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Research Article

# COMPARISON OF VANCOMYCIN PHARMACOKINETIC PARAMETERS BETWEEN A SPECIALIZED CARE ASIAN COHORT AND PUBLISHED WESTERN DATA

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**ABSTRACT**

Individualization of vancomycin therapy through pharmacokinetic approach is deemed to be significant. Published data on vancomycin pharmacokinetic parameters for the specialized care Asian population is limited. The aim of this study was to compare vancomycin pharmacokinetic parameters estimated for a specialized care Asian population and previously published Western data. The study cohort included 37 subjects with 38 sets of vancomycin peak-trough concentrations. The nature of study was a retrospective audit of data routinely collected for Therapeutic Drug Monitoring service. A one-compartment pharmacokinetic model was used to estimate the clearance (CL) and volume of distribution ($V_d$) of vancomycin. The CL and $V_d$ of vancomycin were estimated as 68.6±36.7 ml/min and 1.04±0.66 L/kg, respectively. A significant relationship was demonstrated between the CL of vancomycin and age ($r^2 = 0.614$, $p<0.05$) and also serum creatinine ($r^2 = 0.269$, $p<0.05$). The $V_d$ of vancomycin was not associated with any of the variables tested; namely, age, gender, weight and serum creatinine (all $p>0.05$). No significant difference was demonstrated for the CL of vancomycin between the present study and the published Western data. The $V_d$ of vancomycin showed significant different between studies which may be due to study setting differences. The published data for vancomycin pharmacokinetic parameters from the Western population are comparable with the local data and acceptable for clinical used in our population.

**Keywords:** Vancomycin, Pharmacokinetics, Clearance, Distribution volume.

## INTRODUCTION

Vancomycin inhibits cell-wall synthesis and has a narrow spectrum of activity[1]. It is commonly indicated for gram-positive related infections, such as those caused by methicillin-resistant *Staphylococcus aureus* and coagulase negative Staphylococcus. Serum vancomycin concentrations are monitored to minimize the risk of the development of microorganism resistance, and to avoid potential concentration-dependent adverse events[2]. Although vancomycin did not exhibit a concentration-dependent bactericidal effect[3], maintaining the trough concentrations above the minimum inhibitory concentration is crucial[4]. As such, understanding the vancomycin pharmacokinetics would be an important step in optimizing its dosage regimen.

Vancomycin pharmacokinetics can be influenced by various factors[2]. Patients who receive specialized care such as in the Intensive Care Unit and Cardiac Care Unit are known to show variation in the pharmacokinetic parameters. Individualization in the initiation and maintenance of vancomycin therapy is deemed to be significant. The pharmacokinetic parameters that are used to adjust the vancomycin dosage regimen can be derived by several approaches; for example, manual calculation or computer-aided software such as NONMEM®. Based on the software approach, vancomycin pharmacokinetics has been demonstrated to follow the two- or three-compartment model[5,6]. These multiple-compartment models are difficult to determine by using the manual calculation approach. In local practices, due to access issues and convenience, vancomycin dosage adjustment is routinely based on the one-compartment model by using the Sawchuck-Zaske equation[7]. This simple model allows the use of a calculator or manual calculation to estimate the vancomycin pharmacokinetic parameters. In addition to this, our local patient's pharmacokinetic parameters are always compared with published data pooled from Western populations[8,9,10,11].

Based on the published data and local practice experiences, we were prompted to evaluate the values of vancomycin pharmacokinetic parameters derived from the manual calculation. Hence, the aim of this study was to compare vancomycin pharmacokinetic parameters estimated for our local specialized care population and previously published Western data. Our hypothesis was that vancomycin pharmacokinetic parameters derived for our local specialized population by a manual calculation would be similar when compared with the published data.

## METHODS

The study has been approved by the Universiti Kebangsaan Malaysia Medical Research Ethic Committee (UKM1.5.3.5/244/SPP/NF-001-2011). The cohort of this study included 37 subjects. Informed consent was not required since this was a retrospective audit of data routinely collected by the pharmacists in the Universiti Kebangsaan Malaysia Medical Centre. Data were reported anonymously in accordance with ethical guidelines. The pharmacists were asked to select data only from patients who were admitted to the specialized care units (the Intensive Care Unit, Cardiac Care Unit and High Dependency Unit) between January 2008 and December 2009. These data only include age, gender, body weight on the first day of admission, height, dosage regimen of vancomycin, serum creatinine, and at least one set of vancomycin peak and trough concentrations. The set of concentrations was taken at steady-state which was after at least 24-hour post administration of the initial dose or dosage adjustment. The blood sampling time was noted by the nurse and followed the recommended guideline of therapeutic drug monitoring practice in the medical centre. The peak vancomycin concentration was sampled 1 hour-post of 1 hour infusion, and the trough vancomycin concentration was sampled just before the next dose. None of the subjects received any form of renal replacement therapy before or while the blood samples were taken.

