Ragab et al., 2:2
http://dx.doi.org/10.4172/scientificreports.622

Open Access Scientific Reports

Research Article Open Access

Incidence and Predisposing Factors of Vancomycin-Induced Nephrotoxicity in Children

Ahmed Refat Ragab[1,2]*, Maha Khalid Al-Mazroua[2] and Mona Ahmed Al-Harony[1]

[1]*Department of Forensic Medicine and Clinical Toxicology, Faculty of Medicine, Mansoura University, Egypt*
[2]*Dammam Regional Poison Control Center, Eastern Region, KSA*

Abstract

Objective: To determine the pattern of vancomycin-associated nephrotoxicity in children, and to examine potential predisposing factors for nephrotoxicity, including average serum trough concentrations >10 mg/L.

Subjects and methods: Patients ≥ week old to ≤ 15 years with normal baseline serum creatinine values who received vancomycin for ≥ 48 hours between October 2010 and September, 2012 were retrospectively evaluated. Nephrotoxicity was defined as a serum creatinine increase of ≥ 0.5 mg/dL or ≥ 50% baseline increase over two days. Patients with average serum trough concentrations ≥ 10 mg/L were compared with a lower trough group.

Results: Renal toxicity occurred in 72 (27.2%) of the studied pediatric 265 cases. High trough vancomycin levels>10 µg/dl were presented in 59 pediatric patients suffering from nephrotoxicity. Cases admitted to the ICU, to whom aminoglycoside medication was administered concurrently with vancomycin medication, showed a significant, high renal toxicity incidence (p value 0.03 and 0.05, respectively).

Conclusions: Renal function and continuous monitoring of vancomycin trough level for children receiving vancomycin therapy and admitted to the ICU, and given other aminoglycoside medications, is mandatory.

Keywords: Vancomycin therapy; Renal toxicity; Vancomycin nephrotoxicity; Pediatric toxicity

Introduction

Vancomycin is a bactericidal; glycopeptide antibiotic, widely used in children for treating methicillin-resistant *Staphylococcus aureus* (MRSA) infections [1].

In fact, vancomycin trough serum concentrations between 10 and 15 mg/L have been recommended for serious infections caused by MRSA (including endocarditis, osteomyelitis, meningitis and pneumonia), and strains with elevated vancomycin MICs of 2 mg/L [2,3]. Although this consensus statement excluded recommendations for children, aggressive vancomycin dosing regimens are nonetheless being used with pediatric patients. This dosing may increase the incidence of nephrotoxicity in children.

Vancomycin-associated renal toxicity has been a point of controversy since 1958, when Geraci et al. [4] published the first case series, linking the two. Since then, several studies have reported an association between vancomycin serum trough concentrations and renal toxicity [5-7].

Although vancomycin has been associated with nephrotoxicity, causality has not been firmly established. Data in adult patients indicate that higher vancomycin doses (or higher serum trough concentrations) are associated with increased nephrotoxicity [8-10]. Nephrotoxicity data associated with higher vancomycin trough attainment through aggressive dosing in the pediatric population is lacking, although rates might be higher with increased troughs, as evident in adults.

However, the definition of renal toxicity as well as the patient population and disease severity, has varied among these studies. Therefore, we performed a retrospective observational clinical study, with the main goal of determining the overall rate and predisposing factors associated with development of nephrotoxicity in children receiving vancomycin, including those achieving high average vancomycin serum trough concentrations of ≥ 10 µg/ml.

Subjects and Methods

Study setting

This study was conducted at Dammam Maternal and Child Hospital (DMCH), a community-based, secondary care hospital. All pediatric patients receiving vancomycin are routinely monitored according to guidelines by toxicologists who perform pharmacokinetic analyses to assess toxicity and goal trough attainment. All Dammam Poison Control Center (DPCC) clinical toxicologists are trained, and have undergone internal competency training and testing in making pharmacokinetic calculations, both by manual calculation and with the use of an institution-based computer kinetic program. Steady-state serum trough concentrations are generally obtained and baseline and periodic serum creatinine (SCr) values are monitored in all patients.

