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Original Article

THE EFFECT OF VANCOMYCIN DOSES GREATER THAN 2 GRAMS ON SERUM CREATININE AND VANCOMYCIN TROUGH LEVELS

HANINE MANSOUR, JEFFREY A. BUSH, MICHAEL BRITO, PAUL NOVOTNY, CALE COURTNEY, JORDAN MUSTONEN, KIM TOWEY

[1]PharmD, BCPS Clinical Assistant Professor School of Pharmacy, Department of Pharmacy Practice Lebanese American University Byblos, Lebanon, [2]PharmD, BCPSClinical Assistant ProfessorSchool of Pharmacy, Department of Pharmacy PracticeLebanese American UniversityByblos,Lebanon, [3]PharmD student University Of Florida, College of Pharmacy-St. Petersburg Campus Seminole, Florida.

Email: hanine.mansour@lau.edu.lb

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ABSTRACT

Objective: To assess the effect of vancomycin doses greater than 2 grams on renal function and vancomycin trough levels

Methods: This is a retrospective, pharmacokinetic study performed in a tertiary care level II trauma center. 3579 electronic charts of patients who received vancomcyin at the medical facility between January 2010 and December 2011 were reviewed. Only 30 patients met the inclusion criteria of the study. Included patients were those who were at least 18 years of age who received doses greater than 2 grams of vancomycin for at least 48 hours. Patients in the intensive care units, pregnant or on hemodialysis and were not included in the study. The mean weight for the participants was 154.67 kg.

Results: Patients were dosed based on the institution's vancomycin dosing protocol such as 15-20 mg/kg per dose where the frequency was determined based on the estimated creatinine clearance using cockroft gault equation. A loading dose of 25-30 mg/kg was administered in few cases. Two out of thirty subjects had shown an increase of serum creatinine of ≥ 0.3mg/dL when receiving maintenance doses greater than 2 grams of vancomycin. A Z approximation test was used where a standard error of 0.043 with an α error equal to 0.05 and a 95% confidence interval of (-0.024-0.144) were found. The use of doses greater than 2 grams of IV vancomycin did not show a statistically significance increase in serum creatinine. The two subjects who did have a significant increase in serum creatinine were receiving concomitant nephrotoxins.

Conclusion: The use of doses greater than 2 grams of IV vancomycin did not show a statistically significant increase in serum creatinine. Patients whom serum creatinine increased were on other nephrotoxin agents that could have contributed to the acute kidney injury that was seen in these patients.

Keywords: Vancomycin, Creatinine, Nephrotoxins, Renal function.

INTRODUCTION

Vancomycin is the empiric drug of choice at our institution for gram positive infections and for invasive MRSA infections. It is a bactericidal glycopeptide that has been in practice since 1956. (1) However, it has been associated with some adverse events particularly nephrotoxicity. Studies reported an increase in nephrotoxicity with the use of doses greater than 4 grams per day and /or trough levels greater than 15 mcg/ml.(2,3) on the other hand, nephrotoxicity has been linked to the findings of some impurities in the formulation which was referred as as the "mississippi mud". (4,5) However, with proper fermentation level, the impurities were reduced and side effects such as nephrotoxicity was reduced too. (4-7)Since recent guidelines recommended targeting levels of 15-20 mcg/ml for patients with complicated infections such as endocarditis, osteomyelitis, pneumonia and bacteremia, with a target AUC: MIC ratio of greater or equal to 400; pharmacists at our institution were using doses greater than 4 grams per day or greater than 2 grams per dose in order to achieve these levels based on 15-20 mg/kg dosing for obese patients. (1,8,9) However, several studies were published associating nephrotoxicity with high trough levels and vancomycin doses greater than 4 grams. (2,3,10,11,12,13,14) In one particular study, intensive care unit patients were at higher risk of developing nephrotoxicity while on vancomycin than non-ICU patients.(3) Also, several reports identified the use of nephrotoxin agents concomitantly with vancomycin lead to nephrotoxicity.(1,3,15,16,17)

In this study, nephrotoxicity or acute kidney injury was defined as an increase of 0.3 mg/dl or a 50% increase from the baseline. (18)

In order to evaluate the risk of nephrotoxicity associated with the use of doses greater than 2grams/ dose, a retrospective analysis was conducted to evaluate patients admitted and treated at bayfront Medical center, a level II trauma center, with vancomcyin doses greater than 2 grams and studied the impact of this dose on renal function and on trough levels.

