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Research Article

DESIGNING A FEASIBLE METHOD TO PREDICT VANCOMYCIN TROUGH LEVELS IN PEDIATRIC POPULATION USING PATIENTS' PARAMETERS

Ghada Elba *[1], Ahmed El Mallah [2], Rana Itani [3], Nabila Droubi [4]
[1]Faculty of Pharmacy, Beirut Arab University, Beirut, Lebanon
[2]Professor of Pharmacology & Therapeutics, Vice Dean for Students affairs at Faculty of Pharmacy, Pharos University, Alexandria, Egypt, Canal El Mahmoudia Street, Qism Sidi Gabir, Alexandria, Egypt
[3] Faculty of Pharmacy, Beirut Arab University, Beirut, Lebanon, Fouad Arslan Street, Beirut, Lebanon, P.O.Box: 11-5020 Riad El Solh 1107 2809 Lebanon
[4]AlMakassed General Hospital (MGH), Beirut, Lebanon, Fouad Arslan Street, Beirut, Lebanon, P.O.Box: 11-6301 Riad El Solh Beirut 1107 2210 Lebanon
*Corresponding Author Email: ghadaelba@gmail.com

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ABSTRACT

Background: The cost of measuring trough levels serves a barrier to many hospitals which affects drug monitoring, therefore a research directed towards designing a feasible method to predict vancomycin trough levels was conducted Methods: A retrospective study was conducted at AlMakassed General Hospital (MGH). MGH is a 240 bed tertiary teaching center in Beirut. Pediatric patient record admitted from January 2012 to March 2015 were retrieved. Forty five patients between the ages of 1 year and 12 years were included. Two methods were used to predict vancomycin trough levels using pharmacokinetic estimations. The predicted trough levels were calculated using vancomycin multiple dose equation. A third method using multiple regression analysis was conducted to predict vancomycin trough levels based on patients' characteristics. The percentage difference between the real and predicted trough level were calculated in all methods. Results: The multiple regression analysis conducted in those between 1 year and 12 years showed a coefficient of correlation of 0.85 between the trough levels and patients' parameters with a p-value < 0.001. Forty percent of the patients had a difference below 30 percent from the real trough level. An equation was concluded from the multiple regression analysis to predict trough levels and to design an appropriate dosage regimen. The multiple regression analysis was the only successful method in predicting appropriate trough levels based on patients' parameters.

Key Words: Vancomycin, Therapeutic drug monitoring, trough levels, pediatrics, clinical pharmacy

INTRODUCTION

Vancomycin is a widely used antibiotic in the pediatric population. It has very strong activity against gram positive aerobic bacteria and some gram positive anaerobes and it is the drug of choice for the treatment of Methicillin resistant staphylococcus aureus infections[1-4].

Vancomycin is a glycopeptide antibiotic with high molecular weight, around 1500 Dalton. It inhibits cell wall polymerization by binding to the D-alanine-D-alanine chain in the cell wall, therefore inhibiting cell wall synthesis leading to cell death[5-10].

Vancomycin exhibits time dependent pharmacokinetic so its efficacy is related to the contact time with the organisms when the drug is at its lowest effective concentration. This explains why trough levels are a better monitoring parameter than peak concentrations. Optimal bactericidal effect for time dependent pharmacokinetic antibiotic is seen when the drug concentration is 2-3 times the minimum inhibitory concentration. Staphylococcus aureus and staphylococcus epidermis have minimum inhibitory concentration around 1-2 mg/L. accordingly, vancomycin efficacy is encountered when trough levels are 5-10 mg/L. However, with the accelerated surge of resistance among staphylococcus species, the minimum inhibitory concentration increased to 1.5-2 mg/L which made the optimum target of vancomycin trough levels from 10 to 15 mg/L[11 12].

These figures are also supported by the ASHP recommendations. Trough concentrations below 10 mg/L increased the incidence of vancomycin resistant staphylococcus aureus leading to therapeutic failure. Higher trough levels are sometimes needed when the infections are more severe, invasive and complicated. In such cases, practitioners usually aim for vancomycin troughs of 15-20 mg/L with close monitoring of toxic side effects. Trough concentration should be obtained before the next dose at steady state concentration and this is usually 30 minutes before the third or fourth dose[12].