Inclusion and exclusion criteria

In our retrospective study, eligible patients were one week (and not born prematurely before 37 weeks gestational age) to 15 years of age; had received vancomycin for at least 48 hours between November 2010 and October 2012; and had normal baseline SCr values (defined as ≤ 0.6 mg/dL for patients ≤ 1 month old and ≤ 0.9 mg/dL for those > 1 month old). The definition of normal renal function was applied to the start of vancomycin therapy only. Patients were required to have had one or more serum vancomycin concentrations and repeat SCr values. Premature neonates and infants cared for in the neonatal intensive care

***Corresponding author:** Ahmed Refat Ragab, Department of Forensic Medicine and Clinical Toxicology, Faculty of Medicine, Mansoura University, Egypt, E-mail: ahmedrefat1973@yahoo.com

Received January 31, 2013; **Published** February 22, 2013

Citation: Ragab AR, Al-Mazroua MK, Al-Harony MA (2013) Incidence and Predisposing Factors of Vancomycin-Induced Nephrotoxicity in Children. 2: 622 doi:10.4172/scientificreports.622

unit were excluded because DMCH used a separate dosing guideline, and the low muscle mass of these infants may impair prediction of renal impairment.

Study design

A retrospective cohort design was employed to assess the effect of vancomycin serum trough concentrations on the occurrence of renal toxicity. The study protocol was approved by the Dammam Poison Control Center review board. Patients were identified using the toxicology clinical monitoring database, Online Analytical Toxicology Request and Result (OTARR). Only the first course of vancomycin was evaluated if multiple courses were given during the study period. Electronic medical records and pharmacokinetic monitoring forms were reviewed. Pertinent data, including demographics, laboratory details, vancomycin dosing and pharmacokinetics were collected on standardized forms. Concomitant use of nephrotoxins, such as aminoglycosides, cyclosporine, tacrolimus, furosemide or amphotericin was recorded. The Dammam Maternal and Child Hospital protocol for intravenous administration of vancomycin requires measurement of steady state trough concentrations, with a target of 5 to 10 μg/ml for both serious and non-serious infectious status.

A MEDLINE search was performed using the keywords vancomycin, renal toxicity, renal failure, creatinine and creatinine clearance. Based on this literature review, renal toxicity was defined as either a 0.5 mg/dL increase from baseline in SCr, or a ≥ 50% increase from baseline in SCr based on serial SCr measurements [8-10]. Baseline SCr and age- and sex-adjusted CrCl calculations were made before administration of vancomycin in all patients, using the following formula [11]:

Estimated creatinine clearance=(140-*age*) (*weight in kg*) / (72 × *serum creatinine*)×0.085 (*women only*)

Baseline vancomycin clearance (L/h) was obtained from pharmacokinetic values from the first steady-state vancomycin concentration, using the population volume of distribution. High trough therapy was defined as an average serum trough concentration of >10 mg/L, and low trough therapy as an average serum trough concentration of <10 mg/L for all concentrations throughout therapy.

Grouping of the studied patients

An average trough was calculated using all measured serum concentration results throughout therapy. Baseline vancomycin clearance (L/h) was obtained from pharmacokinetic values from the first steady-state vancomycin concentration, using the population volume of distribution. High trough therapy was defined as an average serum trough concentration of ≥ 10 mg/L, and low trough therapy as an average serum trough concentration of<10 mg/L for all concentrations throughout therapy.

Statistical analysis

All comparisons were unpaired and all tests of significance were 2-tailed. Continuous variables were compared using the Student t test for normally distributed variables, and the Mann-Whitney U test, for non-normally distributed variables. The χ^2 test was used to compare categoric variables. The primary data analysis compared patients who met the study definition for renal toxicity with those who did not. Values were expressed as mean (SD) for continuous variables, and as a percentage of the group from which they were derived for categoric variables. P was two-tailed, and P ≤ 0.05 was considered statistically significant. We performed multiple logistic regression analyses using SPSS for Windows version 19.0 (SPSS Inc., Chicago, Illinois). Multivariate analysis was performed using models that were judged a priori to be clinically sound [11].

Results

Table 1 shows the demographic and clinical data characteristics of the studied pediatric cases, receiving vancomycin therapy. The total number of cases was 265, of which 130 were male. The gender factor has no clinically significant difference between high and low trough vancomycin level. Some parameters in the studied table showed a significant difference, when comparing a low vancomycin trough level <10 μg/ml with a high vancomycin level more than 10 ng/ml, as shown in mean age, meningitis, dermal infectious status, vancomycin dosage, and finally frequencies of ICU admitted cases (0.03, 0.026, 0.031, 0.001, 0.023, 0.12, 0.04), respectively.

