Steady-state pharmacokinetic analysis of vancomycin in Iranian pediatric patients

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ABSTRACT

Background: Large inter-individual variability has been reported for vancomycin pharmacokinetics in pediatric patients. On the other hand, the pharmacokinetic parameters of vancomycin should be known in order to individualize its dosage regimen. Therefore, this study was designed and conducted to assess the steady-state vancomycin serum concentration and pharmacokinetics in a population of Iranian pediatric patients.

Methods: Vancomycin serum concentration at steady-state was determined in 62 children who were treated with vancomycin intermittent intravenous infusion. Also individual steady-steady pharmacokinetic parameters (total body clearance, apparent volume of distribution and elimination half-life) were determined in 30 patients who had both peak and trough vancomycin levels assuming one-compartment model. Calculated pharmacokinetic parameters were compared among patients with different underlying diseases and also with the results of similar studies that used one-compartment pharmacokinetic model for description of serum concentration of vancomycin at steady-state.

Results: More than half of the measured vancomycin serum concentrations were outside the recommended therapeutic range. Median trough concentration was significantly lower in critically ill patients as compared to patients of other disease categories. Although critically care patients showed greater values of apparent volume of distribution and also vancomycin clearance, no statistically significant difference of the calculated pharmacokinetic parameters could be detected among different groups of patients. While calculated volume of distribution for patients of this study was greater than those of similar studies, this difference could not be considered statistically significant in the majority of disease categories

Conclusion: It may be concluded that design of vancomycin dosage regimens according to the recommended and general guidelines in literature (e.g. based on patient creatinine clearance) could not result in the desired therapeutic serum concentrations in the study population.

Keywords: Vancomycin, Steady-state Pharmacokinetics, Pediatric Patients

INTRODUCTION

Vancomycin (VCM) is a glycopeptide antibiotic against Gram positive-bacteria including methicillin-resistant *Staphylococci*. It is also an alternative to penicillin in the treatment of infections caused by other sensitive bacteria in the

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patients with a history of serious penicillin allergy (1-2).

Recommended therapeutic concentrations for vancomycin to minimize the possibility of adverse effects and also to keep an effective drug level, are: peak levels (serum concentrations one to two hours post end of infusion) below 25-40 mg/L(3) or not greater than 30 mg/mL(4) and trough concentrations less than 10 mg/L(3).

Though there are some controversy about the need for routine monitoring of vancomycin serum concentration, pediatric patients with high clearance or short half lives (1) require monitoring mostly to prevent the emergence of bacterial resistance (5). Since pharmacokinetic profile of vancomycin has great variability in infants and children (6), individualization of dosing regimens by measurement of vancomycin concentrations provides more accurate dosing in neonatal and pediatric populations (5).

Although a two or three compartment model is best model which describes the pharmacokinetics of vancomycin, the complexity of such models could be problematic in clinical practice and hence a one-compartment model is frequently used (7).

Since there is not any published report on vancomycin pharmacokinetics in Iranian pediatric patients and there are some reports that design of vancomycin dosage regimens based on the recommended methods in the literature for prediction of vancomycin trough level could not lead to desired therapeutic serum concentrations (8-10) this study was conducted to assess the vancomycin serum concentration and steady-state pharmacokinetics in Iranian pediatric patients.

MATERIAL AND METHODS

Study design

After receiving approval from the ethics committee of Tehran University of Medical Sciences, the study was conducted prospectively in Imam, Vali-e- Asr and Children's Medical Center hospitals of Tehran Medical Sciences University in Iran from March 2006 up to July 2007.

Selection of patients

Sixty two children (39 males and 23 females) who were treated with vancomycin for different infections enrolled in the study (Tables 1). No changes (including dose individualization) were made in treatment protocol of the patients during the study. Inclusion criteria were: (a) to receive a constant dose of vancomycin (fixed dose and dosing interval) at least for 72 hrs to ensure achievement of the steady state condition; (b) age of more than one month and less than eighteen years old. Patients with severe renal dysfunction (patients under dialysis), or hypersensitivity to the drug were excluded from the study.

