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Original Article

Vancomycin Concentration and Monitoring Practice in Pediatric Oncology and Non-oncology Patients: A Retrospective Single Center Study

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A B S T R A C T

Objectives : Cancer patients may have higher clearance of vancomycin in comparison to the general population.This study is a retrospective chart reviewfrom a tertiary care center in Saudi Arabia. It explores whether plasma concentrations of vancomycin in pediatric oncology patients are different from those of other pediatric patients. **Methods :** Pediatric oncology and non-oncology patients treated with vancomycin during the period from January 2011 to December 2012 were included. Data were extracted about demographics, diagnosis, and vancomycin monitoring parameters. Linear regression models were constructed to test the effect of different variables on the log transformed vancomycin concentration adjusted for time of concentration determination. **Results :** One hundred cases (73 oncology and 27 non-oncology)were analysed. Mean predose vancomycin concentration was around 9 microgram/mL and there was no significant difference between oncology and non-oncology patients. Oncology patients had significantly higher creatinine clearance values and vancomycin doses ($p < 0.001$ and 0.003 respectively). Being an oncology patient, was shown to be an independent predictor for the concentration of vancomycin after adjustment of all other factors (beta: (0.283), 95%CI : (-0.557) – (0.008), p=0.044). **Conclusion:** Pediatric oncology patients may need higher vancomycin doses to achieve plasma concentrations comparable to non-oncology patients.

Key Words: MRSA, febrile neutropenia, pharmacokinetics

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1. INTRODUCTION

Vancomycin is a glycopeptide antibiotic that inhibits cell wall synthesis. Due to its large molecular size and lipophilicity, vancomycin is only effective against Gram positive bacteria. It is usually reserved for the treatment of Methicillin-Resistant *Staphylococcus aureus* (MRSA) infection. Vancomycin needs therapeutic drug monitoring (TDM) for assuring optimal therapeutic effect. According to the latest American Society of Health System Pharmacists (ASHP) guidelines for vancomycin monitoring in adults, a ratio of ≥ 400 between the area under the 24 hour concentration-time curve and the minimum inhibitory concentration (MIC) of vancomycinis the most accurate known method for monitoring efficacy and avoiding toxicity (Rybak et al., 2009). This, however, needs frequent blood sampling. Trough serum vancomycin concentration is a more practical method for monitoring and should ideally be maintained above 10 microgram/mL to avoid development of resistance. Trough concentrations of 15–20 microgram/mL are recommended for serious or severe infections(Rybak et al., 2009).

Gram positive bacteria are a common cause of infection in cancer patients with febrile neutropenia (Freifeldet al., 2011). The reported rate of vancomycin failure in MRSA infections is already more than 50% (Kullar, 2011 and Mahjan et al., 2012). One of the identified independent factors for this failure is initial vancomycin trough < 15 mg/dL (Kullar, 2011). In cancer patients either adults or pediatric it is crucial to start vancomycin with the most appropriate dose to avoid any treatment failure or further morbidity in such immunocompromised population.

The effect of malignancy on vancomycin clearance has been studied in adults and children with cancer and it was reported that cancer patients may have higher clearance of vancomycin in comparison to the general population (Changet al., 1994, Silva et al, 2012, and Curth et al., 2015). This may impact negatively on the effectiveness of vancomycin therapy in such critical patients because usual doses may fail to achieve the trough concentrations desired to eradicate infection. King Faisal Specialist Hospital and Research Center (KFSH&RC), Jeddah is a tertiary care center with an advanced oncology and stem cell transplant service in Saudia Arabia. Having general pediatric and pediatric oncology services, KFSH&RC, Jeddah admits a relatively large number of patients. It has been noted during pediatric oncology practice at KFSH that patients frequently fail to attain the desired therapeutic trough concentrations of vancomycin on the usually prescribed doses of 40 to 60 mg/kg/d. Hence this retrospective chart review was designed to: 1) explore whether plasma concentrations of vancomycin are indeed systematically different from those of other pediatric patients in the Saudi population; 2) explore the factors that may influence such a difference if it existed; 3) report about the vancomycin dosing and monitoring practice in pediatrics.