MATERIALS AND METHODS

Study design, setting and patients

This is a retrospective study conducted at Bayfront Medical Center in St. Petersburg, Florida. The study was approved by both the Bayfront Medical Center Investigational Review Board and the University of Florida Investigational Review Board. Electronic charts for 3,579 patients that received vancomycin at this facility between January 2010 and December 2011 were reviewed. 30 patients met the inclusion criteria. Included patients were at least 18 years of age who received doses of vancomycin greater than 2 grams for a period of at least 48 hours. Patients were excluded if they were pregnant, undergoing dialysis, had trough levels that were not drawn at steady state or not drawn at all, and intensive care patients. All data were collected from the eligible patient's electronic medical record and included their age, sex, height, weight, serum creatinine levels, vancomycin trough levels, comorbid conditions, and concomitant nephrotoxic drugs that were being administered.(table 1)

Statistical Analysis

A Z approximation test was used to calculate the proportion of acute kidney injury with doses greater than 2 grams. Standard error and a 95 % confidence interval were calculated where a standard error of 0.043 was found with an alpha error of 0.05 and a confidence interval between -0.024 and 0.144.

Table 1: Patients' demographics

Age	Sex	Height (in)	Actual weight (kg)	IBW (kg)	BMI
29	M	78	155.36	91.40	39.59
45	M	72.4	162.55	78.52	48.08
57	M	75	161.36	84.50	45.85
72	M	70	120.91	73.00	38.24
56	M	72	136.36	77.60	40.68
51	M	76	174.00	86.60	46.62
64	M	69	147.30	70.70	47.84
55	F	63	175.05	52.40	68.38
37	M	70	223.27	73.00	70.47
56	F	66	154.36	59.30	60.15
46	F	72	142.73	73.10	42.67
69	F	66	143.09	59.30	50.92
52	M	73	149.64	79.90	43.51
55	M	76	157.73	86.60	42.23
34	M	77	190.91	89.10	49.80
45	M	72	145.45	77.60	43.40
59	F	66	151.82	59.30	59.30
69	M	73	147.73	79.90	42.87
63	M	76	140.91	86.80	37.73
37	M	70	143.18	73.00	45.19
22	F	71.4	156.82	71.72	47.57
43	M	67	188.64	66.10	64.99
55	M	62	149.00	54.60	61.27
52	M	73	145.45	79.90	42.21
50	M	77	150.00	89.10	39.13
22	F	70	167.73	68.50	52.94
29	F	68	121.55	63.90	40.65
21	F	66	141.59	59.30	50.27
26	M	72	139.09	77.60	41.50
63	F	65	159.09	57.24	58.24

Average age of 47.8 ± 14.9, Actual Weight of 154.76kg ± 20.52kg, Average BMI of 48.74 ± 9.22, 20 Males and 10 Females

Loading Dose	**25-30mg/kg (seriously ill:sepsis, meningitis, pneumonia, infective endocarditis)**
Maint. Dose	**15-20 mg/kg**
Target Trough	**10-15 µg/ml:**
(min >10 µg/ml to avoid development of resistance)	cellulitis, pyelonephritis ***hold dose if >16**
	15-20 µg/ml:
	Bacteremia, endocarditis, osteomyelitis, meningitis, PNA, CNS or biliary infections, MIC >1 ***hold dose if >20**
Max Dose	**2g per IDSA guidelines; individualized can go up to 3 grams if needed**
	(age, wt, indication, level)
Initial Interval	**CrCl ≥ 100 ml/min: Q8h**
	CrCl 80-99: Q12h
	CrCl 60-79: Q18h
	CrCl 40-59:Q 24h
	CrCl 30-39:Q 36h
	CrCl ≤ 29 ml/min: pulse dosing, may dose q 48 or 72 hrs when levels come back at steady state
	Hemodialysis:
	15 mg/kg dose, redose when
	serum ≤ 20 mcg/ml

Fig. 1: Vancomcyin dosing protocol.