Drug administration and sampling

Vancomycin was administered by intermittent intravenous infusion over 10 minutes to 1 h at doses ranging from 54 to 2000 (646±560) mg/day (50±18 mg/kg) and the dosage interval ranging from 6 to 12 hrs. Blood samples (2-2.5 mL) were collected from a peripheral or central vein or artery. Blood samples which were drawn within 30 minutes prior to the administration of the next dose were used for measurement of trough vancomycin concentrations (Css_{trough} or pre-dose sample). Samples collected 60-180 minutes post end of vancomycin infusion were used for determination of Css_{peak} (post dose sample) (1). Blood samples were centrifuged at 3000 rpm for ten minutes to separate the serums. Serum samples were kept frozen at -20 ºC until the time of drug analysis. A total of 100 vancomycin serum levels (58 trough and 42 peak samples) were measured of which 39 patients had both peak and trough samples. 19 patients had just trough values and the rest had only peak serum levels.

Drug concentration analysis

Serum concentrations of vancomycin were analyzed by Fluorescence Polarization Immunoassay (FPIA) (TDx/TDxFLx, Abbott Laboratories) which showed a coefficient of variation (CV) of 5.85% at a concentration of 7 mg/L, 3.26% at 35 mg/L, and 3.48% at 75 mg/L (11).

Pharmacokinetic analysis

Individual vancomycin pharmacokinetic parameters including elimination rate constant (k, in $hour^{-1}$), elimination half-life ($t_{1/2}$, in hour), apparent volume of distribution at steady state (V_d, L/kg) and clearance (CL, L/h/kg) were determined assuming a one-compartment model using two serum vancomycin concentrations and taking into account to have a constant pharmacokinetic in patients which had both peak and trough measurements using the following equations:

$$K_e = \frac{\ln(\frac{C_{ss}peak}{C_{ss}trough})}{\Delta t} \qquad [1]$$

$$CL = K_e.Vd \quad [2]$$

$$Vd = \frac{Dose}{(C_{ss}peak - C_{ss}trough)} \times e^{-K_e.t} \quad [3]$$

in which K_e is the elimination rate constant (in $hour^{-1}$), C_{ss}peak and C_{ss}trough are peak and trough concentrations(in mg/L) at steady-state as described above,Vd is apparent volume of distribution at steady state in L/kg, Dose is the administered vancomycin dose(mg/kg), Δt is the time interval (in hours) between measured peak and trough concentration and t is the time (in hours) to the measured peak from beginning of the infusion(12).

Statistical analyses

Kruskal-Wallis non-parametric method followed by Steel-Dwass multiple comparisons test were used to determine statistical difference of various pharmacokinetic parameters and also measured vancomycin levels (peak and trough concentrations) among different groups of patients. Calculated parameters between males and females were compared by Mann-Whitney U test. Median and inter-quartile of pharmacokinetic parameters range are also reported. To compare the values of this study with other reports, mean and standard errors of the mean pharmacokinetic parameters were determined. Statistical significance was considered at p-values less than 0.05. All statistical analyses were carried out using StatsDirect 2.7.2 (StasDirect Ltd., UK).

RESULTS

Median peak and trough concentrations for patients with different underlying disease are presented in table 2. Of 62 patients 31 patients were also on nephrotoxic and 25 patients were on ototoxic drug therapy, respectively. More than 50 % of measured vancomycin trough concentrations were outside the range of 5-15 mg/L. About 62% of measured peak levels were either greater than 40 mg/L or lower than 20 mg/L.

The median daily administered dose (per kilogram of body weight) was not different among patients in various disease groups (p-value>0.05). As it could be found from table 2, the lowest and highest vancomycin trough concentrations were observed in critically-ill patients and patients with no definite disease, respectively. Statistically significant differences were observed between median trough concentrations in critically- ill patients with both patients in heart disease group (p-value=0.0435) and patients with no definite underlying disease (p-value= 0.0385).Other differences between median trough levels could not be considered significant.

Of 39 patients who had peak and trough measurements, pharmacokinetic parameters were calculated for 30 (9 female and 21 male) patients. One patient had peak and trough concentrations related to different dosing regimens. Peak vancomycin levels were less than trough concentrations in eight patients because of either inaccurate sampling times or other unknown reasons.

As could be found from table 3, patients with calculated pharmacokinetic parameters could be categorized in heart disease group, patients with hematological disorders or critically ill patients. Although critically care patients showed greater values of apparent volume of distribution and also vancomycin clearance, no statistically significant difference of the calculated pharmacokinetic parameters could be detected among different groups of patients.