The pharmacokinetic parameters of vancomycin were estimated by using first-order kinetics with one-compartment model. The parameters estimated include the constant rate of elimination ($K_e$), the volume of distribution ($V_d$) and the clearance (CL). The $V_d$ was calculated by using the Sawchuck-Zaske equation[7,12]. The $K_e$ and CL were estimated using the following equations:

$$K_e\ (hr^{-1}) = (\ln C_{peak} - \ln C_{trough}) / t_{peak\text{-}trough}$$

$$CL\ (L/hr) = K_e \times V_d$$

Statistical analyses were performed using the SPSS software version 15.0 (SPSS, Chicago, USA). Data were summarized as mean ± SD. Univariate linear regression has been used to evaluate the relationship between several predictors and the pharmacokinetic parameters. The differences in pharmacokinetic parameters, between the present study and previously published data, were analysed using one sample t-test with two-tailed significance. A significance level of $p<0.05$ was used.

**RESULTS**

A total of 37 subjects with 38 sets of vancomycin concentrations were available for analysis. All subjects were Asian origin (Malay 40.5%; Chinese 48.7%; Indian 8.1% and other 2.7%). The background description of the studied population is presented in TABLE 1.

The estimated pharmacokinetic parameters for the present 37-strong study population are presented in TABLE 2. A difference in terms of practice settings between the present and previous studies was noted. None of the demographic and estimated pharmacokinetic parameters was significantly different with previously published findings, except for the $V_d$ value. A significant relationship was demonstrated between the CL of vancomycin and age ($r^2$ = 0.614, $p<0.05$) and also serum creatinine ($r^2$ = 0.269, $p<0.05$). The $V_d$ of vancomycin was not associated with any of the variables tested; namely, age, gender, weight and serum creatinine (all $p>0.05$).

**Table 1: shows the description of the studied population**

| Parameter | Value |
|---|---|
| Number of subjects | 37 |
| Age (years; mean±SD;) | 50.0±16.6 |
| Gender | male 62%; female 38% |
| Weight (kg; mean±SD) | 66.1±12.7 |
| Height (cm; mean±SD) | 163.5±0.1 |
| Body mass index (kg/m$^2$; mean±SD) | 26.0±4.6 |
| Serum creatinine (µmol/L; mean±SD) | 82.3±57.0 |
| Creatinine Clearance (mL/min; mean±SD)* | 74.9±25.5 |
| Total daily dose (mg/kg/day; mean±SD) | 19.4±9.2 |
| Number of concentration set (peak & trough) | 38 |

*Using Cockroft and Gault equation[10]

**Table 2: Shows comparison of vancomycin parameters between previously published studies and the present study**

| Reference | n | Setting | Age (years) | Weight (kg) | $CL_{Cr}$ (mL/min) | $CL_{vanco}$ (mL/min) | $V_d$ (L/kg) |
|---|---|---|---|---|---|---|---|
| Matzke et al. 1984[8] | 11 | Medical | 46.5±16.6 | 67.8±5.2 | 87.6±22.3 | 62.7±25.3 | 0.72±0.35* |
| Kitzes-Cohen et al. 2000[9] | 15 | Surgery | 60.0±9.0 | 79.3±12.0 | 82.0±27.1 | 78.3±32.6 | 0.65±0.15* |
| Llopis-Salvia & Jiménez-Torres, 2006[10] | 30 | ICU | 67.0±27.0 | 75.0±12.5 | 70.2±33.3 | 57.6 | 1.32* |
| del Mar Fernández de Gatta Garcia et al. 2007[11] | 46 | ICU | 59.3±16.9 | 71.5±16.9 | 65.5±48.1 | 60.0±39.7 | 1.68±2.19* |
| Present study | 37 | ICU, CCU, HDU | 50.0±16.6 | 66.1±12.7 | 74.9±25.5 | 68.6±36.7 | 1.04±0.66 |

Value is mean ± SD; n = number of subjects; ICU = intensive care unit; CCU = cardiac care unit; HDU = high dependency unit; $CL_{Cr}$ = Creatinine clearance; $CL_{vanco}$ = vancomycin clearance; $V_d$ = volume of distribution; *Significant different compared to the present study ($p<0.05$).

