IJBPAS, March, 2018, 7(3): 391-405

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

POPULATION PHARMACOKINETICS OF VANCOMYCIN IN SAUDI PATIENTS

MISFER HADI ALSALOM [1, 2], HAMID ZENTOU[*3], MOHAMED SALAH OMAR[4]

1: Department of pharmaceutical sciences, Riyadh Colleges of Dentistry & Pharmacy, KSA

2: Pharmacy department, Habuna General Hospital, Ministry of Health, KSA

3: Department of Chemical and environmental engineering, UPM,Serdang 43400, Malaysia

4: Department of Microbiology in Riyadh Colleges of Dentistry & Pharmacy, KSA

***Corresponding Author: E Mail: hamidzen@gmail.com; Tel: +60192576419**

Received 2nd Oct. 2017; Revised 5th Nov. 2017; Accepted 15th December 2017; Available online 1st March 2018

ABSTRACT

The present work aims to study the pharmacokinetics parameters of vancomycin in Saudi patients, also to develop new equations for the prediction of these parameters from the population data based on their lab data. Data were coded individually, and analyzed as a single cohort or with stratification by the gender, age, and age group. The statistical software SPSS 22 was used for all analyses. 131 patients met the inclusion criteria and their data were analyzed in this study. The patients' sample comprised 83 males (63.4%) and 48 females (36.6%). The mean age was 44.0±27.5 years (mean±SD) with an age range of 0.5-86 years. The mean weight of patients was 60.8±31.2 kg (range, 3-176 kg) and mean height 140.3±42.0 cm (range, 30-185 cm). The dosing rate of vancomycin in these patients was 11.74±89.24 mg/hr (range, 1.83-562.5 mg/hr, n=131). These is no statistically significant difference between newborn-infant group in k_{el} (t-test, p=0.408). Although the half-life of vancomycin in newborns and infants was almost double its respective value in children, the difference was statistically insignificant (t-test, p=0.154). There is no significant difference in V_d between the two groups (newborn/infant & children) (t=0.681, p=0.509). When V_d was normalized to body weight as usually reported in population pharmacokinetics, the difference stayed insignificant (t=1.86, p=0.087). The lack of insignificant difference may be due to the assumption of normality of calculated data. The small

sample of newborns, infants and children may render the data non-normally distributed; hence t test may not be the appropriate choice for this analysis.

Keywords: Vancomycin, Saudi , patients ,population , pharmacokinetics , model

1. INTRODUCTION:

Population pharmacokinetic can be defined as the study of variability in the plasma drug concentration between individuals when standard dosage regimens are administered [1]. This model consists of the collection of pharmacokinetic parameter estimates in a given patient population which provides the means to store past experience with behaviors of drugs, and apply it to the care of future patients [2].

Population pharmacokinetic seeks to identify the extent of these changes so that if such changes are associated with clinically significant shift in the therapeutic index, dosage can be appropriately modified [2]. Vancomycin, an antibiotic with glycopeptide structure, is one of a few antibiotics available to treat patients infected with methicillin-resistant *Staphylococcus aureus* and methicillin resistant coagulase-negative *staphylococcal* species. Vancomycin is used only for the treatment of antibiotic *pseudo membranous* colitis, which is caused by a toxin produced by *Clostridium Difficile*, a spore-forming, G (+) obligate anaerobic bacillus (in absence of oxygen). Its' pharmacokinetics could be changed by the patient conditions such as renal function [3] age [4], body weight [5], critical illness [6], type of dialysis [7] and type of infection [8]. According to (Freeman *et al*., 1993) following the widespread appearance and increasing prevalence of MRSA, the worldwide usage of vancomycin has increased tremendously [9]. It is bactericidal to most susceptible Gram (+) bacteria at levels 0.5 - 3 mg/L (MIC). *Staphylococci* including *ß*-lactamase producing and methicillin resistant species are killed at levels <10 mg/L (MIC). Resistant mutants are very rare, except for vancomycin resistant *enterococcus*. The emergence of vancomycin-intermediate susceptible and vancomycin-resistant pathogens [10]. Vancomycin kills bacteria mainly by inhibiting bacterial cell wall synthesis. However, it also damages the bacterial cell membrane and interferes with bacterial RNA synthesis. Approaches to dosing of vancomycin include empirical dosing [10] and dosing by monograms [11, 12]. *S aureus* quickly developed resistance to early antibiotics. It is mode of action of vancomycin that inhibits the polymerization