Median vancomycin apparent volume of distribution was greater in male than female patients (p-value= 0.0195) (Table 3). However, this difference could not be considered statistically significant within group of patients with heart diseases (p-value= 0.1625). Other vancomycin pharmacokinetic parameters did not differ between males and females. Values of pharmacokinetic parameters with assumption of one-compartment pharmacokinetic model for vancomycin in different studies on similar pediatric populations (6), (27-28) are depicted in table 4. Summary of pharmacokinetic parameters for all patients included in this study is presented in table 5.

DISCUSSION

About two-third of the patients included in the current study showed vancomycin serum concentrations outside the recommended ranges which have been reported previously(3,4), hence target vancomycin concentrations may not be achieved in these patients according to the suggested dosing regimens in literature(1,2,7). In a similar study, more than 50 percent of the patients had vancomycin levels outside the recommended therapeutic range (13).

It has been reported that the commonly used methods for prediction of vancomycin pharmacokinetic parameters based on patients characteristics, especially creatinine clearance vary widely in prediction of vancomycin trough concentrations as compared to the observed values and it has been concluded that none of these types of methods are sufficiently reliable to replace monitoring of vancomycin serum concentration (8). It has been found that

Table 1. Characteristics of the patients included in the study

Age	Number (%)	Male/ Female	Weight(kg) mean ±SD (range)	*SCr (mg/dL) mean ± SD (range)	*a	*b
Under 1 year	22 (34.5)	13/9	5.1±1.7 (2.6-8.0)	0.5±0.3 (0.2-1.3)	15 (68)	12 (55)
1-18 years	40 (64.5)	26/14	19.7±12.5 (5.0-50.0)	0.5±0.2 (0.3-1.0)	16 (40)	13 (33)

a: Number(%) of patients with concurrent ototoxic drug therapy
b: Number(%) of patients with concurrent nephrotoxicdrug therapy
SCr: Serum Creatinine

Table 2. Summary of peak and trough concentrations measured in the study patient

Underlying disease (number of patients)	Total number of measured trough levels	Median trough conc. in mg/L (interquartile range)	Total number of measured peak levels	Median peak conc.in mg/L (interquartile range)
Heart diseases(22)	20	14.8(12.0)	18	21.1(21.7)
Hematologic disorders(17)	15	9.8(6.7)	8	17.5(18.5)
Critical care patients(8)	8	3.9(3.8)	6	9.2(16.2)
Cystic fibrosis(5)	5	9.4(6.4)	4	8.0(3.5)
Galactosemia(2)	2	8.8(9.2)	1	11.6
other diseases(8)	8	15.7(12)	5	25.1(6.5)

Table 3. Median (inter-quartile range) of calculated pharmacokinetic parameters

Patients group	Number of patients	[a] $t_{1/2}$(h)	[b] Vd(L/kg)	[c] CL(L/kg/h)
Heart diseases	14	3.5(1.7)	0.51(0.39)	0.09(0.02)
Hematological disorders	6	3.0(2.5)	0.68(1.06)	0.15(0.19)
Critically ill patients	6	3.4(0.6)	0.84(0.65)	0.16(0.20)
Other diseases	4	3.0(2.2)	0.34(1.10)	0.06(0.14)
All male patients	21	3.3(2.0)	0.62(0.81)	0.10(0.14)
All female patients	9	3.0(3.1)	0.29(0.37)	0.06(0.06)

[a] Elimination half-life; [b] Apparent volume of distribution at steady-state ; [c] Total body clearance

Table 4. Comparison of vancomycin pharmacokinetic parameters of pediatric patients in different studies

Underlying disease	[†]Age (years)	[‡a] t1/2 (h)	[‡b]Vd (L/kg)	[‡c]CL (L/kg/h)	Reference
Heart diseases	<2	4.5±0.6	0.56±0.07	0.24±0.11	Current study
Heart diseases	<2	5.8±0.4	0.41±0.03	0.05±0.003	6
Heart diseases	2-10	2.9±0.5	0.51±0.13	0.12±0.02	Current study
Heart diseases	2-10	5.6±0.2	0.42±0.03	0.05±0.05	6
Malignancy	6±4.7	10.5±1.4	0.62±0.06	0.11±0.02	21
Malignancy/Hematologic	7.8±1.8	4.6±1.6	1.24±0.66	0.18±0.06	Current study
Not stated	6.9±3.0	3.5±0.8	0.63±0.06	0.13±0.01	28
Critically care	<2	6.1 (2.7-17.5)	0.68 (0.50-1.06)	0.08	27
Critically care	>2	4.9 (3.6-15.4)	0.69 (0.39-1.20)	0.10	27
Critically care	5.4±2.0	3.3±0.5	1.06±0.40	0.21±0.08	Current study

