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Vancomycin-Associated Nephrotoxicity and the Use of Higher Trough Concentrations in Infants and Children

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Vancomycin remains one of the mainstays of empiric therapy in pediatric patients at risk for infections with resistant Gram positive organisms. Approved by the Food and Drug Administration (FDA) in 1958, vancomycin was the first glycopeptide antibiotic and provided a unique mechanism of action in treating *Staphylococcal* and *Streptococcal* infections. Wide-spread use over the past 50 years eventually has led to reduced sensitivity to vancomycin and the development of resistance.[1]

In 2009, the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), and the Society of Infectious Diseases Pharmacists (SIDP) published a consensus statement on vancomycin monitoring in adults.[2] The group recommended maintaining trough vancomycin serum concentrations above 10 mcg/mL for most infections. A higher target of 15-20 mcg/mL was suggested for patients with complicated methicillin resistant *Staph. aureus* (MRSA) infections, including pneumonia, meningitis, endocarditis, and osteomyelitis, as well as strains with vancomycin minimum inhibitory concentrations (MICs) of 2 mg/L. The higher range for vancomycin troughs was suggested in order to provide an area under the concentration time curve to minimum inhibitory concentration ratio (AUC/MIC) of at least 400. While these recommendations were made only for adults, many pediatric institutions have begun to apply the higher trough concentration range in some, or all, of their neonatal and pediatric patients.

Incidence and Risk Factors for Nephrotoxicity

Escalation of vancomycin doses to achieve higher serum trough concentrations may improve efficacy against MRSA infections, but at the risk of increased nephrotoxicity.[3,4] Earlier this year, Burgess and Drew evaluated this risk in a retrospective cohort review of 191 adults at Duke University.[4] The authors evaluated the impact of several known risk factors for nephrotoxicity, including concomitant nephrotoxic agents, advanced age, comorbidities, total vancomycin doses of 4 grams or greater, or trough concentrations of 15 mcg/mL or greater. Nephrotoxicity occurred in 12% of patients. In univariate analysis, having a high trough concentration was the only factor associated with an increased risk of developing nephrotoxicity (OR 3.67, 95% CI 1.49-9.03). In multivariate analysis, concomitant use of piperacillin-tazobactam, was also associated with an increased risk for nephrotoxicity (OR 2.48, 95% CI > 1.11, p = 0.032). The use of higher serum trough concentrations in patients receiving the common empiric regimen of vancomycin and piperacillin-tazobactam may produce a significantly higher incidence of nephrotoxicity than what most clinicians have come to associate with vancomycin use.

In the last four years, more than two dozen papers have re-examined the dosing, efficacy, and toxicity of vancomycin in infants and children.[5-11] In 2011, McKamy and colleagues conducted a retrospective study to assess the incidence of nephrotoxicity in 167 infants and children (1 week to 18 years of age) treated with vancomycin.[5] As in most studies described in this issue of the newsletter, acute kidney injury (AKI) was defined as an increase in serum creatinine of $\geq$ 0.5 mg/dL increase over baseline or a $\geq$ 50% increase in serial creatinine measurements over a period of at least 2 days. Fourteen percent of patients met the criteria for AKI, considerably higher than the 5-7% incidence of nephrotoxicity traditionally reported with vancomycin in children. The frequency of AKI was significantly higher in patients with a serum trough concentration $\geq$ 15 mcg/mL compared to those with lower troughs (28% versus 7.3%, p = 0.0001). Multivariate analysis also identified high serum trough values as a risk factor for nephrotoxicity, along with the use of furosemide and admission to an intensive care unit. Although all patients had normal serum creatinine values for age, this study has been criticized for not fully addressing the potential confounding effect of worsening renal function

during treatment as the result of disease progression.