The main adverse effects encountered with vancomycin are hypersensitivity, nephrotoxicity and ototoxicity. Hypersensitivity of vancomycin includes two types; red man syndrome and anaphylaxis. Red man syndrome is related to the rate of vancomycin infusion, the incidence was 14% if 1 gram was infused over 10 minutes and 3.4% if 1 gram was infused over 1 hour. This lead to a recommendation of infusing doses up to 1 gram over 1 hour interval and higher doses reaching 2 grams over 1.5 to 2 hours interval[13 14].

A meta-analysis suggested that levels above 15 mcg/dl may cause nephrotoxicity[11 15 16]and other human studies suggested that trough levels of 10 mcg/dl are associated with nephrotoxicity but no correlation was found between peak and nephrotoxicity[12]. The frequency of ototoxicity was reported to be 1-9% and the incidence is low when vancomycin is not given with ototoxic drugs.

Trough levels are an important monitoring parameter if not the only one available in hospitals for the assessment of vancomycin efficacy and safety[12]. Measurement of vancomycin trough levels is costly to many of the patients especially in developing countries which forces many practitioners to give vancomycin without proper monitoring. A systemic review conducted in 2014 in china to evaluate the quality of the vancomycin monitoring guidelines stated the guidelines didn't consider the cost of vancomycin therapeutic monitoring which was a barrier to monitor the vancomycin properly [17].

Another study conducted in Brazil in 2010 found the cost to monitor vancomycin was considered a limiting factor in many hospitals as the price is almost equal to the mean price of one vial[18].

Trough levels are an important monitoring parameter if not the only one available in hospitals for the assessment of vancomycin efficacy and safety [12]. This study was conducted to find a feasible and cheap model to predict the vancomycin trough levels without measurement and so facilitate its dosing in pediatrics.

Aim of the study

Designing a feasible method to incorporate different patient parameters and dosage regimen given in determining the trough level. This study also aims at providing an alternative method in determining vancomycin trough levels other than measuring them.

METHODS AND MATERIALS

Data Collection

A retrospective study was conducted at Al Makassed General Hospital (MGH). MGH is a 240 bed tertiary teaching center located in Beirut. The study was approved by the Institutional review board (IRB) of the hospital. It was conducted on the pediatrics floor and included all pediatric patients taking vancomycin admitted from January 2012 to March 2015. Data was collected from the archived electronic medical hospital records. Medical records were reviewed for age, gender, weight, height, serum creatinine, and vancomycin dosage regimen and trough levels.

Inclusion Criteria

- All pediatric patients between 1 and 12 years.
- Patients on vancomycin and with at least three doses of vancomycin.
- Patients with at least one trough level measured in the lab.

Exclusion Criteria

- All patients without trough level.
- All patients with genetic abnormality.
- All patients with renal impairment.
- All patients with malignancies.
- All patient with inaccurate vancomycin trough level timing

A total of forty five patients were included.

Methods Used

Three methods were evaluated for predicting trough levels. Two methods were based on pharmacokinetic estimation and one method used the multiple regression analysis.

In the first two methods predicted trough levels were calculated using the multiple dose equation (equation 1 below)[11]. In method one, pediatric elimination rate constant (kel) values reported in literature[11] were used in the multiple dose equation to calculate vancomycin trough levels whereas in method two the pediatric elimination rate constant (kel) was determined using the vancomycin clearance equations (equations 2 and 3 below)[11]and used to calculate the vancomycin trough levels. In the third method multiple regression was used and a stepwise multiple regression analysis was conducted and the best model with the highest significance was chosen.

The percentage difference between the predicted and real trough levels were calculated in all three methods using equation 4. In multiple regression analysis, Pearson correlation coefficient (r) and coefficient of determination (r^2) were determined.

Equation 1: $C = (D/V)*(e^{-ket})*[(1 - e^{-nket})/ (1 - e^{-ket})]$

Equation 2: $kel = Cl/V$

Equation 3: $Cl = 0.695(CrCl) + 0.05$

where C is the vancomycin predicted trough level concentration, D is the dose given per day, n is the number of administered doses, τ is the dosage interval, kel is the elimination rate constant, Cl is vancomycin clearance in mL/min/kg, V is the volume of distribution in liters and CrCl is creatinine clearance in mL/min/kg.

Equation 4: % difference= ((real trough - predicted trough) / real trough) * 100

Statistical Analysis

Statistical analysis was conducted using Megastat for Excel. Multiple regression analysis was used to predict the trough level from the patients' parameters and the dose given and a stepwise regression analysis was done by the software to evaluate all the possible combinations. ANOVA and post-hoc tests were used when appropriate to test for the significance. A p-values less than 0.05 was considered statistically significant.