[a] Elimination half-life ; [b] Apparent volume of distribution at steady-state ; [c] Total body clearance
[†] Values are either mean ± SD or range (in parentheses) ; [‡] Values are either mean ± SE or range (in parentheses)

Table 5- Summary of pharmacokinetic parameters calculated for all patients of the study

	Vd (L/kg)	CL (L/kg/hr)	t1/2 (hr)
Mean	0.76	0.13	3.7
Standard error of mean	0.17	0.02	0.4
Upper 95% confidence limit of mean	1.10	0.17	4.6
Lower 95% confidence limit of mean	0.43	0.09	2.9
Upper quartile	0.86	0.16	4.4
Median	0.53	0.10	3.3
Lower quartile	0.25	0.05	2.4
Centile 95	2.86	0.30	6.9
Centile 5	0.07	0.02	1.5

individualization of vancomycin dosing regimens by measurement of concentrations provides more accurate dosing in neonatal and pediatric populations (5, 14, 15).

Individualization of serum vancomycin concentration is more important in patients receiving concurrent aminoglycosides, dialyzing patients and those with rapid change in renal function (16). Also burn patients (17-19), neonates, and pediatric patients with cancer or heart disorders require monitoring when they are on vancomycin therapy (20-23). Therefore the underlying disease for which the children are hospitalized is an important factor to cause the serum concentration of vancomycin to be out of the target range. In this study 35.5% of patients had heart problems for which many of them were using drugs like furosemide or inotrops, dopamine or dobutamine. It has been shown that there is a significant correlation between the total daily furosemide dose and the V_d and it appears that large doses of furosemide could reduce the V_d in this population (5).Also, drugs with important hemodynamic effects like inotrops may enhance vancomycin clearance by improving cardiac output and/ or renal blood flow (24). In comparison with a reported study (5), higher values of clearance and volume of distribution were observed in our study. However, these differences could not be considered statistically significant except for that of vancomycin half-life in patients older than 2 years. Smaller values of vancomycin volume of distribution and clearance in cardiac diseases patients could result in the observed differences in vancomycin trough concentrations as compared to those patients with hematological disorders and critically ill patients in the current study.

The result of a study (21) has shown a significant lower half -life and higher clearance in the patients with different types of malignancies compared with control patients. Although resulting values for volume of distribution obtained for vancomycin is comparable to other similar studies, the observed mean half-life was two times greater than those reported in other investigations. Similar to results of the reports, patients with hematological malignancies in this study showed shorter elimination half-life. (21).

The wide inter-individual variability of vancomycin pharmacokinetics in intensive care unit patients who were treated with drugs such as dopamine and /or dobutamin and /or furosemide to improve hemodynamics suggests that the estimated creatinine clearance is not always considered as an accurate predictor of vancomycin clearance. In fact , some patients co-treated by drugs effective on hemodynamic, require much higher vancomycin dosages than those estimated on the basis of only creatinine clearance and the possibility of having a sub-therapeutic serum vancomycin concentrations should be considered when these drugs are co-administered (24). Larger apparent volume of distribution is another explanation for obtaining lower values of vancomycin serum levels (even sub-therapeutic) than expected in the critically ill patients of this study.

The study of Llopis-Saliva and colleagues (25) also verifies that volume of distribution seems to be larger in ICU patients. In this study, ICU patient showed higher Vd and clearance than the patients in other disease groups, however in most cases, large inter individual variability (particularly in critically ill patients) resulted in differences that could not be considered statistically significant.

The significant difference observed in vancomycin volume of distribution between male and female patients in the current study could be due to the fact that most of the female patients had various types of cardiac diseases. Another reason for importance of individualization of vancomycin dosage regimen in our patients is that, 31/62 (50%) and 25/62 (40%) of the patients were on nephrotoxic or ototoxic drugs together, respectively. When vancomycin trough or peak concentration increases, synergistic renal- or oto-toxicicity of vancomycin with these drugs also increases, respectively (26).

CONCLUSION

In summary, design of vancomycin dosage regimens based on the recommended methods and guidelines in the literature could not lead to desired therapeutic serum concentrations in our pediatric population. Large variation in vancomycin pharmacokinetic parameters observed among population of this study along with the difference of vancomycin pharmacokinetics between patients of this and others similar studies further explain the need for individualization of vancomycin administration.

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