2. MATERIALS AND METHODS

2.1. Study population and data collection

We conducted a retrospective review of the charts of all pediatric patients aged from 1 month to 15 years who were treated with vancomycin in KFSH&RC, Jeddah during their admission in the general pediatric floors or pediatric oncology and Stem Cell Transplantation (SCT)floors in the period from January, 2011 to December, 2011 and who had at least one vancomycin trough concentration determined. Data were collected from the hospital's electronic system and it included: diagnosis (according to which patients were classified into oncology or non-oncology patients), age, sex, height, weight, documented or suspected infection, indication of vancomycin therapy when available, initial vancomycin dose and subsequent dose changes if any, initial vancomycin trough concentration and subsequent concentrations if any, concurrent nephrotoxic medications, dosage and concentration timing and serum creatinine levels taken before the start of therapy. Patients who received only two vancomycin doses or less and patients who had no appropriate trough time measurement (i.e. before passing the distribution phase) were excluded. Vancomycin concentrations were measured by Vancomycin (VANC2) Roche/Hibatchi cobas c (311 /501) system. This assay is based on a homogeneous enzyme immunoassay technique used for the quantitative analysis of vancomycin in human serum or plasma. KFSHRC's Institutional Review Board approved the review of patients' medical records. Consents were waived because of the retrospective nature of the study.

2.2. Statistical method

Statistical analysis was performed on STATA version 11.0. Numeric data were presented as mean ± the standard deviation as well as the median and quartiles and were compared between the groups of oncology and non-oncology patients by ANOVA or by Mann Whitney U test according to data distribution; the latter test was also used to compare data of the ordinal type. Categorical data were presented as percentages and were compared by Chi square test. Alpha values were all set at 0.05 and were two sided. Vancomycin concentration data were examined for normality of distribution and were converted to the log scale in face of right skewness. Univariate linear regression models were constructed to test the effect of different variables on the log transformed vancomycin concentration. Factors were then entered into a multiple regression model using a backward Wald method with a threshold of 0.05 for factor removal from the model.

3. RESULTS

One hundred cases that had undergone measurement of vancomycin concentration were identified. The study population showed a male predominance and the age ranged from one month to 15 years. Seventy three patients were from oncology wards and twenty seven were from non-oncology wards. Gender distribution was not significantly different between oncology and non-oncology patients, neither was the age distribution and although the weight and height differed significantly between the groups, the body mass index (BMI) did not differ (Table 1). Febrile neutropenia and bacteremia constituted more than 60% of the documented indications of vancomycin therapy in oncology patients while bacteremia was the indication of vancomycin only in around 26% of non-oncology patients. The majority of vancomycin prescriptions for oncology (70%) as well as non-oncology patients (78%) were empirical with no documented organism in culture. Only 2 (7.4%) of non-oncology patients were on concomitant medications with nephrotoxic potential. This was in contrast to oncology patients of whom 18 (58%) were on potentially nephrotoxic medications while on vancomycin.

Medications included tacrolimus (one non-oncology and nine oncology patients), amino glycosides (one non-oncology and 17 oncology patients) and methotrexate in one oncology patient. Yet only three cases of renal impairment were documented among oncology patients and none among non-oncology patients. Oncology patients had significantly higher creatinine clearance values than non-oncology ones and the initiation per kg daily dose given to them was significantly greater ($p < 0.001$ and 0.003 respectively).

Table 2 focuses on the vancomycin monitoring practice in general and it compiles data about initial and adjusted doses and about all concentrations obtained for all patients under a single summary. Including dosage adjustment values after vancomycin concentration assays, still oncology patients had significantly higher average daily doses of vancomycin than those of non-oncology patients (49.6 ± 9.9 versus 39.2 ± 11.3; $p \leq 0.001$). Generally speaking, the time from starting vancomycin to the first plasma concentration determination was around 17 hours and this was similar in oncology and non-oncology patients. Analysis of all trough concentrations of vancomycin, initial and repeated, revealed a mean concentration around 9 microgram/mL and there was no significant difference between oncology and non-oncology patients in that regard ($p = 0.825$).

Table 3 shows that there was non statistically significant difference between oncology and non-oncology patients in the initial plasma concentration of vancomycin ($p = 0.68$). For patients for whom a second vancomycin concentration was measured (10 non-oncology and 30 oncology patients), the vancomycin concentration was numerically but not statistically lower in the oncology group. Only one non-oncology patient required a third check of vancomycin concentration versus 3 oncology patients. Two out of the latter three required a forth check. Vancomycin concentrations were hovering around the 15 microgram/mL with the third and forth checks in oncology patients and around the 12 microgram/mL in non-oncology patients.

Table 4 shows results of linear regression of the log vancomycin concentration on various factors. Results show that gender and the time of drawing the sample in relation to the dose to be the only two factors potentially associated with vancomycin concentration ($p=0.009$ and 0.027 respectively). Multiple regression analysis using the backward Wald method showed loss of association between gender and the log concentration of vancomycin after adjustment for all other factors. However, all other factors included were shown to be significantly associated with the concentration of vancomycin after adjustment (Table 5). The age at initial dosing and the total daily per kg dose were positively associated while the time interval between the last dose and concentration determination and the creatinine clearance were negatively associated. The fact of whether or not the patient is an oncology patient, was shown by multiple regression to be an independent predictor for the concentration of vancomycin after adjustment of all other factors ($p = 0.044$).