RESULTS

Descriptive Analysis of Patients' Demographics

Forty five patients were reviewed, 56 % were males and 44 % were females. The mean age was
4.81 ± 3.11 years. The mean weight, height and serum creatinine were 17.32 ± 9.18 kg, 101.80 ± 18.55 cm and 0.33 ± 0.16 mg/dl respectively. The mean dose was 52.12 ± 10.95 mg/kg/day and the mean trough levels were 11.21 ± 6.82 mg/dl as shown in table 1.

Table 1: Descriptive data

Variable	Mean ± St. Dev / percentage
Gender: Male Female	 56 % 44 %
Age (years)	4.81 ± 3.11
Weight (kg)	17.32 ± 9.18
Height (cm)	101.80 ± 18.55
Serum creatinine (mg/dl)	0.33 ± 0.16
Dose (mg/kg/day)	52.12 ± 10.95
Trough levels (mg/dl)	11.21 ± 6.82

Comparison between Results Obtained By Method One and Method Two

The percentage difference between the predicted and real trough levels in method one (literature based method) was below 15 % in 2% of the patients. In method two (adult equation based) the difference between the predicted and real trough levels was below 15 % in 13 % of the patients as shown in table 2.

Table 2: Comparison between Results Obtained By Method One and Method Two

	Percentage difference between predicted and obtained trough levels		
	Below 10 % No. (%)	Below 15 % No. (%)	Below 25 % no. (%)
Literature values method	1 (2)	1 (2)	3 (6.6)
Adult equations method	4 (8)	6 (13)	9 (20)

Multiple Regression Analysis

A stepwise multiple regression analysis was performed to incorporate the dose and patients' parameters to predict the trough level. The p-values were below 0.05 and so an equation was concluded. Tables 3 shows the best regression model in all possible combination of variables.

Table 3: Multiple Regression Analysis

No. Of Variables	Age	Weight	Height	Serum creatinine	Dose	Interval	r^2	Combined p-value
1				**0.0005**			0.544	**0.0005**
2				**0.0061**	**0.0211**		0.684	**0.0002**
3		0.2475		0.1285	**0.0141**		0.713	**0.0004**
4	0.2102	0.0937		0.1049	**0.0147**		0.747	**0.0008**
5	0.5421	0.2879	0.9163	0.1248	**0.0218**		0.748	**0.0026**
6	0.6769	0.3165	0.8885	0.1510	0.0560	0.9148	0.748	**0.0077**

Note: Values in columns 2 to 6 indicate p-value for each variable in its combination with other variables. Significant results are in bold, highest coefficient of determinations are underlined

The best equation obtained by multiple regression is shown below

Predicted trough =

-9.3316 - 0.038(height) + 0.277(weight) - 0.4518(age) + 4.1863(interval factor) +0.26(dose/kg/day) + 21.47(Scr)

Note: interval factor = (24-interval) / (24)

DISCUSSION

The data extracted showed trough levels were not measured in almost 37% of the patients and this was attributed to the high cost of the test.

The data extracted showed that 40 % of those whose trough levels were measured had values above the therapeutic range which put them at a risk of toxicity.

A systemic review and meta-analysis done by S. J. van Hal et al in 2013 in Australia concluded a significant correlation between nephrotoxicity and vancomycin trough levels and trough levels above 15 mcg/dl have higher odds of nephrotoxicity than lower troughs[15].

Mergenhagen et al also conducted a meta-analysis in 2014 which reviewed more than 5 studies concluded a true relation between high trough levels and nephrotoxicity with the highest incidence in trough levels above 15 and 20 mcg/dl[16]. This implies the importance of trough level monitoring for therapeutic safety especially in pediatric patients whose pharmacokinetics change rapidly until they reach maturity.

Data extracted also stated that 11 % of the patients had trough levels below the therapeutic range. This group is at higher risk of developing resistance. ASHP report highlighted that studies showed increased risk of therapeutic failure and resistance with trough levels below 10 mcg/dl[12]. Percentages obtained from this study indicate the importance of trough level monitoring to achieve therapeutic efficacy.

Beside the high cost of vancomycin monitoring and the importance of the trough level in determining therapeutic efficacy and safety, data extracted showed that there was a great variability in trough levels obtained due to the different dosage regimens used in the hospital. These findings led to the importance of developing appropriate methods to predict vancomycin trough levels instead of measuring them and to assess the variability of trough levels in relation to patients' parameters to conclude an appropriate dosing regimen.