In 2013, Ragab and colleagues evaluated the incidence of nephrotoxicity in 265 infants and children (1 week-15 years of age) treated with vancomycin.[6] Seventy-two patients (27.2%) met the criteria for AKI. Among the patients who developed AKI, 82% had serum vancomycin trough concentrations of 10 mcg/mL or greater. When the patients were divided into groups by vancomycin trough concentrations of < 10 mcg/mL, 10-15 mcg/mL, and > 15 mcg/mL, the incidence of nephrotoxicity per group was 33.3%, 41%, and 87.5%, respectively. Other factors associated with AKI were admission to the intensive care unit (OR 2.91, 95% CI 1.70-8.61, $p < 0.03$) and the use of multiple nephrotoxic agents (OR 9.11, 95% CI 4.11-24.13, $p < 0.05$).

Totapally and colleagues conducted a similar retrospective study of the risk factors for vancomycin-associated AKI in 284 children (median age 2.23 years) receiving 391 courses of therapy.[7] The average dose used in these patients was 34.2 $\pm$ 12.4 mg/kg/day, which is below current dosing recommendations in most pediatric references. Acute kidney injury was defined as a decrease in estimated glomerular filtration rate (calculated using the Schwartz formula) of $\geq$ 50% after initiation of vancomycin. Forty nine patients (17%) developed AKI. The relatively high incidence of AKI was unexpected in patients treated with these lower doses. Patients with AKI had a slightly higher mean vancomycin trough concentration compared to those without AKI (8.9 $\pm$ 5.3 mcg/mL and 7.7 $\pm$ 4.8 mcg/mL, respectively) but the difference was not statistically significant. Regression analysis identified associations between the development of AKI and the administration of multiple nephrotoxins (OR 2.23, 95% CI 1.27-3.93, $p < 0.001$) as well as a baseline BUN to serum creatinine ratio of 20 or greater (OR 1.9, CI 1.1-3.3, $p < 0.05$). Serum creatinine returned to baseline upon discontinuing treatment in 87% of cases.

Investigators at Johns Hopkins University published a retrospective study of 175 children, 3 months to 18 years of age who received vancomycin at their institution.[8] All patients had normal renal function at baseline. Acute kidney injury was defined as a decrease in estimated glomerular filtration rate of $\geq$ 50% from baseline. Twenty-four patients (13.7%) met criteria for AKI. The average daily vancomycin dose was significantly higher in the group who developed AKI, compared to those who did not (65.3 $\pm$ 15.5 mg/kg/day versus 54.7 $\pm$ 16.6 mg/kg/day, $p = 0.004$). One quarter of the patients with AKI had received doses of 80 mg/kg/day or more. The patients with AKI also had higher vancomycin trough concentrations during therapy compared to those without AKI (26.6 $\pm$ 18.8 mcg/mL versus 11.7 $\pm$ 5.9 mcg/mL, $p = 0.001$). Multivariate regression analysis revealed a significant increase in the risk for AKI with each 5 mg/kg increase in vancomycin dose (OR 1.16, 95% CI 1.01-1.33) or additional day of therapy (OR 1.11, 95% CI 1.01-1.22). As anticipated, concomitant use of other nephrotoxic drugs was also associated a higher risk for AKI (OR 5.02, 95% CI 1.09-23.19).

In contrast, Moffett and colleagues at Texas Children's Hospital found no substantial increase in vancomycin-associated nephrotoxicity in a case-control study of 418 children admitted to their cardiac intensive care unit.[9] Thirty patients (7.2%) met criteria for vancomycin-associated AKI, defined by the authors as a doubling of serum creatinine within the first 72 hours of therapy. Each of these patients was matched to three patients with AKI who had not received vancomycin to serve as the controls. The patients with vancomycin-associated AKI were more likely to have received extracorporeal membrane oxygenation and had been exposed to multiple nephrotoxic agents. Vancomycin doses were no different between the patients with vancomycin-associated nephrotoxicity and the controls. The authors concluded that vancomycin-associated nephrotoxicity occurs infrequently, but that patients receiving higher doses, longer treatment courses, or multiple nephrotoxins are at higher risk and should be closely monitored.