Table 2 clarifies the variable parameters related to the renal profile in children receiving vancomycin therapy that showed a significant difference in the frequencies of nephrotoxicity, time of occurrence of nephrotoxicity, peak and end of the therapy of serum creatinine level, frequencies of very high increase serum creatinine level above baseline (>0.5 mg/dl), and mean vancomycin clearance rate at peak and end of vancomycin medication course (p value 0.0001, 0.04, 0.03, 0.03, 0.02, 0.0001, 0.02, and finally 0.043).

The effect of the vancomycin trough level, duration of vancomycin

Characteristics	Low trough	High trough (n.=99)	P value
Male, n(%)	82(49.3)	48(48.5)	0.263
Mean age, y (± SD)	2.1 ± 1.9	1.7 ± 1.3	0.03
Mean weight, Kg (± SD)	7.37 ± 11.7	6.1 ± 7.4	0.188
Infection type, n (%)			
Bactermia	72(43.3)	47(47.4)	0.351
Pneumonia	66(39.7)	28(28.8)	0.833
Meningitis	7(4.2)	13(13.1)	0.026*
Dermal infection	6(3.6)	12(12.2)	0.031*
Myocarditis	5(3.1)	4(4.1)	0.435
Arthritis	6(3.6)	7(7.1)	0.712
Endocarditis	4(2.4)	2(2.1)	0.551
Chronic illness, n (%)			
Malignancy	5(3%)	11(11.1)	0.672
Prematurity	21(12.6)	16(16.6)	0.183
Congenital heart disease	11(6.6)	13(13.1)	0.417
Respiratory disease	12(7.2)	7(7)	0.123
Respiratory distress syndrome	11(6.6)	2(2)	0.327
Concomitant nephrotoxin, n (%)			
Aminoglycosides	52(31.3)	12(12.2)	0.051
Cyclosporine	6(3.6)	3(3)	0.341
Tacrolimus	3(1.8)	1(1)	0.360
Non-Steroidal anti-inflammatory	17(10.2)	10(10.1)	0.172
Amphotericin	3(0.02)	3(0.03)	0.562
Loop diuretic "frosemide"	22(13.25)	18(10.8)	0.342
Initial Vancomycin Dose (mg/kg/d) Mean (± SD)	36.1(24.6)	47.4 (15.5)	0.001*
Overall Vancomycin dose therapy (mg/kg/d) Mean (± SD)	32.2 ± 22.3	41.2 ± 17.3	0.032*
Duration of vancomycin therapy(d) Mean (± SD)	12.1 ± 8.4	14.4 ± 5.1	0.120
Duration of hospital stay (d) Mean (± SD)	17.2 ± 14.1	22.4 ± 15.1	0.471
ICU admission			
N(%)	38(22.9)	37(37.4)	0.041*
Duration stay (d) (± SD)	15.3(12.1)	9.3(4.1)	0.371

P value significant ≤ 0.05

Table 1: Demographic, base line and patient's characteristic of children receiving vancomycin (total n=265).

Parameters	Low trough (n=166)	High trough (n.=99)	P value
Nephrotoxicity during therapy, N(%)	13(7.8)	59 (59.9%)	0.0001*
Time of nephrotoxicity, Mean (± SD)	6.3(3.7)	3.2(1.4)	0.04*
Vancomycin dose at toxicity time, (mg/kg) Mean (± SD)	33.6(10.1)	46.2(13.7)	0.03*
Serum creatinine level Mean (± SD)			
Baseline	0.57(0.2)	0.67(0.51)	0.325
Peak	0.68(0.3)	0.81(0.34)	0.03*
End of therapy	0.54(0.7)	0.62(0.6)	0.02*
Serum creatinine ≥ 0.5 mg/dl above baseline N(%)	4	19	0.001*
Vancomycin clearance (L/h) Mean(± SD)			
Baseline	2.2 (2.1)	1.9(1.1)	0.231
Peak	1.85(1.7)	1.53(0.7)	0.029*
End of therapy	2.1(1.9)	1.81(1.3)	0.0.43*

Table 2: Renal kinetics profile in children receiving vancomycin.

therapy and concomitant nephrotoxin medication (aminoglycosides) are clearly shown in table 3. The percentage of nephrotoxity occurrence clearly shows a significant difference in the previously mentioned predisposing factors (0.002, 0.04 and 0.0001).

Figure 1 shows the percentage of renal toxicity, according to the vancomycin level. The highest percentage was found in the vancomycin therapy >20 µg/ml (87.5%), with a significant difference when compared with low vancomycin trough level <10 µg/ml.

