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Prediction of Vancomycin Dose for Recommended Trough Concentrations in Pediatric Patients With Cystic Fibrosis

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Abstract

Vancomycin is a key antibiotic used in the treatment of multiple conditions including infections associated with cystic fibrosis and methicillin-resistant *Staphylococcus aureus*. The present study sought to develop a model based on empirical evidence of optimal vancomycin dose as judged by clinical observations that could accelerate the achievement of desired trough level in children with cystic fibrosis. Transformations of dose and trough were used to arrive at regression models with excellent fit for dose based on weight or age for a target trough. Results of this study indicate that the 2 proposed regression models are robust to changes in age or weight, suggesting that the daily dose on a per-kilogram basis is determined primarily by the desired trough level. The results show that to obtain a vancomycin trough level of 20 μg/mL, a dose of 80 mg/kg/day is needed. This analysis should improve the efficiency of vancomycin usage by reducing the number of titration steps, resulting in improved patient outcome and experience.

Keywords

Biostatistics, Clinical Pharmacology (CPH), Infectious Diseases (INF), Pharmacology (PHA), Pharmacokinetics and drug metabolism

Vancomycin is a key antibiotic used in the treatment of multiple conditions including cystic fibrosis (CF). Obtaining the proper trough concentration is a major goal to achieve optimal patient outcome,[1–9] which is complicated by increasing antimicrobial resistance. In the case of children, there are also no guidelines on therapeutic monitoring of vancomycin from the Infectious Disease Society of America. The present study sought to develop a method to estimate the dose needed to obtain a desired trough concentration in children with cystic fibrosis. This analysis is expected to allow appropriate vancomycin trough concentrations to be established with fewer titration steps, resulting in the achievement of more effective and more rapid treatment effects.

Methods

Approval to conduct this study was obtained (January 5, 2017) from the Sacred Heart Clinical Investigation Review Board, Sacred Heart Health System. A retrospective chart review was performed on pediatric cystic fibrosis patients treated with vancomycin from 2011 to 2016 at a tertiary children's hospital. Inclusion criteria were aged between 1 month and 18 years old, at least 1 vancomycin serum trough concentration, and being treated for a CF exacerbation. Data were obtained from 45 children aged 20–214 months, with a mean age of 158 months. Creatinine levels ranged from 0.2 to 0.9 mg/dL, with a mean of 0.5 mg/dL. BUN values ranged from 1 to 20 mg/dL, with a mean of 8.6 mg/dL. The BUN/creatine ratio ranged from 3:1 to 63:1, with a mean of 16:1.

In this population, vancomycin was administered with a daily loading dose ranging from 42 to 120 mg/kg intravenously. Maintenance doses ranged from 14 to 20 mg/kg at 6- or 8-hour intervals. Total daily dose ranged from 42 to 84.8 mg/kg. Vancomycin trough was measured 30 minutes before the next dose, ranging from 5.2 to 26.7 μg/mL and with a mean trough of 12.8 μg/mL. For the purposes of this study, all trough values were obtained after 24 hours just before giving the first dose of the day. Statistical analysis was done on the dose-trough concentrations that were determined by the clinical team at the time an acceptable dose-trough combination had been attained. Thus, these data represent the best attainable concentration for each

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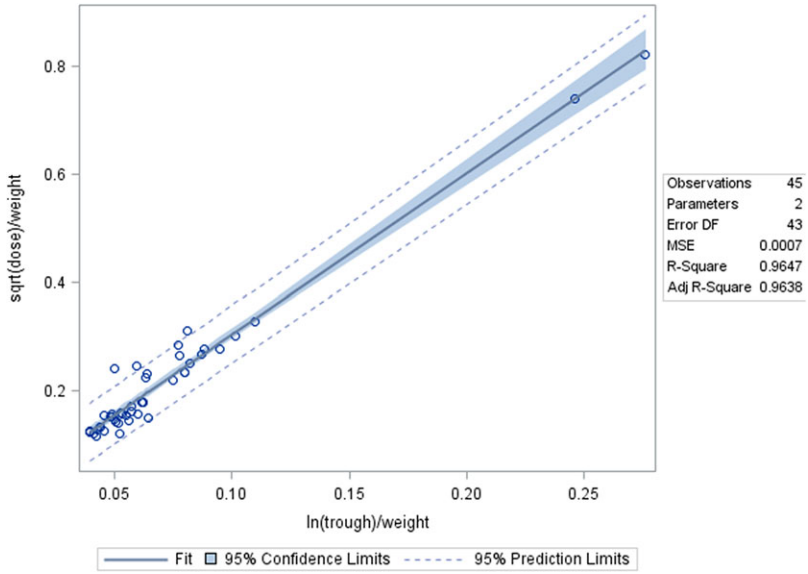