From the data obtained the creatinine clearance was calculated using the Cockcroft and Gault equation. Patients were evaluated for the occurrence of acute kidney injury or an increase in vancomycin trough levels oẽ 15 mcg/ml. In this study, the medical center standard dosing procedures were followed. The current standard dosing procedure is 15-20 mg/kg per dose and the frequency is determined based on the renal function. Loading dose of 25-30 mg/kg were used depending on the patients' clinical status as stated in the institution's vancomcyin dosing protocol.(Figure 1)

RESULTS

During the course of the study, 3579 patient charts were reviewed. Of these, 30 patients met the study inclusion criteria (as discussed in the Methods section). (13). (43.3%) of the 30 patients were recorded as having a vancomycin trough level >15 µg/ml and 6 of these 13 patients recorded a trough of greater than 20 µg/ml. Only 2 (6.67%) of the 30 patients experienced acute renal injury as defined by an increase in serum creatinine of >0.3 mg/dl. Of these 2 patients, one subject experienced a clinically significant increase in serum creatinine of 0.4mg/dl with a corresponding trough level of 22.2mcg/mL. Figure 2 illustrates the changes in serum creatinine. This patient's serum creatinine remained elevated at an increase of > 0.3 mg/dl from baseline for 5 consecutive days. The other subject noted an increase in serum creatinine of 0.9 mg/dl with a trough level of 13mcg/mL. This patient had a clinically significant increase in serum creatinine 2 days following initiation of vancomycin treatment and the patient's serum creatinine remained elevated for 6 consecutive days.

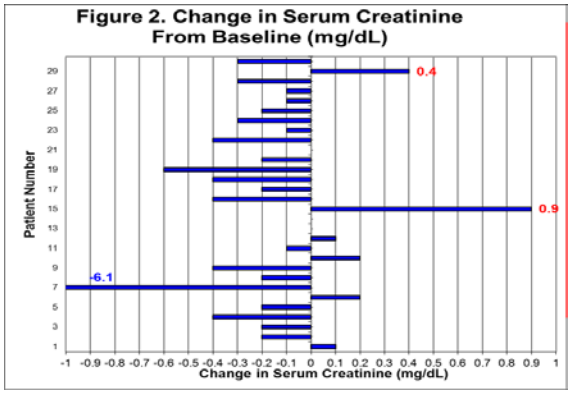

Fig. 2: Change in Serum Creatinine From Baseline (mg/dL)

Both subjects were receiving nephrotoxic agents concomitantly (Tables 1,2). The subject with an increase in serum creatinine of 0.9mg/dl notably refused the use of a nephroprotective agent (acetylcysteine). 13 of the 30 patients (43.3%) received loading doses (Table 2). Only 1 of these patients, who weighed 191kg with an estimated creatinine clearance of 147 ml/min, experienced a clinically significant increase in serum creatinine after receiving an initial 3g loading dose (a 0.6mg/dl increase in serum creatinine within 27 hours following loading dose administration). This is the same patient who experienced a 0.9mg/dl change in serum creatinine at steady state. This patient also received contrast dye concomitantly (Table 2). The only other patient who experienced clinically significant changes in serum creatinine did not receive a loading dose; their patient-specific information was also included in Table 1.

All 30 patients were classified as obese according to the National Heart, Lung, and Blood Institute's Body Mass Index (BMI), of which 17 patients (56.7%) had a diagnosis of diabetes, 21 patients (70%) had a diagnosis of hypertension, and 14 patients (46.7%) were using at least 1 additional antibiotic concomitantly (Table 2). **[19]** 22 patients (73.3%) were receiving potentially nephrotoxic agents concomitantly, including the only 2 subjects that displayed acute renal injury as defined by an increase in serum creatinine of >0.3 mg/dl. 5 subjects had an initial serum creatinine of >1.5 mg/dl prior to starting vancomycin therapy. When vancomycin trough levels were reached, all 5 patients had a lower serum creatinine level compared to baseline. Upon completion of the study, a statistical analysis was preformed to interpret the clinical significance of the given results. A Z approximation test was used where a standard error of 0.043 with an α error equal to 0.05 and a 95% confidence interval of (-0.024-0.144) were found. Upon the results of the statistical findings only two patients included in the study were found to have a clinically significant increase in serum creatinine of ≥ 0.3mg/dL when receiving a maintenance dose greater than two grams of vancomycin. Overall, an intravenous maintenance dose of vancomycin greater than two grams did not show a statistically significant increase in serum creatinine.