Discussion

Methicillin-resistant staphylococcus aureus (MRSA) infection in children is treated mainly by vancomycin, which is a bactericidal glycopeptide antibiotic. There are two medical schools regarding the use of vancomycin therapy in the treatment of serious infection caused by MRSA. One of these suggests keeping the trough serum vancomycin concentration at 5-10 µg/ml as with other non-serious infections, and the other advises increasing the vancomycin level to between 10-15 µg/ml. The protocol applied in Dammam Maternal and Child hospital is the 1st vancomycin protocol that keeps the level between 10-15 µg/ml.

The current study was performed to clarify the vague relationships among different variables in the studied pediatric cases, such as age, weight, indication of vancomycin therapy, admission status, duration of therapy, concomitant nephrotoxin usage with vancomycin medication, vancomycin dosage, and level and renal function status in studied children. The definition of renal failure terminology applied in the current study followed that in many documented references [8-10], as previously mentioned.

In the studies of the incidence of renal failure in adult patients treated with vancomycin ranged from 12% to 42%,and this percentage was markedly elevated to reach its maximum percentage (43%), when other aminoglycoside medications were used with vancomycin therapy [9,10].

In the present study, 27.2% of the studied children suffered from renal toxicity during vancomycin therapy, and the incidence of renal toxicity increased when the vancomycin trough level became >10 µg/ml (41%, and reached its peak in 87.5% in cases with serum trough vancomycin levels of more than 15 µg/l). In accordance with the presented figures, several adult and pediatric studies documented the previously noted information [8,9].

Other factors have been reported that can affect the incidence of occurrence of renal toxicity, beside the vancomycin serum level. These include duration of vancomycin therapy, concomitant usage

Parameters	Renal Toxicity Absent (94)	Renal Toxicity Present (72)	P
Vancomycin trough, µg/mL Mean(SD)	8.4(3.1)	17.1 (4.7)	0.002*
Duration of vancomycin therapy>14 d N(%)	13(13.8)	31(43.1)	0.04*
Serum creatinine level Mean (± SD) mg/dl			
Maximum	0.56(0.4)	0.91(0.37)	0.000*
Change	0.12(0.2)	0.83(0.22)	0.000*
Vancomycin clearance (L/h) Mean(± SD)			
Minimum	2.4(2.2)	1.7(0.9)	0.231
Change	0.2(0.03)	1.1(0.01)	0.029*
Concomitant nephrotoxins, n (%)			
Aminoglycosides	26(27.6)	38(52.7)	0.001*
Cyclosporine	3(3.1)	6(8.3)	0.728
Tacrolimus	2(2.1)	2(2.7)	0.921
Non-Steroidal anti-inflammatory	6(6.3)	11(15.2)	0.414
Amphotericin	1(1.1)	4(5.5)	0.827
Loop diuretic "frosemide"	17(18.1)	23(31.9)	0.071

P value significant ≤ 0.05

Table 3: Vancomycin therapy and changes in renal functions.

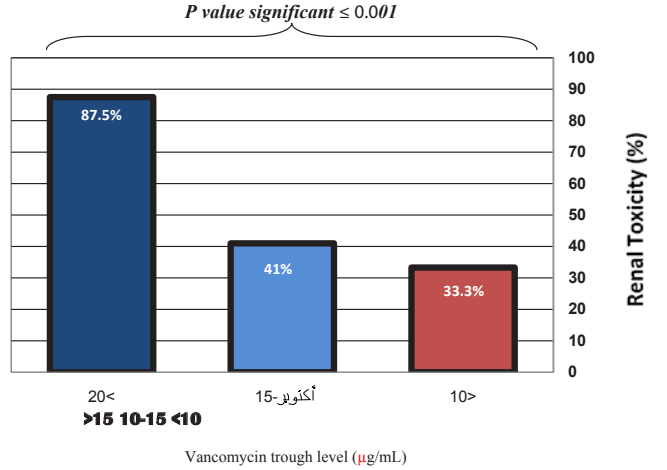

Figure 1: Occurrence of renal toxicity, stratified by vancomycin steady-serum trough concentration.

of aminoglycosides, ICU admission status, and age and weight of the studied pediatric cases.