In the pediatric population dosing of vancomycin is mainly dependent on the literature reviews unlike adults in which dosing regimens, Cmax, Cmin, Kel, vancomycin clearance and other parameters can be calculated using simple equations[11]. The first aim of the study was to predict trough levels of the pediatric population based on pharmacokinetic estimations and determine the percentage difference between the predicted trough and the real trough measured. In the literature based method we used the pediatric literature elimination rate constant to predict the trough levels using the multiple dose equation whereas in the adult based method we calculated the elimination rate constant using the adult equations and then predicted the trough using the obtained value.

We predicted the trough levels using the literature based method and the difference between the predicted values and the real was below 15 % in only 2 % of the patients. On the other hand, method two showed that 13% of the patients had a percentage difference below 15 % from the real values. With these low values method one and two failed to predict accurate vancomycin trough levels for this group and so they were excluded.

On the other hand, the multiple regression analysis yielded very promising results. All six models obtained showed p-values < 0.01 and so all models were highly statistically significant. Two models had the highest coefficient of determination (r^2 = 0.75). Of these two models, the model with all the variables was chosen.

The variables of the chosen model which predicted best the trough levels were age, weight, height, total daily dose, serum creatinine and dose interval. The analysis of variance resulted in a p-value of 0.0077.

An equation was deduced which incorporated age, weight, height, daily dose, serum creatinine and dose interval to predict the trough levels for patients between the age of 1 year and 12 years. This equation succeeded in predicting almost 75% (r^2 = 0.75) of the data. A study conducted by Rosanne Thalakada et al in 2012 on 170 patient to predict vancomycin intervals using multiple regression generating a coefficient of determination of 0.42[19] .

The equation of the multi regression analysis to predict vancomycin trough levels in pediatric from 1 year to 12 years is
Predicted trough = -9.3316 - 0.038(height) + 0.277(weight) - 0.4518(age) + 4.1863(interval factor) + 0.26(dose/kg/day) + 21.47(Scr)
N.B. interval factor = (24-interval) / 24
A t-test was conducted between the real trough level and the trough levels obtained by the new equation and it showed a p-value above 0.05 which means there is no difference between the trough levels obtained by the new equation and the real ones. Therefore, the new equation can be used as an alternative to measuring the trough levels.
The trough levels were divided into four groups, real trough levels obtained by 40 mg/kg/day dosing, predicted trough levels obtained by 40 mg/kg/day dosing, real trough levels obtained by 60 mg/kg/day dosing and predicted trough levels obtained by 60 mg/kg/day dosing. ANOVA was conducted between these four groups and it showed a p-value below 0.05 and so statistical significance. The post-hoc analysis showed that there is a difference between the 40 mg/kg/day dosing regimen and the 60 mg/kg/day dosing regimen in both the predicted and the real. The 60 mg/kg/day dosing regimen obtained better trough level than those on 40 mg/kg/day dosing.
The post-hoc analysis conducted also showed no statistical significance and hence no difference between the real and predicted trough levels in both the 40 mg/kg/day dosing and the 60 mg/kg/day dosing, so again this supports the use of the equation in predicting trough levels as an alternative to measuring them.
With these significant results the multiple regression analysis conducted showed the best model to predict vancomycin trough levels in those between 1 year and 12 years. This model is simple with a prediction of 75% for vancomycin trough levels in pediatrics so it could be used as a guide to the empirical therapy of vancomycin. The authors assume a better correlation would be obtained with a larger sample size so a prospective study with a larger number of patients will be conducted to validate this equation. Until then this equation is recommended to guide the therapy especially in settings when vancomycin trough level couldn't be obtained.

STUDY LIMITATION

The small sample size of the study was the main factor that affected the significance of many of the results. This small sample size is due to the high cost of measuring the vancomycin troughs which was a limitation to many patients. We assumed that the vancomycin followed one compartmental model kinetics. The retrospective nature of the study also was considered a limitation.
A prospective study with a larger sample size is to be conducted to confirm the results of the study and validate the equation obtained.

CONCLUSION

Monitoring of vancomycin is of high importance especially in the pediatric population where pharmacokinetics are not fully developed. On the other hand the cost of monitoring of trough levels is a limitation to its application in many hospitals. The equation obtained from the multiple regression method is a practical and feasible tool to predict vancomycin trough levels. This equation can be used as a guide for the empiric therapy of vancomycin until further prospective studies with a larger sample size could validate it. The creation of a computer software is planned to simplify the calculations of vancomycin trough levels to practitioners.

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