Only 2 patients from the study (6.67%) experienced a clinically significant increase in serum creatinine as defined by the Acute Kidney Injury Network (AKIN) criteria as an increase in serum creatinine of >0.3 mg/dl.**(**20**)** 28 patients (93.33%) displayed no clinically significant serum creatinine increase. It shall be noted that the two patients who showed a statistically significant increase in serum creatinine were also receiving nephrotoxic agents concomitantly during the evaluation of renal function. The inclusion of concomitant nephrotoxins where not factored into the statistical analysis of the results and their effect on kidney function cannot be ruled out.

Table 2: Effect on vancomcyin dose on serum creatinine, trough levels in the light of a loading dose and concomitant nephrotoxins

Patient	LD	Serum Creatinine (mg/dL)			Vancomycin Troughs (mcg/mL)	Concomitant Nephrotoxins
		Initial	At.Trough			
1	No	1.9	1.7	-0.2	31.8	Lisinopril, Oxacillin
2	Yes	7.9	1.6	-6.3	17.5	Levofloxacin, Tobramycin
3	Yes	1.3	1.1	-0.2	27.5	Levofloxacin, Lisinopril
4	Yes	1.0	1.2*	0.2	21.5	Levofloxacin, Lisinopril
5	Yes	1.0	0.9**	-0.1	16.6	Levofloxacin
6	No	0.8	0.9	0.1	18.1	Levofloxacin, Lisinopril
7	Yes	0.9	0.9	-	16.6	Lisinopril
8	Yes	0.9	0.9	-	17.5	Lisinopril
9	No	1.2	1.0	-0.2	17.4	-
10	No	0.7	0.6	-0.1	15.1	Lisinopril, Enalapril
11	No	1.0	0.8	-0.2	24.3	-
12	No	0.6	0.5	-0.1	36	Levoflaxacin
13†‡	No	0.7	1.1	0.4	22.2	Gentamicin, Zosyn, Radiopaque Contrast Agent
14	No	1.0	1.1	0.1	14.2	-
15	No	0.8	0.6	-0.2	12.7	Levofloxacin
16	Yes	1.1	0.7**	-0.4	10.7	Amoxicillin, Levofloxacin
17	No	0.8	0.8, 0.6**	-0.2	14.1	-
18	Yes	0.7	0.9	0.2	13.6	-
19	Yes	1.6	1.2	-0.4	14.7	Enalapril
20	No	1.0	0.6	-0.4	11.3	Enalapril, Lisinopril
21	No	1.2	1.0	-0.2	8.3	Oxacillin
22	Yes	1.5	1.1	-0.4	11.0	-
23	Yes	1.4	0.8	-0.6	6.9	Lisinopril, Enalapril, Levofloxacin, Glipizide
24	No	0.8	0.8	-	12.0	Ibuprofen
25	No	1.9	1.5	-0.4	11.1	Lisinopril, Enalapril
26	No	0.8	0.5	-0.3	11.8	Lisinopril, Enalapril
27	No	0.7	0.6	-0.1	12.6	-
28	Yes	0.9	0.6	-0.3	12.5	Gentamicin, Levofloxacin, Penicillin G
29	No	1.2	0.9	-0.3	12.4	-
30†‡	Yes	1.3	2.2	0.9	13	Ibuprofen, Lisinopril, Enalapril, Radiopaque Contrast Agent, Zosyn

LD= loading dose, * SCr obtained ~18 hours prior to vancomycin trough, ** SCr obtained ~18 hours before and after vancomycin trough, † Patient did not receive nephroprotective agents with contrast, ‡ Patient showing significant increase in serum creatinine

DISCUSSION

According to the recent 2009 consensus guidelines on therapeutic monitoring of vancomycin, targeting a vancomycin trough level between 15-20 mg/l improves patients clinical outcomes (1). However, emerging data suggest maintaining Vancomycin trough≥ 15 mg/l increases the risk of nephrotoxicity. (6) Since vancomycin is mainly eliminated through glomerular filtration, any change in renal function whether it would increase or decrease would have an effect on Vancomycin serum concentration which links the association between Vancomycin levels and renal function.(6)