Not all studies have shown a relationship between serum concentrations or dose and AKI. In 2013, Cies and Sahankar published the results of a retrospective cohort study of 113 pediatric intensive care unit patients given vancomycin.[10] Patients were divided into two groups: a high-dose cohort whose doses were adjusted to achieve a trough concentration of at least 15-20 mcg/mL and a control group treated with standard dosing guidelines designed to achieve a trough of 5-15 mcg/ mL. The mean trough concentration was 17.8 $\pm$ 3.1 mcg/mL in the high-dose group and 8.4 $\pm$ 3.1 mcg/mL in the controls. The frequency of nephrotoxicity was greater in the high-dose group, but the results were not significantly different (8.8% versus 5.4% in the controls, $p = 0.72$). No patients developed severe renal dysfunction. In multivariate analysis, the only factors associated with nephrotoxicity were vasopressor use (OR 11.1, 95% CI1.4-85, $p = 0.021$) and duration of therapy (OR 1.19, 95% CI 1.04-1.37, $p = 0.011$).

Are Higher Troughs Necessary?

While the correlation between trough concentrations > 15 mcg/mL and AUC/MIC values of at least 400 has been established in adults, until recently there has been no comparable correlation between trough and AUC/MIC values in the treatment of Staphylococcal infections in infants and children. To address this question, several investigators have examined MRSA isolates taken from children with active infection to establish the frequency of elevated MIC values which would indicate MIC creep.

In a 2010 report in the *Pediatric Infectious Diseases Journal*, Zheng and colleagues at Chicago's Children's Memorial Hospital reviewed data from 306 MRSA isolates collected between 2000 and 2007.[12] Vancomycin MIC testing was done by Etest, with confirmation by broth microdilution and agar dilution methods. There was no change in MIC results over time, by any of the three methods, suggesting no increase in vancomycin resistance. Similar results were published by Goldman and colleagues in their 2013 evaluation of vancomycin MIC data from 208 MRSA isolates.[13] The isolates, obtained between 2006 and 2009, were each tested with broth microdilution, Etest, and Vitek 2. The authors found no increase in MICs or evidence of heteroresistance. Unlike data in adults, these reports show no evidence of MIC creep in children.

Pharmacokinetic simulation has also been used to assess the relationship between vancomycin serum concentrations and AUC/MIC ratios in children. Frymoyer and colleagues used a vancomycin dose of 15 mg/kg every 6 hours and an MIC of 1 mcg/mL to evaluate the ability of standard doses to achieve an AUC/MIC greater than 400 in children.[14] The serum trough concentrations of 7-10 mcg/mL achieved with this dosing in the simulation met the goal AUC/MIC in over 90% of children. In a subsequent analysis, the authors used the same methodology to evaluate the relationship between trough concentrations and AUC/MIC ratio in neonates.[15] Using 1,702 serum vancomycin concentrations previously collected in 249 neonates, the authors found that with a trough concentration of 10 mcg/mL, 89% of the study neonates would have had an AUC/MIC over 400.

In a letter to the editor following the first of Frymoyer's papers, however, Hahn and Vinks questioned the extrapolation of their findings. While conducting a validation study of another pharmacokinetic model, the authors found that only 67% of patients with trough concentrations between 8 and 10 mcg/mL had an AUC > 400.[16] These authors suggest that clinicians move beyond the use of vancomycin trough concentrations and instead utilize individual AUC/MIC data to guide therapy in patients with invasive Staphylococcal infections.