of peptidoglycan (an essential component of the bacterial cell wall), is the drug of choice for MRSA isolates. 17 Vancomycin is less bactericidal against MSSA than are β-lactam agents, and vancomycin has been associated with clinical failure in treatment of MSSA infections [13]. Vancomycin was first approved by the Food and Drug Administration in 1958, and resistance first emerged in coagulase-negative *staphylococci* in 1987 [14]. In 1996, the first clinical isolate of *S aureus* with reduced susceptibility to vancomycin was identified in Japan [15]. Risk factors for infection with *S aureus* with reduced vancomycin susceptibility include antecedent vancomycin use and prior MRSA infection [16]. Therapeutic drug monitoring (TDM) is defined as the clinical laboratory measurement of a chemical parameter and, with appropriate interpretation will directly influence prescribing procedure [17]. It is unnecessary to employ TDM for the majority of medication. TDM is used mainly for monitoring drugs with narrow therapeutic index, which are known to cause therapeutic and adverse effect at the same time, drugs with marked pharmacokinetic variability and also have difficult monitoring of target concentration [18]. Early reports regarding the possibility of nephrotoxicity and ototoxicity had led a concern about the use of vancomycin and its serum concentration monitoring [19]. This aims to study the pharmacokinetics parameters of vancomycin in Saudi patients to develop new equations for the prediction of these parameters from the population data based on their lab data.

2. MATERIELS AND METHODS

2.1 Study design:

After receiving approval from an Institutional Review Board (IRB) at King Saud University, the study was conducted prospectively at King Khalid University Hospital (KKUH), Riyadh, Kingdom of Saudi Arabia, from September 5, to October 26, 2014. One-hundred thirty one patients, newborns and adults (79 males and 45 females) who were treated with vancomycin with complete data regarding dosage regimens, serum drug concentration, and precise timing of dose administration and blood sampling over the entire course of vancomycin therapy for different infections enrolled in the study. Patient is included in the study if: he/she received vancomycin as treatment or prophylaxis within the indicated period or is not suffering from other diseases and not on a chronic therapy for diseases such as epilepsy or diabetes, etc. The cases of pregnant women, outpatients, non-Saudis, allergic or hypersensitive to vancomycin and

patients on chronic therapy for other ailments were excluded from the study.

2-2. Data collection:

It was done retrospectively using a data collection form. Pertinent patient information and parameters of vancomycin therapy were recorded and included demographic data (age, gender, body weight, height, IBW, BMI, BSA and diagnosis), serum creatinine, BUN and vancomycin treatment parameters (dose, dosing interval, sampling time, infusion time, peak and trough or random serum concentration (LEVEL). The information required to complete the data collection form was obtained from the TDM, patient records and from pharmacokinetic lab in the hospital.

2. 3. Pharmacokinetic analysis

Individual vancomycin pharmacokinetic parameters including elimination rate constant (k_{el} , hr^{-1}), elimination half-life ($t_{1/2}$, hr), apparent volume of distribution (Vd, L/kg) and total body clearance (CL, L/h.kg) was determined assuming a one-compartment model using two serum vancomycin concentrations and taking into account to have constant pharmacokinetics in patients who had both peak and trough measurements using the following equations:

$$\mathbf{k_{el} = \frac{\ln (C_{ss}^{max} / C_{ss}^{min})}{\Delta t}} \quad \text{(eq. 1)}$$

$$\mathbf{t_{½} = \frac{0.693}{k_{el}}} \quad \text{(eq. 2)}$$

$$\mathbf{CL = k_{el}.V_d} \quad \text{(eq. 3)}$$

$$\mathbf{V_d = \frac{D(1 - e^{-k_{el}\tau_{in}})}{k_{el}.\tau_{in}(C_{ss}^{max} - C_{ss}^{min}.(e^{-k_{el}\tau_{in}})}} \quad \text{(eq. 4)}$$

In which $\mathbf{k_{el}}$ is the elimination rate constant (in hr^{-1}), ($\mathbf{C^{max}}$) is the peak concentration in mg/L and (C^{min}) is trough concentrations in mg/L at steady-state as described above, V_d is apparent volume of distribution at steady state in L/kg, (D) is the dose of vancomycin administered in mg/kg, Δt is the time interval (hr) between measured peak and trough concentration and τ_{in} (hr) is the infusion time (duration of infusion) which will be set at 1 hour.

roF adolescent, adult and elder patients $\mathbf{k_{el}}$ was calculated using the following population equation (Matzke): $\mathbf{k_{el} = 0.00083\ CL_{cr} + 0.0044}$ (eq. 5)

Where **CLcr** is the creatinine clearance (mL/min).