**DISCUSSION**

In specialized care such as critically ill patients, the vancomycin pharmacokinetic parameters are subjected to rapid alterations and show significant inter-individual and intra-individual variations[13].These changes are not only influenced the blood concentration of vancomycin, but also the efficacy. The recommended target 24-hour area under the curve per minimum inhibitory concentration (24-hr AUC/MIC) for vancomycin is up to 400 mg.h/L[2]. Achieving this recommended target is crucial in optimizing the efficacy and in minimizing the development of resistance organisms. As such, understanding the pharmacokinetic characteristics of the vancomycin is imperative. In our local practice and many other countries, dosage adjustment for vancomycin is carried out by manual calculation which followed one-compartment pharmacokinetic model. The reference pharmacokinetic parameters were based on published data from Western countries and were sometimes derived from computer-aided software and based on multiple-compartment pharmacokinetic model. Hence, there is no certainty that the manual calculation is sufficient to assist the dosage adjustment of vancomycin for our local population.

The present study has shown that age and serum creatinine concentrations are associated with the CL of vancomycin. A study by Vance-Bryan et al. has also reported similar findings[14]. It is known that vancomycin undergoes glomerular filtration as the important route of excretion. The rate of renal glomerular filtration is acceptably estimated by the creatinine clearance[15]. The significant influence of aging on the reduction of renal function is well established[16]. Beyond the age of 30 years, glomerular filtration and renal blood flow rates decline in a linear fashion. Thus, the performance of renal filtration in octagenarians may drop to at least fifty percent of those measured in young adults. In addition to this, the age associated reduction of renal mass may also contribute to higher risk of renal failure[17]. In the present study, although significant, the relationship between CL of vancomycin and CL of creatinine was moderate ($r^2$ = 0.269). This suggests that other elimination mechanisms, such as renal tubular secretion, may also be significant[18].

The influence of age, gender, weight and serum creatinine on the $V_d$ of vancomycin was evaluated in the present study. The $V_d$ of vancomycin has been reported between 0.4 – 1.0 L/kg of body weight[8,19]; thus, vancomycin may be considered as a highly water soluble drug. It is believed that body composition in term of water and fat distribution differs significantly with age. As such, age has been identified as an indirect factor that may be useful in predicting the $V_d$ of vancomycin[11,20]. In the present study, it was postulated that the $V_d$ of vancomycin will be affected by gender and body weight. This postulation was made since there is a clear different in body fat distribution between male and female[21]. It is also known that an increased body weight signifies higher fat distribution[22]. Body water content may be lower in the presence of higher adipose tissues. Nevertheless, these postulations were not proven by the present study. Several other factors may be more predominant and have diminished the effect of age, gender and weight on the $V_d$. These predominant factors may include the use of high volumes of intravenous fluids and possible renal impairment as all of the subjects were considered as critically ill[11,23].

The vancomycin pharmacokinetic parameters, namely CL and $V_d$, were compared with four other studies[8,9,10,11]. The CL of vancomycin reported in this present study did not differ significantly with these published data. This finding is expected as the CL of creatinine was also shown no significant different. CL of vancomycin is known to be positively correlated with the CL of creatinine[24]. None of the subjects have received any form of renal replacement therapy. This exclusion criterion has eliminated the extreme group of subjects with renal failure, which may demonstrate apparent limited CL of vancomycin. In addition to this, other excretion pathways may also be important[2]. As such, the Sawchuck-Zaske equation which follows the one compartment model is an acceptable approach in determining the CL of the vancomycin, especially in subjects with sufficient renal function.

The $V_d$ of vancoycin estimated in the present study, which was 1.04±0.66 L/kg, is significantly different with the published data. We speculate that differences in the study settings may have contributed to this observation. The $V_d$ value was higher than that reported by Matzke et al.[8] and Kitzes-Cohen et al.[9], and lower than that reported by Llopis-Salvia et al.[10] and del Mar Fernández de Gatta Garcia et al.[11] In Matzke et al. and Kitzes-Cohen et al. studies, the studied subjects were patients from medical and surgical settings, respectively[8,9]. On the other hand, Llopis-Salvia et al. and del Mar Fernández de Gatta Garcia et al., have employed critically ill patients as their subjects[10,11]. In general, medical and surgical settings are known to utilize less intravenous fluids compared to intensive care setting. A larger $V_d$ of vancomycin may probably resulted from aggressive fluid resuscitation in the latter setting[25]. The present study has included subjects from the Cardiac Care and High Dependency units who were less severe than those in the Intensive Care Unit but more severe than those in the medical and surgical units. This may explain the value of $V_d$ of vancomycin estimated in the present study.

As conclusion, the CL of vancomycin derived for our local population by a manual calculation was within the range of published Western data. The $V_d$ of vancomycin estimated was significantly different when compared to the Western data due to clinical setting differences. The published data for vancomycin pharmacokinetic parameters from the Western population are comparable with the local data and acceptable for clinical used in our population.

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