In the current study of 72 cases suffering from renal toxicity, there were 38 pediatric cases who were given aminoglycosides, as well as vancomycin therapy. About one third (37.4%) of the studied pediatric cases with high trough vancomycin levels were admitted to the ICU. The effects of vancomycin dosage were remarkable in the present study. The studied pediatric cases with high trough vancomycin levels of >10 µg/dl were associated with high mean overall vancomycin dose (41.2 mg/kg/d), when compared with low trough level <10 µg/ml (32.3 mg/kg/d), with a significant difference p<0.05. In accordance with our results, one study of adult cases found a significant inverse nephrotoxicity percentage among patients receiving a high dose of vancomycin therapy, and who were admitted to the ICU [10].

In the present study, most of the pediatric cases suffering from nephrotoxicity induced by vancomycin therapy had associated with increasing serum creatinine level, that returned to the average baseline concentration at the end of therapy or hospital discharge. In accordance with the present findings, one study done by Jeffries et al. [9] stated

that 72% of the studied cases of patients suffering from vancomycin-induced nephrotoxicity had a high creatinine level, that returned to baseline at the time of hospital discharge.

Regarding the time of occurrence of vancomycin-induced renal toxicity, several studies reported that the onset of renal toxicity mainly occurs after a lapse of 1-3 weeks from the onset of vancomycin therapy in adult patients [2,9,10]. In the present study, the time of occurrence of renal toxicity occurred in the first week, for renal toxicity associated with both high and low trough vancomycin levels.

The duration of vancomycin therapy plays an important role in the induction of vancomycin-induced nephrotoxicity. Hidayat et al. [2] stated that increasing the duration of vancomycin therapy was associated with an increase in the incidence of occurrence of renal toxicity, and about 30% of the studied cases associated with nephrotoxicity were patients receiving vancomycin therapy for more than 14 days, while it was only 6.3% in adult patients receiving vancomycin therapy for less than one week.

Summary and Conclusion

The present work discussed the impact of vancomycin therapy in the renal function of the pediatric population. The result of this study clarified that vancomycin-induced renal toxicity existed in about 27.2% of the studied cases, and with high trough vancomycin level of >10 μg/dl, the incidence of renal toxicity significantly increased. Admission to the ICU, prolongation of vancomycin therapy and concurrent administration of other aminoglycoside medications during vancomycin therapy increased the incidence of renal toxicity in pediatric studied cases. In conclusion, renal function and continuous monitoring of vancomycin trough levels for children receiving vancomycin therapy, and admitted to the ICU and given other aminoglycoside medications, is mandatory.

References

1. Gerber JS, Coffin SE, Smathers SA, Zaoutis TE (2009) Trends in the incidence of methicillin-resistant *Staphylococcus aureus* infection in children's hospitals in the United States. Clin Infect Dis 49: 65-71.
2. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A (2006) High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. Arch Intern Med 166: 2138-2144.
3. Ryback M, Lomaestro B, Rotschafer JC, Moellering R Jr, Craig W, et al (2009) Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 66: 82-98.
4. Geraci JE, Heilman FR, Nichols DR, Wellman WE (1958) Antibiotic therapy of bacterial endocarditis. VII. Vancomycin for acute micrococcal endocarditis; preliminary report. Proc Staff Meet Mayo Clin 33: 172-181.
5. Kralovicova K, Spanik S, Halko J, Netriova J, Studena-Mrazova M, et al. (1997) Do vancomycin serum levels predict failures of vancomycin therapy or nephrotoxicity in cancer patients? J Chemother 9: 420-426.
6. Zimmermann AE, Katona BG, Plaisance KI (1995) Association of vancomycin serum concentrations with outcomes in patients with gram-positive bacteremia. Pharmacotherapy 15: 85-91.
7. Elting LS, Rubenstein EB, Kurtin D, Rolston KV, Fangtang J, et al (1998) Mississippi mud in the 1990s: Risks and outcomes of vancomycin-associated toxicity in general oncology practice. Cancer 83: 2597- 2607.
8. Hermsen ED, Hanson M, Sankaranarayanan J, Stoner JA, Florescu MC, et al. (2010) Clinical outcomes and nephrotoxicity associated with vancomycin trough concentrations during treatment of deep-seated infections. Expert Opin Drug Saf 9: 9-14.
9. Jeffries MN, Isakow W, Doherty JA, Micek ST, Kollef MH (2007) A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant *Staphylococcus aureus* pneumonia. Clin Ther 29: 1107-1115.
10. Lodise TP, Lomaestro B, Graves J, Drusano GL (2008) Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. Antimicrob Agents Chemother 52: 1330-1336.
11. Concato J, Feinstein AR, Holford TR (1993) The risk of determining risk with multivariable models. Ann Intern Med 118: 201-210.