The creatinine clearance for adolescent, adult and elder patient was calculated by Cockroft and Gault formula as follows:

$$CL_{cr\ (males)} = \frac{(140 - Age)W}{72\ S_{cr}} \qquad \text{(eq. 6)}$$

$$CL_{cr\ (females)} = CL_{cr\ (males)} \times 0.85 \qquad \text{(eq.7)}$$

Where age is in years, W is the weight (kg) and S_{cr} is the serum creatinine concentration (mg/dL).

For pediatric patients (newborns, infants and children), creatinine clearance was be calculated using Schwartz formula:

$$CL_{cr} = \frac{0.55\ L}{S_{cr}} \qquad \text{(eq. 7)}$$

Where L is the length of the patient (cm) and S_{cr} is the serum creatinine concentration (mg/dL).If S_{cr} will be provided in µmole/L units, it will be converted to mg/dL units through multiplying by the conversion factor of (0.0113).

2.4. Moral confirmation:

The present study was approved by the Institutional Review Board & Ethical Committee of Riyadh Colleges of Dentistry & pharmacy (RCsDP)

2-5.Statistical analyses: Data were coded individually, and analyzed as a single cohort or with stratification by the gender, age, and age group. The statistical software package SPSS 22 was used for all analyses (IBM Corp. Released 2014. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) Descriptive statistics including numbers and percentages for categorical variables and mean and standard deviations (SD) for continuous variables were calculated. The level of significance for all tests was set at 0.05. Results were analyzed and, depending on the type of data, appropriate statistical tests were used for comparisons (e.g., an independent t-test was used to compare continuous variables such as age). For data that were not normally distributed, either the Wilcoxon rank sum or Mann-Whitney U test was used. The chi-square and Fisher exact tests were used to assess the differences in case of discrete variables. Agreement among responses of physicians was assessed using the Kendall-tau rank correlation, Spearman rho test and kappa statistic. Additional analyses (e.g., analysis of variance and Kruskal-Wallis tests) were used when appropriate. If the question of data normality arose (based on a probability plot, Shapiro-Wilk test and/or Kolmogorov-Smirnov test), log-transformed

data were used followed by a parametric test. Otherwise, a nonparametric alternative was used. Homoscedasticity and heteroscedasticity were tested by both plotting the residuals and Breusch-Pagan test. Pearson or Spearman correlation coefficients were also utilized to investigate the correlation between variables of interest. One-way analysis of variance was performed for testing any significant difference between the pharmacokinetic parameters as a function of age groups with Scheffe, Duncan or Student-Neuman-Keuls as post hoc tests.

3. RESULTS AND DISCUSSION

One-hundred thirty one patients met the inclusion criteria and their data were analyzed in this study. The patients' sample comprised 83 males (63.4%) and 48 females (36.6%). The mean age was 44.0±27.5 years (mean±SD) with an age range of 0.5-86 years. The mean weight of patients was 60.8±31.2 kg (range, 3-176 kg) and mean height 140.3±42.0 cm (range, 30-185 cm). Table 1 shows the distribution of age, weight and height as a function of gender.

Patients were classified according to their age into 5 age groups, namely, newborns (0-2 months), infants (2 months -2 years), children (2-12 years), adolescents (13-19 years), adults (20-65 years) and elders (over 65 years). The age distribution in these groups is reported in Figure (2).

The ideal body weight for these patients averaged 56.76±11.77 kg (mean±SD) with a range of 14-80 kg, and the body mass index (BMI) was found to be 26.66±5.63 kg/m2 with a range of 15.8-46.5 kg/m2. It is noteworthy to mention that BMI was only calculated for those patients who are older than 18 years of age. A new variable was created using BMI called obesity where patients were classified into 6 groups according to their calculated BMI. Table 2 shows the distribution of patients according to variable obesity.

Vancomycin is prescribed in case of infections in all hospital wards. Figure 2 shows the wards from which our present sample was originated.

Serum creatinine concentration (S_{Cr}) in these patients averaged 125.64±144.07 μmol/L (range, 10-815 μmol/L) or 1.43±1.63 mg/dL (range, 0.11-9.21 mg/dL). The creatinine clearance (CL_{cr}) was calculated using Cocroft and Gault method for adults or Schwartz formula for pediatric patients. The results of creatinine clearance in our sample of patients are reported in table 3.

In the present study, we have observed that, there was no statistically significant

difference in $\mathbf{CL_{cr}}$ between males and females (t-test, p=0.328).

Vancomyin concentration demonstrates no change in the incidence (30%) of levels at sub therapeutic values (< 5µ g/mL) between the compared years. Furthermore, therapeutic levels (10µg/mL<) [20]. On contrast, there was an extremely significant difference in $\mathbf{CL_{cr}}$ between the patients with respect to their age groups (ANOVA, p<0.0001). Scheffe and Tukey post hoc tests of ANOVA showed that the source of this difference was originated from the adults group whereas all other groups are similar to each other (Figure 3).