Table (1): Demographic patient characteristics

Parameter	Total [n= 100)	Non-oncology patients [n=27]	Oncology patients [n= 73]	P value
Gender Males [n, (%)]	72 (72)	17 (75.3)	55 (63)	0.315
Age in years at initial vancomycin dose Mean ±SD Median (Quartiles)	5.3 ± 3.7 5.0 (2.1-7.7)	4.2 ± 4.2 2.4 (0.54-8.0)	5.7 ± 3.5 5.8 (2.6-7.7)	0.071
Height in cm Mean ± SD Median (Quartiles)	102.2 ± 27.1 101 (80-120)	88.8±24.0 90 (71-92.3)	107±26.7 110 (88-122)	0.003*
Weight in kg Mean ± SD Median (Quartiles)	16.66 ±10.6 14.9 (10.7-17.9)	13.2±10.2 8.4 (5.9-17.5)	18.0 ±10.5 15.9 (11.5-18.9)	0.047*
BMI in kg/m^2 Mean ± SD Median (Quartiles)	17.2 ± 8.8 14.8 (10.5-21.0)	16.4±7.9 16.2 (9.6-21.1)	17.4±9.2 14.6 (10.7-21.4)	0.611
Creatinine clearance in ml/min Mean ± SD Median (Quartiles)	154 ± 42.2 154 (130.8-190)	120.9 ± 47.5 114 (88-150)	167.5 ± 32.2 169 (148-193)	<0.001*
Initial total daily dose (in mg/kg) Mean ± SD Median (Quartiles)	46.9 ± 10.6 44.7 (40.0-56.6)	41.5±11.9 39.5 (30.5-54.8)	48.7±9.5 46 (41.5-56.6)	0.003*

* = statistically significant difference;
"n" refers to the number of cases with available data for each analysis.

Table (2): Data of vancomycin dosing and initial concentration

Parameter	Total	Non-oncology patients	Oncology patients	P value
Dose of vancomycin (initial and changed in mg/kg/day) (n) Mean ± SD Median (Quartiles)	(142) 46.7 ± 11.5 44.4 (39.65-58.17)	(42) 39.2±11.3 39.2 (30-44.1)	(100) 49.6± 9.9 49.8 (41.5-58.4)	0.000*
Time from initial dose or dose change to level (in hours) (n) Mean ± SD Median (Quartiles)	(126) 17.6 ± 8.7 15.9 (13.0-18.8)	(29) 23.5 ± 31.8 16.1 (12.3-21.7)	(97) 17.0 ± 8.1 15.7 (13.2-18.4)	0.064
Serum concentration of vancomycin in microgram/mlin all samples taken from all patients (n) Mean ± SD Median (Quartiles)	(146) 9.2 ± 5.4 8.0 (5.9-10.7)	(38) 9.1 ± 5.9 8.6 (4.8-11.6)	(108) 9.3 ± 5.2 7.8 (6.1-10.6)	0.825

* = statistically significant difference;

"n" refers to the number of cases with available data for each analysis.

Table (3): Data of vancomycin monitoring

Parameter	Total	Non-oncology patients	Oncology patients	P value
Vancomycin first level in microgram/ml (n) Mean ± SD Median (Quartiles)	(100) 9.02 ± 5.3 7.7 (5.5-10.8)	(27) 8.7 ± 4.7 8.7 (4.7-12.2)	(73) 9.2 ± 5.6 7.4 (5.7-10.6)	0.684
Vancomycin concentration category at the initial level [n,(%)] -Less than 10in microgram/ml -10 microgram/ml or more	71 (71) 29 (29)	18 (66.7) 9 (33.3)	53 (72.6) 20 (27.4)	0.561
Vancomycin second level in microgram/ml (n) Mean ± SD Median (Quartiles)	(40) 9.3 ± 5.1 8.2 (6.4-10.5)	(10) 10.7 ± 8.7 8.74 (5.8-11.3)	(30) 8.8 ± 3.2 8.0 (6.7-10.6)	0.311
Vancomycin concentration category after the second level [n,(%)] -Less than 10in microgram/ml -10 microgram/ml or more	(40) 28 (70) 12 (30)	(10) 7 (70) 3 (30)	(30) 21 (70) 9 (30)	1.0
Vancomycin third level in microgram/ml (n) Mean ± SD Median		(1) 5.19	(3) 15.1 ±8.5 10.5	---------
Vancomycin forth level in microgram/ml (n) Mean ± SD Median			(2) 15.2 ± 6.4 15.2	————————