Figure 1. Plot of regression line using model 1 ($\sqrt{dose}/weight$ against $\sqrt{trough}/weight$). Using this model, the linear fit is greatly improved after transforming dose and trough. The 95% prediction interval is illustrated by the outer dotted lines, which estimate the dose for a given child. The 95% confidence interval shown in the shaded area represents the estimate of the mean dose for all children of a given weight. Dose (mg/kg), trough (μg/mL).

patient, which ranged from 1 day to several days in some cases. Statistical Analysis System (SAS/STAT) version 9.4 was used for the statistical analysis of the data.

Results

Previous studies have attempted to fit dose against trough without any transformations, resulting in a poor fit. In the current study, fitting the raw data of dose (mg/kg) against trough (μg/mL) resulted in an r^2 of 0.0005 and also indicated a very poor linear fit, in agreement with previous results.[1,2,4,6] To improve the linear fit, regression models were developed to obtain prediction models with better statistical properties.[10]

As a first step, dose and trough were transformed by dividing dose and trough each by the weight (kg) of the child. This resulted in improving the linear association between dose and trough ($r^2 = 83\%$) with a final equation of $dose/weight = 0.19 + 4.17^{*}trough/weight$(weight [kg]). An attempt to further improve the strength of the linear fit was done by taking the square root of the dose and the natural log of the trough followed with a division of the transformed dose and trough by the weight of the child. Dose is transformed to $\sqrt{dose}/weight$, and trough is transformed to $\ln(trough)/weight$.

This transformation creates a very strong linear association between dose and trough, with a final equation of $\sqrt{dose}/weight = 0.006 + 2.98^{*}\ln(trough)/weight$ for model 1. Although the intercept is nonsignificant and a no-intercept model could be used, the estimated slope is significantly different from zero ($P < .05$), and the regression has an excellent fit, with $r^2 = 96\%$, explaining 96% of the total variability in dose from the regression of dose on trough, as shown in Figure 1.

A table of predicted daily doses required for target trough concentrations based on weight (Table 1) is in good agreement with previous estimates that trough values in children of 20 μg/mL are unattainable at typical daily doses of 60 mg/kg. These data suggest trough values of 20 μg/mL would require a daily dose

Table 1. Predicted Daily Dose for Specified Trough Based on Weight of Child

	Daily Dose (mg/kg)					
Weight (kg)	Trough 10 μg/mL	Trough 12 μg/mL	Trough 14 μg/mL	Trough 16 μg/mL	Trough 18 μg/mL	Trough 20 μg/mL
5	47.6	55.4	62.5	69.0	74.9	80.5
10	48.1	55.9	63.0	69.5	75.5	81.0
15	48.5	56.4	63.5	70.0	76.0	81.6
20	49.0	56.9	64.0	70.6	76.6	82.2
25	49.4	57.4	64.6	71.1	77.2	82.8
30	49.9	57.9	65.1	71.7	77.7	83.4
35	50.3	58.4	65.6	72.2	78.3	84.0
40	50.8	58.8	66.1	72.7	78.9	84.5
45	51.7	59.3	66.6	73.6	79.4	85.1
50	51.7	59.8	67.2	73.8	80.0	85.7
55	52.2	60.3	67.7	74.4	80.6	86.3

The predicted daily dose for various trough concentrations based on the weight of the child is shown using model 1. The model predicts that for each additional mg/mL in trough desired, an additional 3 mg/kg of vancomycin is required. The model predicts that for a given trough level, the dose of vancomycin needed increases only modestly per kilogram of body weight.