In the present study also we were investigated the degree of renal impairment in these patients. The results of this classification on our sample of patients are shown on figure 4.

Most of the patients in the study sample were suffering from mild to moderate renal impairment. There is no way to ascertain how chronic is the degree of renal impairment in these patients due to the lack of data regarding proteinuria, BUN and baseline values of creatinine clearance just before hospitalization. In the present data, no statistically significant differences between males and females in the degree of chronic kidney disease (Chi-square test, p=0.865). The dosing rate of vancomycin in these patients was 11.74±89.24 mg/hr (range, 1.83-562.5 mg/hr, n=131). All vancomycin concentrations were considered at steady state due to the short half-life of the drug. The minimum serum concentration of vancomycin (C_{ss}^{min})) (i.e., trough level) and its maximum serum concentration (C_{ss}^{max}) (i.e., peak level) were only monitored in newborns, infants and children. Therefore, our trough and peak levels only represent these patients. In adolescents, adults and elders, peak level is not monitored and only trough is reported. In newborns and infants combined trough and peak levels were found to be 14.09±7.74 mg/L (range, 1–38 mg/L, n=131) and 24.68±13.51 mg/L (range, 2–66 mg/L, n=21), respectively. These values, on the average, were within the normal reported values in literature where normally the trough level is between 5-15 mg/L and peak level is between 30-40 mg/L. The lowest values of trough concentrations was observed in adolescents compared to other age groups and the highest trough levels, on the average, were observed in elder groups. This observation is logical since the renal function in elders is usually lower than that in other age groups and the result is consistent with the fact that vancomycin is predominantly eliminated via the renal route (Figure 4).

Calculation of Elimination rate constant (k_{el}) of vancomycin and the half-life ($t_{1/2}$) of the drug:

The elimination rate constant (k_{el}) was calculated from the slope of the decline of the serum concentration vs. time curve for 21 patients since only peak and trough were monitored in these patients. Most of the patients have only trough value. Both peak and trough together were monitored in newborns, infants and children. In adults and elders only trough level was monitored. The average el k value observed in these 21 patients was 0.1349±0.074 hr^{-1} and the half-life ($t_{1/2}$) of the drug averaged 7.52±5.9 hr. Table 4 shows the calculated values for the elimination rate constant and half-life in these patients.

In the present data, we have noted that, There was no statistically significant difference between newborn-infant group in k_{el} (t-test, *p*=0.408). Although the half-life of

vancomycin in newborns and infants was almost double its respective value in children, the difference was statistically insignificant (t-test, *p*=0.154). Numerous studies have shown that a high percentage of TDM tests may provide inaccurate information because of improper collection furthermore, the TDM tests may lead to inappropriate dosage adjustments or over ordering of tests [23,29] In the present data for adolescents, adults and elders k_{el} was predicted from creatinine clearance values using Matzke equation (eq. 5) exploiting the creatinine clearance **(K_{el}□□0 00083CL_{cr} □□0.0044).** Additionally, for the sake of comparison, **k_{el}** was predicted for newborns, infants and children. Table 7 shows the predicted k_{el} and $t_{1/2}$values for all age groups.

Paired t-test shows that there is a statistically significant difference between the calculated and predicted $t_{1/2}$ and k_{el} values and in newborns and infants (t=3.639, p=0.007 for $t_{1/2}$) and (t=3.476, p=0.008 for k_{el}). for other investigators, several studies in the past decades evaluated the utilization of vancomycin in hospitalized adults and pediatric patients, the investigators reported up to 65% inappropriate use of vancomycin based on institution specific recommendations [22-28]. Similarly, paired t-test proved to be extremely significant between the calculated and predicted t in children (t=4.869, p<0.0001). the discrepancy between the calculated and predicted 48 values of half-loves and k_{el} could have arisen from the fact that Matzke equation may not be suitable for the prediction of half-lives in Middle Eastern subjects since it was derived from data taken from Caucasian patients or it may be due to

the small sample size of newborns, infants and children in this study. To clarify this difference in k_{el} between age groups, Tukey post hoc test was performed. The correlation between the predicted and the calculated is weak (Pearson correlation coefficient r=0.126). To compare the difference between the various age groups regarding the predicted half-lives, ANOVA test was performed which proved that the difference is statistically significant (F=5.568, p<0.0001).

To illustrate the difference between the calculated and the predicted values of K_{el} and $t_{1/2}$ f for newborns, infants and children, the predicted values were plotted as a function of the calculated values as shown in figure 6 and figure 7 respectively.