Table (4): Results of single factor linear regression analysis for factor affecting the log serum level of vancomycin

Variable in the equation	Beta coefficient	95% CI of the beta coefficient	p value
Time from last dose to level	(-0.033)	(-0.063) - (-0.004)	0.027*
Total per kg daily dose	0.007	(-0.001) - 0.015	0.105
Age	0.01	(-.014) - 0.033	0.426
Gender	(-0.246)	(-0.429) - (-0.063)	0.009*
BMI	0.002	(-0.01) - 0.015	0.738
Creatinine Clearance	(-0.001)	(-0.003) – 0.001	0.293
Being an oncology case	(-0.115)	(-0.308) - (0.079)	0.243

* = statistically significant association

Table (5): Results of multiple regression analysis for factor affecting the log serum level of vancomycin (n = 88)

Variable in the equation	Beta coefficient	95% CI of the beta coefficient	p value
Time from last dose to level	(-0.047)	(-0.083) – (-0.011)	0.012*
Total per kg daily dose	0.011	0.001-0.021	0.033*
Creatinine clearance	(-0.008)	(-0.012) – (-0.004)	< 0.001*
Age	0.06	0.022 – 0.097	0.002*
Being an oncology case	(-0.283)	(-0.557) – (-0.008)	0.044*

* = statistically significant association

4. DISCUSSION

The current study focuses on the practice of vancomycin dosing and concentration determination of pediatric oncology and non-oncology patients to gain an insight into potential difference in kinetics between those two patient groups. Such insight may generate hypotheses that can be tested to improve future use of such a life-saving antibiotic.

Many clinical practice guidelines recommend that a trough vancomycin concentration should ideally be kept at 10 microgram/mL or above for optimum efficacy. This analysis of real world data however shows that this is mostly not achieved in non-oncology or in oncology

patients. Almost half of the reviewed patients in this study had an adjustment of their vancomycin dose with a second plasma concentration determination but still the proportion of those achieving the 10 microgram/mL target remained at 0.33. The retrospective nature of the present study limits the extent to which we can determine how this impacts on clinical response and organism sensitivity.

Analysis of data about vancomycin dosing and trough concentration in this study showed that although the initial vancomycin total daily dose was significantly higher in oncology versus non-oncology patients, the plasma pre-dose vancomycin concentrations averaged the same values. This may be viewed as an indirect piece of evidence that pediatric oncology patients need bigger doses to achieve a comparable serum concentration to that of non-oncology patients. This may be due to differences in the renal clearance of vancomycin or in the volume of distribution. This conclusion however would be too bold to make in face of the retrospective

observational nature of the study with the presence of several confounding factors that might influence such result. To overcome this, we concentrated on the relation between the vancomycin concentration and time at which the pre-dose plasma sample was drawn and for that we constructed a regression model. To be able to construct a linear model for the right skewed vancomycin concentration data the model had its y-axis variable as the log of the vancomycin concentration. Indeed, the model showed a significant inverse linear association between the time and the log concentration (beat coefficient: -(0.033), $p = 0.027$). A multiple regression model was used to correct for all possible confounding factors and to test for the existence of factors that influence the association. As would be expected, the total daily dose of vancomycin was positively and significantly associated with the concentration and the time from the last dose to the level determination was negatively and significantly associated. Also it was noted that creatinine clearance was negatively and significantly associated with the vancomycin concentration and this can easily be explained by the fact that vancomycin clearance is predominantly renal. Age at initial dosing was significantly and positively associated with the concentration and so it would be expected that children with older ages would have higher vancomycin levels for the same per kg daily dose. Being an oncology patient was shown in the current study to be associated with having lower vancomycin plasma concentrations, even after adjustment for factors like age, dose, and creatinine clearance. These results agree with those of some previous studies in pediatric oncology patients. For example it has been reported that the usual dose of 60 mg/kg/day is not adequate to achieve the therapeutic trough concentration of > 15 microgram/mL (Silvaet al., 2012 and Abdel Hadi et al., 2016). The same observation was noted by Piro et al. who retrospectively analyzed the records of 56 pediatric oncology patients; they received 82 courses of vancomycin without a control group. They concluded that pediatric oncology patients require higher doses than recommended to achieve therapeutic trough, considering trough range from (5-15 microgram/mL) as therapeutic. Yet this range is different from that in more recent recommendations (Piroet al., 2009). In a prospective study, Chang (1995) compared vancomycin clearance in 33 infants and children who had cancer to 31 children without cancer and he found that cancer patients required higher vancomycin doses to achieve the same peak and trough levels.