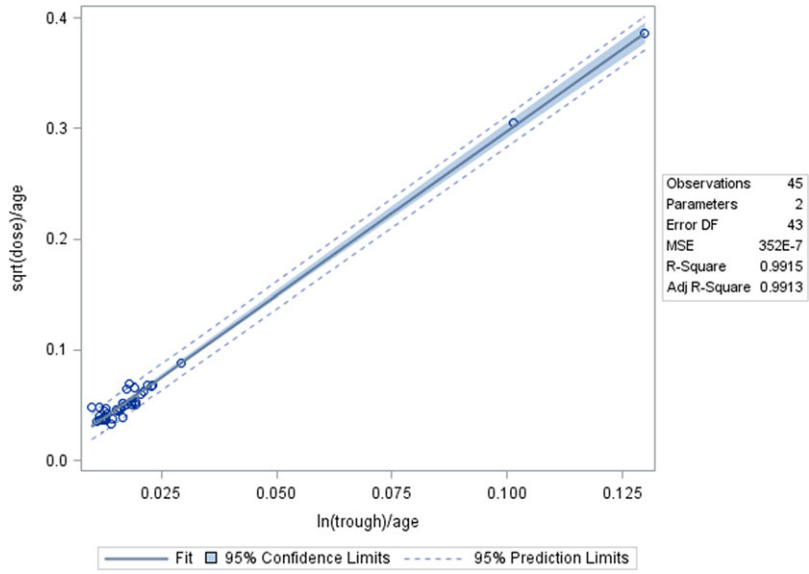

Figure 2. Plot of regression line using model 2 ($\sqrt{dose}/age$ against $\ln(trough)/age$). Using this model, the linear fit is greatly improved after transforming dose and trough. The 95% prediction interval is illustrated by the outer dotted lines, which estimate the dose for a given child. The 95% confidence interval shown in the shaded area represents the estimate of the mean dose for all children of a given age. Dose (mg/kg), trough (μg/mL), age (months).

of approximately 80 mg/kg for children with weights between 5 and 55 kg ($r^2 = 96\%$). Because the age of a child and the corresponding weight are highly correlated measurements a second regression model is developed based on the age (in months) of the children. In model 2, dose is transformed to $\sqrt{dose}/age$ and trough is transformed to $\ln(trough)/age$.

This transformation creates a very strong linear association between dose and trough with a final equation of $\sqrt{dose}/age = 0.00138 + 2.964^{*} \ln(trough)/age$ for model 2. Similar to model 1, the intercept is nonsignificant, and the estimated slope is significantly different from zero ($P < .05$), and the regression has an excellent fit, with $r^2 = 96\%$, explaining 99% of the total variability in dose from the regression of dose on trough, as shown in Figure 2. A table of predicted daily doses required for target trough concentrations based on age (Table 2) is in good agreement with the results in Table 1 for model 1, also suggesting that trough values in children of 20 μg/mL are unattainable at typical daily doses of 60 mg/kg.

Table 2. Predicted Daily Dose for Specified Trough Based on Age of Child

	Daily Dose (mg/kg)					
Age (Months)	Trough 10 μg/mL	Trough 12 μg/mL	Trough 14 μg/mL	Trough 16 μg/mL	Trough 18 μg/mL	Trough 20 μg/mL
20	47.0	54.7	61.6	68.0	73.9	79.3
40	47.3	55.1	62.6	68.5	74.4	79.8
60	47.7	55.5	62.5	68.9	74.8	80.3
80	48.1	55.9	62.9	69.4	75.3	80.8
100	48.5	56.3	63.4	69.8	75.8	81.3
120	48.9	56.7	63.8	70.3	76.3	81.8
140	49.3	57.1	64.5	70.8	76.8	82.3
160	49.7	57.6	64.7	71.2	77.2	82.8
180	50.0	58.0	65.1	71.7	77.7	83.3
200	50.4	58.4	65.6	72.2	78.2	83.8

The predicted daily dose for various trough concentrations based on the age of the child is shown using model 2. The model predicts that for each additional μg/mL in trough desired, an additional 3 mg/kg of vancomycin is required. The model also predicts that with age there is minimal change in the daily dose of vancomycin needed per kilogram, of weight.

Discussion

In this study, the transformation of the dose–response curve to incorporate the weight of the participant in the prediction of the dose improves previous models significantly.[1,2,4,6] Although other studies have discussed the use of the area under the curve/minimum inhibitory concentration as a better predictor,[11] the current analysis suggests that modeling of dose-trough can be predictive with the proper transformation. In the current analysis, dividing dose and trough each again by weight appears to take into account the volume of distribution more effectively than weight alone. Using patient age in place of patient weight gives similar results because age and weight are strongly correlated with each other. Pediatricians and clinical pharmacologists can choose between models 1 and 2, depending on which variable is more suitable for the patient. The prediction models proposed were also applied to another data set (different diseases, n = 40) with $r^2 = 93\%$ and correlation of 96%, suggesting that this model

is not limited to CF applications in children (data not shown). It was also observed that children with more weight require a slightly higher dose (per kilogram of weight), roughly equivalent to an additional 1 mg in the daily dose for each additional 10 kg of weight in the child. If a child weighs 20 kg, then to reach trough concentrations of 15 and 20, the required dose is 67.4 and 82.2 mg/kg, respectively. Using the recommended daily dose of 60 mg/kg results in a trough concentration of around 13 μg/mL.

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