Also, in in order to attain high trough levels, based on their weights, patients might require higher doses such as greater than 4 grams per day. Recent studies showed that there is an association between high-dose Vancomycin therapy and risk of nephrotoxicity. (2,21) Some data showed that this could be linked to the concomitant administration of nephrotoxins, vasopressor therapy and underlying physiological impairment.(21) On the other hand, some studies identified high dose Vancomycin (> 4 gm/day) as an independent risk factor for nephrotoxicity, when compared to administration of < 4 gm/day.(2) A prospective cohort analysis showed that patients with mean trough levels≥ 15mg/l had a significantly increased incidence of nephrotoxicity.(22) In this study, patients that developed nephrotoxicity were more then likely receiving other nephrotoxic medication and the timing of these troughs were not known to be taken prior to or after the onset of nephrotoxicity.(2) In a retrospective analysis that focused on patients that had been diagnosed with healthcare-associated pneumonia, Vancomycin troughs of ≥ 15 mg/l were associated with nephrotoxicityin both of these studies, patients were simultaneously on nephrotoxin agents such as contrast dye and some patients were on vasopressors. (10,22) Prabacker and colleagues found that nephrotoxicity with vancomycin troughs is uncommon when vancomycin was administered for more than 5 days; however, they did not identify the high dose of vancomycin used. (14) Our study looked at 3579 patients where 30 patients met the inclusion criteria. Out of the thirty patients, 6 patients did have Vancomycin trough levels greater than 20 mg/l. Out of those six patients, an increase in serum creatinine levels was observed in 2 patients. moreover, like previous studies, patients who received nephrotoxic medications were not excluded. It is also important to mention that in one of the patientswho developed an increase in serum creatinine by 0.9mg/dl and their vancomycin level was above 20 mg/l had received radiopaque contrast without any renal protective measures taken prior to the contrast's administration.

By looking at our patients' weight, the included patient are classified as obese. This brings up another point as to the reason behind our results where no relationship between high dose vancomycin therapy and increase in serum creatinine and/ or nephroxicity was noted. Due to the pharmacokinetic changes, morbidly obsese patients require larger doses and shorter dosage intervals compared with normal weight patients to achieve steady-state vancomycin concentrations.(23) Vancomycin clearance is 2.5 times greater in the morbidly obese patients compared with matched normal weight subjects.(23) By looking at our patients' dosing intervals we did not have one patient on a q 8hr regimen which is very routine for morbidly obese patients. Also, we used the Cockcroft-Gault equations to estimate their creatinine clearance and it has not been shown to be the most accurate method in this patient population when compared to Salazar and Corcoran equation. This could have lead us to believe that their creatinine clearance was worse than it actually was giving us inadequate dosing intervals.

When comparing our study to the previous mentioned studies what we called high-dose Vancomycin therapy was not what had been studied in the past. When looking at studies they used doses of Vancomycin > 4 gm per day as compared to our≥ to 2 gm per day. When dealing with our patient population where the mean weight was observed to be 154.67 kg, the use of 4 gm per day may not have been sufficient to reach the desired peak and trough concentrations. It has been suggested that when dosing obese patients the dosing range showed be near the 30 mg/kg of total body weight range. It is not our practice to maintain a patient on this high dose. We use the range of 15-20 mg/kg of total body weight. It is important to note, our study had several limitations. One limitation as previously mentioned that we did not exclude patients based on any confounding issues that they may have presented with. We did not exclude any patients that had a high serum creatinine to begin with or pre-existing renal dysfunction. Our study population limited our findings to a specific patient population. Finally, our sample size being only 30 patient may not have given us a true indication of the dosing policy used.

CONCLUSION

The use of doses greater than 2 grams of IV vancomycin did not show a statistically significant increase in serum creatinine. Nephrotoxicity has been observed only in cases where other nephrotoxin agents were concurrently administered. Clinical trials with larger number of patients may be needed in order to detect any nephrotoxic effect of vancomycin when given in doses greater or equal to 2 grams per dose.

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