Current data suggest that clinical cure often occurs in children without achieving target vancomycin serum concentrations.[17,18] Le and colleagues conducted a retrospective cohort study of vancomycin at two pediatric hospitals to evaluate the relationship between dosing and AUC/MIC ratios.[18] The authors used population-based pharmacokinetic modeling (NONMEM) to estimate vancomycin pharmacokinetic parameters from data obtained in 702 children between 3 months and 21 years of age. One hundred and sixteen MRSA isolates from these patients were used to provide MIC data. The mean empiric vancomycin dose was 45 $\pm$ 12 mg/kg/day (range 39-52 mg/kg/day). Mean estimates of volume of distribution and clearance (0.63 $\pm$ 0.36 L/kg and 0.12 $\pm$ 0.04 L/kg/hr, respectively) were in agreement with earlier studies in children. Initial vancomycin doses produced a mean AUC of 449 $\pm$ 216 mg•hr/L and a mean trough concentration of 12 $\pm$ 8 mcg/mL.

Using these data for their simulations, along with age, weight, and serum creatinine, the authors found an AUC of 400 mg•hr/L correlated with a serum trough concentration of 8-9 mcg/mL, much lower than that suggested from data in adults. Based on the results of their analysis, the authors suggest that vancomycin AUC/MIC is a more effective target than serum trough concentrations in treating children. For children with normal renal function, they recommend an initial dose of 60 mg/kg/day (15 mg/kg every 6 hrs) in children $\geq$ 12 years of age and 70 mg/kg/day (17.5 mg/kg every 6 hrs) in those 3 months to 12 years of age. These empiric treatment doses are estimated to achieve an AUC/MIC $\geq$ 400 in approximately 75% of patients. The authors noted that use of the recommended daily doses with an 8-hour interval was similarly effective in achieving the target AUC/MIC ratio, but should be expected to produce a lower trough concentration. The use of doses greater than 80 mg/kg/day was not recommended.

Summary

Recent guidelines recommending vancomycin trough concentrations of 15-20 mcg/mL in adults for the treatment of resistant Gram positive infections have been adopted by some children's hospitals. The increase in dose needed to achieve these levels in infants and children, however, has been associated with a significant increase in the incidence of vancomycin-associated AKI. New

data suggest that the frequently used combination of vancomycin and piperacillin-tazobactam may further increase the risk. With little evidence to support the need for higher vancomycin troughs in children and growing evidence of an association between trough concentrations $\geq$ 15 mcg/mL and nephrotoxicity, there is no clear reason to change dosing practices. A target vancomycin concentration of 10-12 mcg/mL remains appropriate for initial dosing in infants and children.

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Formulary Update

The following actions by the Pharmacy and Therapeutics Committee at their September 2014 meeting:

1. Hyaluronic acid-lidocaine (Restylane-L®) was added with restriction to Otolaryngology for management of vocal cord paralysis.
2. Pembrolizumab (Keytruda®), a human programmed death receptor-1 (PD-1)-blocking antibody, was approved for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumaband, or if BRAF V600 mutation positive, a BRAF inhibitor, for outpatient use.
3. Leuprolide depot (Eligard®) was added for outpatient use only.
4. Restrictions on IV acetaminophen (Ofirmev®) were updated to add a hard-stop of 24-hours on orders and removal of PRN orders.
3. Tetracaine-oxymetazoline topical anesthetic solution was added to the Formulary to replace Gross's solution.
4. Based on a recent FDA Safety Alert, topical benzocaine (Baby Orajel™) was removed from the Formulary and viscous lidocaine was restricted to patients > 2 years of age. The Safety Alert is available at http://www.fda.gov/drugs/drugsafety/ucm250024.htm.
5. Penicillamine capsules were removed from the Formulary. Tetanus toxoid vaccine was discontinued.
6. Pediatric multi-trace element (Peditrace™) was added to Formulary to replace Multitrace-4® neonatal trace elements.

Pediatric Pharmacotherapy is available on the University of Virginia School of Medicine website at http://www.medicine.virginia.edu/clinical/departments/pediatrics/education/pharm-news/home.html. For comments or suggestions for future issues, please contact us at mlb3u@virginia.edu.