Table (1): Demographic characteristics of patients' sample as a function of gender.

	Mean±SD (Range) (n)			p-value (Sig)
	Males	Females	Total	
Age(Years)	46.3 ± 27.9 (0.5 – 85) (n=79)	40.1 ± 26.5 (0.5 – 85) (n=45)	44.0 ± 27.5 (0.5 – 86) (n=124)	0.231* (NS)
Weight(Kg)	62.4 ±30.6 (3 – 147) (n=83)	57.9±32.3 (4 – 176) (n=8)	60.8± 31.2 (3 – 176) (n=131)	0.427* (NS)
Height(Cm)	144.9±42.1 (31 – 185) (n=83)	132.2 ±41.0 (30 – 170) (n=48)	140.3±42.0 (30 – 185) (n=131)	0.096* (NS)

NS=Not significant; * Student's t-test for independent samples; There were no statistically significant differences in age, weight or height between males and females (p>0.05)

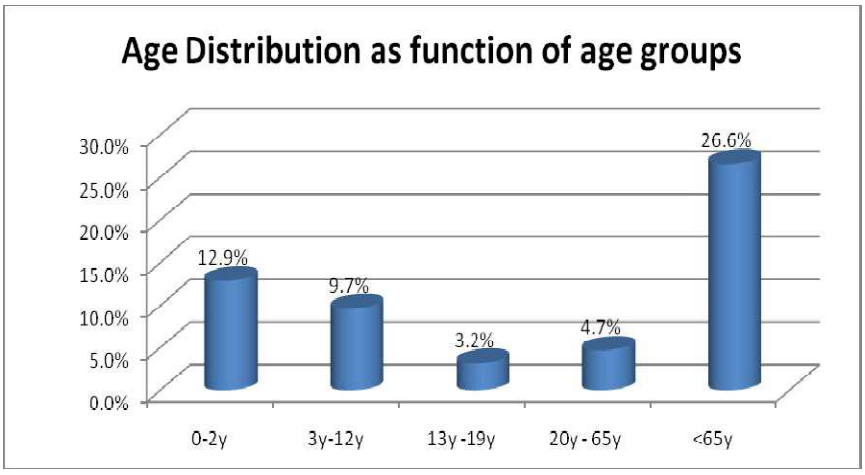


Figure 1: Age distribution as function of age groups

Table (2): Obesity variable

Group	N%	Group	N%
Underweight (BMI<18.5)	5(5.3)	Obese class 1 (BMI=30-35)	11 (11.7)
Normal (BMI=18.5 – 24.9)	33 (35.1)	Obese class 2 (BMI=35 – 40)	7 (7.4)
Overweight (BMI=25 – 30)	35 (37.2)	Morbidly obese (BMI>40)	3(3.2)

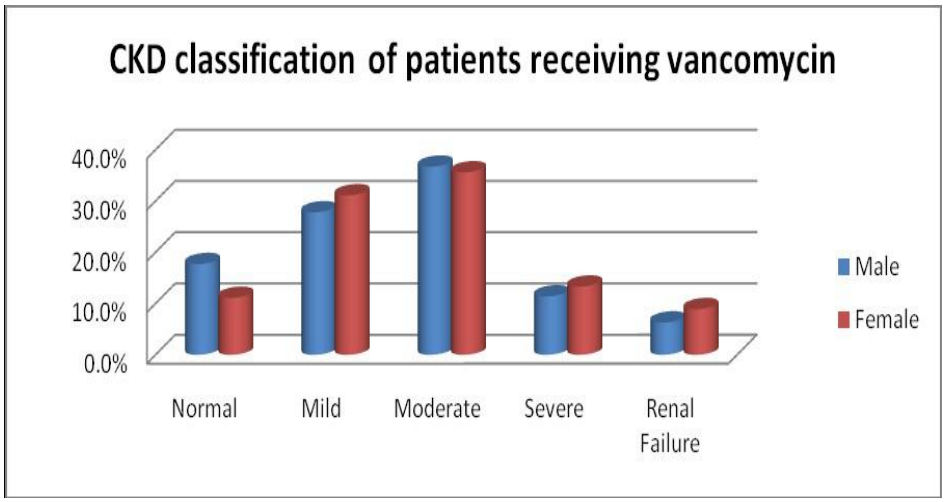


Figure 2: The hospital wards in which vancomycin were prescribed for patients in this study

Table 3: Creatinine clearance as a function of age group in patients receiving vancomycin

