Letters to the Editor

Vancomycin Dosing Practices, Trough Concentrations, and Predicted Area Under the Curve in Children With Suspected Invasive Staphylococcal Infections

To the Editor—I read with interest the article by Dr Chhim and colleagues [1] on vancomycin dosing in pediatric patients. Their experience with vancomycin dosing and exposure is valuable, and I agree that the optimal therapeutic measure to guide vancomycin therapy in children is still unknown. Maximizing achievement of the target that is associated with the best outcomes in adults (ie, vancomycin area-under-the-curve [AUC]/minimum inhibitory concentration ratio >400) is a rational approach given the absence of pediatric data. Along these lines, Chhim and colleagues [1] predicted AUC (= vancomycin daily dose/vancomycin clearance) in children who received the current recommended vancomycin starting dose of 60 mg/kg per day. However, it is important to point out some areas of potential bias in their methodology.

To predict vancomycin clearance, Chhim and colleagues [1] used a model published by Chang [2].

\[
\text{vancomycin clearance}_{\text{ml min}} = \text{creatinine clearance}_{\text{ml min}} \times 0.7099 + 1.408
\]

Therefore, creatinine clearance (CrCL) is the main factor determining an individual’s predicted vancomycin clearance. To estimate CrCL, Chhim and colleagues [1] used the original Schwartz equation:

\[
\text{CrCL}_{\text{ml min per kg per hr}} = \frac{k \times \text{Height}_{\text{cm}}}{\text{Serum Creatinine}_{\text{mg/dL}}} \]

where \(k\) is 0.55 for children 1–12 years old [3]. However, the original Schwartz equation was developed and validated using a serum creatinine as measured by the Jaffe methodology [3]. Chhim and colleagues [1] in their study used the newer enzymatic serum creatinine methodology, which on average results in lower measures of serum creatinine. For this reason, an updated Schwartz equation with a lower \(k = 0.413\) was developed to use when the enzymatic serum creatinine methodology is implemented [4]. By applying the original Schwartz equation, the authors’ estimate of CrCL, and therefore vancomycin clearance, will be overpredicted on average by approximately 33% in a child (ratio of \(k_{\text{original}}/k_{\text{updated}} = 0.55/0.413\)). Using the reported median AUC of 379 mg x h/L at a dose of 60 mg/kg per day from their paper, the median vancomycin clearance in their study was 0.158 L/h/kg. This estimate of vancomycin clearance is more than 38% higher than that reported in 3 previous clinical pharmacokinetic studies in similar pediatric populations (including the study by Chang from which Chhim and colleagues obtained their vancomycin clearance model) [2, 5, 6]. The potential overprediction of vancomycin clearance may explain why only 40% of patients receiving a dose of 60 mg/kg per day were predicted to achieve AUC >400 mg x h/L. This finding is in contrast to our previous modeling and simulation work in which approximately 90% of children with normal renal function are predicted to achieve an AUC >400 mg x h/L with a dose of 60 mg/kg per day [7]. It is likely that if Chhim and colleagues [1] used the updated Schwartz equation, the predicted number of patients achieving AUC >400 would be substantially higher. In addition, providing the estimated CrCL of their study population might also help explain the high vancomycin clearance in their population.

References


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Reply to Letter to the Editor—We appreciate the comments from Dr Frymoyer concerning the most appropriate pediatric equation for calculating glomerular filtration rate (GFR) and agree that each method has limitations. Although the original Schwartz equation [1] may overestimate GFR when the newer method for measuring creatinine is used, there are several reasons why we chose to use the original equation instead of the revised Schwartz equation [2]. First, the newer equation was developed from the Chronic Kidney Disease in Children cohort and has not been widely studied in children without kidney disease. Schwartz and colleagues [2] concluded that additional studies in healthy children with a higher GFR are needed before recommending the widespread use of this equation in all children. Also, data from 2 recent studies suggest that the newer equation may underestimate GFR in children with mild kidney disease [3] and in children with normal renal function [4]. Therefore, our institution has not implemented the revised Schwartz equation into routine clinical practice due to the limited data supporting its applicability in children without kidney dysfunction. Finally, Schwartz [5] also suggested that equations used to estimate GFR should correct for differences in body habitus, sex, puberty, infancy, and prematurity. Because our patient cohort included children ages 2 months to 18 years with normal baseline renal function, we chose to use the original Schwartz equation that accounts for differences in age and sex [6].

We agree that the difference in equations used to estimate GFR likely contributes to the difference in predicted area under the curve (AUC) reported in the modeling study by Frymoyer and colleagues [7] and our retrospective study [8]. In addition, we excluded patients with any type of renal dysfunction, so we would expect to observe a faster vancomycin clearance compared with a general pediatric population kinetics study. Our estimate for vancomycin clearance of 0.15 L/h/kg is within the range of reported values for vancomycin clearance in children (0.103–0.157 L/h/kg) that Frymoyer and colleagues [7] used in their original modeling study. These differences in estimated GFR and predicted AUC reaffirm the conclusions by Schwartz and colleagues [5] that more studies are needed in order to generate a widely applicable equation to estimate GFR in pediatric patients. Therefore, we do not believe there is currently a standard method of calculating GFR, and the method chosen should not only be based on the process used for measuring serum creatinine but also be based on the patient population being assessed, as we attempted to do in our study.

References

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