Observing different vancomycin kinetics in oncology patients was not limited to studies on pediatric patients. Al-Kofide et.al. (2010) compared 18 Saudi patients with different types of malignancy to 13 non-cancer patients. The two groups had no significant differences in creatinine clearance or in the dose of vancomycin. Vancomycin peak level was significantly lower in cancer patients while trough levels were similar. It was concluded that adult cancer patients have higher volumes of distribution as well as higher clearance of vancomycin compared to patients with no cancer (Al-Kofide et al., 2010).In a study on elderly Japanese patients with malignancy, it was also shown that they had higher clearance, higher volume of distribution and shorter half-life of vancomycin in comparison to patients without malignancy, even though they had no significant difference in creatinine clearance (Sadoh et al., 2010). The same observations were reported in SCT patients and patients with hematological malignancies especially Acute Lymphoblastic Leukemia (AML) cases (Mdel et al., 2009, Jarkowski, 2012, and Ghehi et al., 2013). Other studies presumed that increased vancomycin clearance in cancer patients occurs only during neutropenia time and resolves after count recovery (Le Normand et al., 1994 and Haeseker et al., 2014). We have found only one report that denied the malignancy effect on vancomycin clearance and that was by, Omote et al. (2009). Yet in the latter study only univariate statistical analysis was done based on the values of vancomycin trough level and in spite of the difference in doses given to oncology and non-oncology children, the authors did not use regression analysis for adjustment. Analysis in the current study takes all important factors into consideration in multivariate regression.

Possible reasons behind this observation of increased clearance of vancomycin in cancer patients include excessive hydration during vancomycin administration or increased tubular excretion of vancomycin in malignant subjects as an indirect effect of a general inflammatory status. This was suggested by Shimada et.al. (2012). They analyzed this phenomenon in a model were they induced osteosarcoma in rats using a chemical carcinogen. They found that rats with induced

malignancy had higher clearance of vancomycin compared to the control group. They proposed that elevated concentrations of interleukin IL-1β, IL-6, and tumor necrosis factor (TNF)-α in the plasma of the rats affects the renal proximal tubular epithelial cells causing enhanced clearance (Shimada et al., 2012).

In general, achieving targeted therapeutic trough concentration (10-20 microgram/mL) in pediatric oncology and non-oncology patients is challenging and could not be achieved in our hospital with the current used doses of 40-60 mg/kg/day. Studies done in children after the new recommendation found that higher initial doses up to 70-85 mg/kg/day are needed (Broome and So, 2011, Frymoyer et al., 2009, and Frymoyer et al., 2011). The higher doses in children look to be safe and not causing nephrotoxicity (McCabe et al., 2009 and Cies and Shankar, 2013).

In the present study, the initial pre-dose vancomycin concentration in pediatric patients averaged around 9 microgram/mL for both oncology and non-oncology patients. Even with dose adjustment and resampling, that was performed in less than half of the patients, the second average concentration hovered around the same initial values. The recommended pre-dose vancomycin concentrations range from 10 microgram/mL to 20microgram/mL, according to the indication, is based on evidence from adult patients. In pediatric population the same recommendations were extrapolated from the adult recommendation due to paucity of pediatric studies that correlate clinical efficacy to the new targeted therapeutic trough concentration in children. In the present study, the main indications for vancomycin therapy were empiric therapy for febrile neutropenia and so we would expect to see serum concentrations around 15 microgram/mL.

An important argument about vancomycin concentration values in the present study is the possibility that they might have been influenced by the inconsistent nature of the sampling time, especially with its being a retrospective study where the sampling time has been left to the casualty of everyday practice rather than being accurately planned. If earlier draws for vancomycin assay would do anything however they might have pushed the vancomycin concentration values up and so values obtained in this study may be over estimations of the pre-dose vancomycin levels rather than under-estimations. We can thus comfortably deduce from this that vancomycin trough concentrations observed in pediatric patients in real practice hardly reach the recommended concentrations for ordinary indications, let alone febrile neutorpenia.

Conclusion: Pediatric oncology patients may need higher vancomycin doses to achieve plasma concentrations comparable to non-oncology patients. Bigger data sets or prospective studies are needed to verify this observation and its associated factors. Generally speaking, the vancomycin trough concentrations encountered in pediatric practice fail to reach those recommended by guidelines. This dictates more attention to vancomycin dosage adjustments in face of sub-therapeutic concentrations to avoid the adverse impact of sustaining such concentrations on treatment efficacy and the development of resistance.

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