Age group	Creatinine Clearance (ml/min) Mean ± SD	
	Males	Females
Newborns &Infants	34.5±11.8	33.2±8.9
Children	58.5±23.5	65.1±20.0
Adolescent	72.6±28.2	81.4
Adults	78.4±30.9	65.5±31.0
Elders	40.2±17.9	26.6±11.8
Total (gender)	53.7±29.8 (n=45)	59.3±30.9 (n=79)
Total	57.3 ± 30.9 (n=124)	

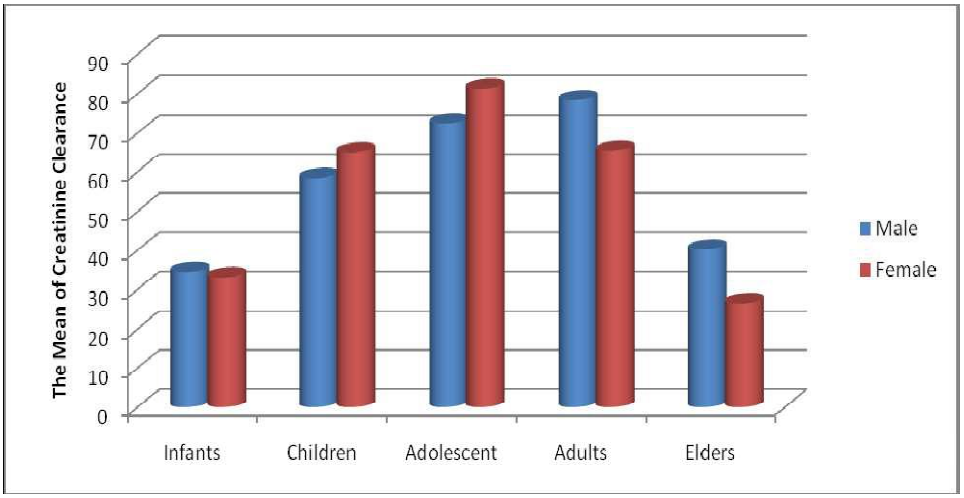
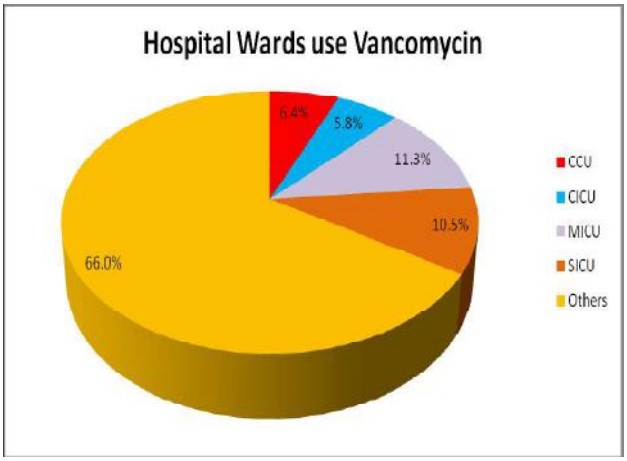


Figure 3: Creatinine clearance as a function of age group in patients receiving vancomycin



Figuer 4: (CKD) classification of patients receiving vancomycin

Table 4: Elimination rate constant and half-life in newborns, infants and children.

puorg egA	$k_{el\ (hr^{-1})}$	$t_{1/2(hr)}$
Newborn sand , infants	0.1243±0.076	8.97±8.04
children	0.147±0.014	4.75±0.45

Table 5: The predicted and calculated k_{el} and $t_{1/2}$values for all age groups

puorg egA	$k_{el\ (hr^{-1})}$		$t_{1/2(hr)}$	
	Calculated	Predicted	Calculated	Predicted
Newborn sand , infants	0.1243±0.076	0.0327±0.0087	8.97±8.04 (n=16)	23.56±10.47 (n=16)
children	0.147±0.014	0.0552±0.0177	4.75±0.45 (n=12)	16.11±13.73 (n=12)
Adolescents	-	0.0665±0.0194	-	11.43±4.6 (n=4)
Adults	-	0.0651±0.0259	-	13.95±10.10 (n=59)
Elders	-	0.0347±0.0145	-	25.51±16.38 (n=33)

