AKI (within the first 7 days of therapy) is concerning. Despite the perceived increase in our institution's empiric vancomycin dosing, the actual difference from 2007 to 2010 was not clinically significant, and there was no difference in the percentage of non-AKI and AKI patients receiving an empiric dose of >60 mg/kg per day. These findings raise the question of underlying kidney injury (not considered in this study), which is intensified with vancomycin and leads to elevated trough serum concentrations. The clinical impact of this identified association is unclear. LikeMcKamy et al [11] and many adult investigators, we used serum creatinine to categorize patients with AKI [6-9]. The pRIFLE criteria define AKI as a decrease in estimated creatinine clearance by at least 50%, which corresponds to an increase in serum creatinine by ≥ 50%, and that was modified to determine AKI in our study sample [12]. The importance of the early serum creatinine changes, as they relate to vancomycin dosing, could be questioned, particularly if AKI was so mild that it was not detected in a clinical setting and thus was not coded. Likewise, the increase in mortality we observed in association with AKI and in association with higher initial

vancomycin trough concentrations in this cohort suggests that these early changes in creatinine may be of more clinical importance than appreciated, but it may also simply reflect that those children were more severely ill than those without AKI. The answers to these questions are beyond the scope of this retrospective study.

Chart documentation can limit available information in retrospective studies. However, our study did include a large number of children. Despite the limited control the study provided for vancomycin dosing and monitoring, vancomycin concentrations were obtained in more than 60% of children exposed to vancomycin in our sample (551 of 859), which allows for a representative evaluation of any association with AKI. Although elevated serum creatinine was used as an exclusion criterion to avoid attributing AKI to vancomycin in patients with prior renal injury, serum creatinine elevation may lag behind a decrease in function. Therefore, some of the elevated vancomycin trough concentrations may have been due to undetected poor baseline renal function. In addition, the pRIFLE criteria provide little guidance for addressing serum creatinine fluctuations that are thought to be normal variation or due to testing variability (ie, change from 0.1 to 0.2 mg/dL). This type of fluctuation occurred in approximately 18% of AKI patients in our sample, and it illustrates a limitation in using pRIFLE criteria alone as the sole AKI determinant. We only evaluated early AKI relative to initial vancomycin concentrations, and thus we cannot address whether ongoing exposure to higher vancomycin serum trough concentrations further increases AKI risk.

CONCLUSIONS

In our pediatric population, we found an initial vancomycin serum trough concentration of ≥15 mg/L and ICU admission to be independent predictors for early AKI development. Higher vancomycin serum trough concentrations may be associated with AKI as determined by elevated SCr. Additional studies are needed to determine the longer-term clinical impact of high initial vancomycin trough concentrations. However, these findings indicate that closer therapeutic drug monitoring and renal function monitoring are clearly warranted for children who receive vancomycin therapy that extends beyond 72 hours and those with initial vancomycin trough concentrations of ≥15 mg/L.

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