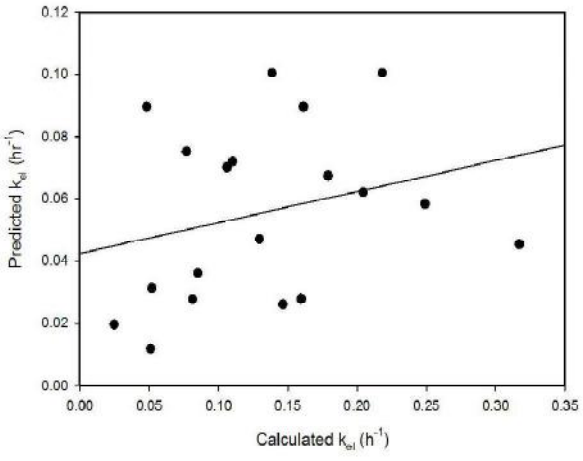


Figure 6: Predicted k_{el} as a function of calculated k_{el}

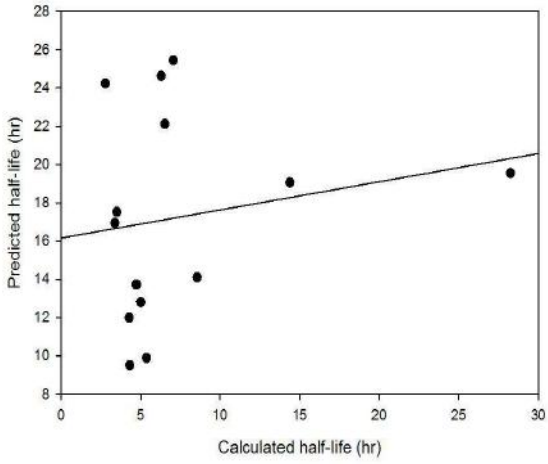


Figure 7: Predicted $t_{1/2}$ as a function of calculated $t_{1/2}$ for newborns, infants and children

4. CONCLUSION

Our results revealed the high variability in vancomycin pharmacokinetics between age groups in Saudi Arabia which is consistent with the reported values for other ethnic groups. There is a great need to monitor both the peak and trough concentrations for all age groups to properly calculate the clearance of the drug and individualize the dosing regimen for our patients. We also concluded that the comparison between various factors affecting vancomycin administration is closely dependent on patient's characteristics.

It was proved that the difference is statistically significant. There is no significant difference in volme distribution between the two groups (newborn/infant & children).

It is recommended that the physicians prescribing the drug should be educated about the pharmacokinetics of this medication. They should learn how to calculate the pharmacokinetic parameters including the elimination rate constant and the clearance of the drug to enable them to tailor the appropriate dosage regimen in order to avoid the dangerous side effect of this medication. A more elaborate study in Saudi patients with a larger sample size and wider spectrum of ages to investigate the various pharmacokinetic aspects of vancomycin is highly recommended.

ACKNOWLEDGEMENT

The authors would like to thank Saudi Ministry of Health for the support and provided facilities.

5. REFERENCES

[1] Aarons,L., Population Pharmacokinetics: Theory and Practice, Br J Clin Pharmacol 1991; 32: 669-670.

[2] Jelliffe R, Schumitzky A, Van Guilder M, *et al*.: Individualizing Drug Dosage Regimens: Roles of Population Pharmacokinetic Models, Bayesian Fitting, and Adaptive Control. Ther. Drug Monit., 15.

[3] Ohnishi. A, Yano .Y, Shimamura. K, and Oguma .T, Evaluation of Bayesian predictability of vancomycin concentration in patients with various degrees of renal function, Biological and Pharmaceutical Bulletin, vol. 24, no. 12, pp. 1446–1450, 2001.

[4] Matzke G. R, Zhanel G. G , and Guay D. R. P , Clinicalpharmacokinetics of vancomycin, Clinical Pharmacokinetics, vol. 11, no. 4, pp. 257–282, 1986.

[5] Bauer L. A, Black D. J, and Lill J. S, ―Vancomycin dosing in morbidly obese patients,‖ European Journal of Clinical Pharmacology, vol. 54, no. 8, pp. 621–625, 1998.

[6] Llopis-Salvia. P, and Jim´enez-Torres N. V, ―Population pharmacokinetic parameters of vancomycin in critically ill patients, Journal of Clinical Pharmacy and Therapeutics, vol. 31, no. 5, pp. 447–454, 2006.

[7] Launay-Vacher .V., Izzedine. H., Mercadal. L., and Deray. G., ―Clinical review: use of vancomycin in haemodialysispatients, Critical Care, vol. 6, no. 4, pp. 313–316, 2002.

[8] Yamamoto M, Kuzuya T, Baba H, Yamada K, and Nabeshima T, ―Population pharmacokinetic analysis of vancomycin in patients with gram-positive infections and the influence of infectious disease type, Journal of Clinical Pharmacy and Therapeutics, vol. 34, no. 4, pp. 473–483, 2009.

[9] Freeman CD, Quintiliani R, Nightingale CH. Vancomycin therapeutic drug monitoring: is it necessary? Ann Pharmacother 1993; 27:594.

[10] Appelbaum P. C, ―Reduced glycopeptide susceptibility in methicillin-resistant Staphylococcus aureus (MRSA),‖ International Journal of Antimicrobial Agents, vol. 30, no. 5, pp. 398– 408, 2007.

[11] Matzke G. R, Kovarik J. M, Rybak M. J, and Boike S. C, ―Evaluation of the vancomycin-clearance:creatinine-clearance relationship forpredicting vancomycin dosage, Clinical Pharmacy, vol. 4, no. 3, pp. 311–315, 1985.

[12] Moellering, R.C., Jr. (2006). Vancomycin: a 50-year reassessment. Clinical Infectious Diseases, 42 Suppl. 1, S3-4, doi:10. 1086/491708.

[13] Engemann JJ, Carmeli Y, Cosgrove SE, et al. Adverse clinical and economic outcomes attributable to methicillin resistance among patients with Staphylococcus aureus surgical site infection. Clin Infect Dis 2003; 36: 592-598.

[14] Schwalbe RS, Stapleton JT, Gilligan PH. Emergence of vancomycin resistance in coagulase-negative staphylococci. N Engl JMed 1987;316:927-931.

[15] Hiramatsu K, Hanaki H, Ino T, *et al*. Methicillin-resistant Staphylococcus aureus clinical strain with reduced vancomycin susceptibility. J Antimicrob Chemother 1997; 40: 135-136.

[16] Fridkin SK, Hageman J, McDougal LK, *et al*. Epidemiologic and microbiologic characterization of infections caused by *Staphylococcus aureus* with reduced susceptibility to vancomycin, United States, 1997 – 2001. Clin Infect Dis 2003; 36: 429-439.

[17] Touw DJ, Neef C, Thomson AH, Vinks AA. Cost-effectiveness of therapeutic

drug monitoring: a systemic review. Ther Drug Monit 2005; 27: 10-17.

[18] Kang JS, Lee MH. Korean J Intern Med. 2009 Mar; 24(1): 1-10. doi: 10.3904/kjim.2009.24.1.1. Review.

[19] Iwamoto T, Kagawa Y, Kojima M. Clinical efficacy of therapeutic drug monitoringin patients receiving vancomycin. Biol Pharm Bull. 2003; 26:876-9.

[20] El Desoky, E. S., Sheikh, A.A., & Al Hammadi, A.Y. (2003). Amino-glycoside and vancomycin serum concentration monitoring and mortality due to neonatal sepsis in Saudi Arabia. Journal of Clinical Pharmacy and Therapeutic, 28 (6), 479-483.

[21] Morrison, A.P., Melanson, S.E., Carty, M.G., Bates, D.W., Szumita, P.M., & Tanasijevi, M.J. (2012). What proportion of vancomycin trough levels are drawn too early?' frequency and impact on clinical actions. American Journal of Clinical pathology, 137(3), 472-478. Doi: 10. 1309/ Ajcpdsysodvlkfoh.

[22] Traugott, K.A., Maxwell, P.R., Green, K., FreiC.,& Lewis, J.S., 2nd (2011). Effects of therapeutic drug monitoring criteria in acomputerized prescriber-order-entry system on the appropriateness of vancomycin level orders.American Journal of Helth-System Pharmacy, 68(4), 347-352.doi:10.2146/ajhp090661.

[23] Askarian, M., Assadian, O., Safaee, G., Golkar, A., Namazi, S., & Movahed, M.R. (2007). Vancoycin use in a large teaching hospital in Shiraz, Islamic Republic of Iran. 2003. Eastern Mediterranean Health Journal, 13(5), 2007.07.011.

[24] You, J. H., Lyon, D. J., Lee, B. S., Kwan, S.M., & Tang, H.Y. (2001). Vancomycin utilization at a teaching hospital in Hong Kobg. American Journal of Health-System Pharmacy, 58 (22), 2167-2169.

[25] Drinkovic, D., Taylor, S. L., Pottumarthy, S., & Morris, A. (1999). Prospective vancomyin audit in Auckland healthcare hospitals. The New Zealand Medical Journal, 112 (1095), 336-339.

[26] Evans, M.E., &Kortas, K.. (1996). Vancomycin use in a university medical center; comparison with hospital infection control practices advisory committee guidelines. Infection Control and Hospital Epidemiology, 17(6), 356-359.

[27] Johnson, S.V., Hoey, L. L., & Vance-Bryan, K. (1995). Inappropriate vancomycin presccribing based on criteria from the Centers for Disease Control and Prevention. Pharmacotherapy, 15 (5), 579-585.

[28] Wright, S. W., & Wrenn, K.D. (1998). Appropriateness of vancomycin use in the emergency department. Annals of Emergency Medicine, 32(5), 531-53.