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# Assessment of Vancomycin Pharmacokinetic Parameters among Malaysian Adult Patients in Penang with Different Kidney Functions

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**ABSTRACT**

**Introduction:** Vancomycin is indicated for highly resistant gram-positive systemic infections. The targeted trough and 24-hour area under the concentration-time curve ($AUC_{24}$) level of vancomycin must be achieved for efficacy and safety. Local population-based pharmacokinetic parameters including the elimination rate constant ($K_e$), half-life ($t_{1/2}$), volume of distribution ($V_d$) and vancomycin clearance ($Cl_{vanco}$) can allow better vancomycin dosing determination. **Objective:** This study aims to determine the pharmacokinetic parameters in the Malaysian adult patients in Penang based on different kidney functions. **Method:** This was a retrospective, single-centered study conducted in the Clinical Pharmacokinetics Department, Penang General Hospital from 1 January 2016 to 31 December 2017. This study included adult patients who had been treated with intravenous vancomycin under therapeutic drug monitoring. The patients' personalised vancomycin pharmacokinetic parameters were determined using a series of pharmacokinetic equations. **Result:** From the recruited 26 patients, 73.1% were male and 46.2% were above 50 years old. A total of 34.6% patients had the actual body weight / ideal body weight ratio of more than 1.0. The median total daily dose was 34.72 mg / kg. The median for $C_{max}$ (peak serum concentration) was 26.0 mg /L while $C_{min}$ (trough serum concentration) was 14.20 mg / L. The median for $AUC_{24}$ is 412.08 mg*hr / L. The overall median for $K_e$ and $t_{1/2}$ were 0.091 $hr^{-1}$ and 7.62 hours, respectively. The median $V_d$ was 0.90 L / kg. It was found that with increasing creatinine clearance, the $K_e$ and $V_d$ increased while the $t_{1/2}$ decreased. **Conclusion:** The vancomycin pharmacokinetic data from this study varied according to different degree of creatinine clearances.

## INTRODUCTION

Vancomycin is a glycopeptide antibiotic introduced in 1958 for the treatment of severe staphylococcal or gram-positive systemic infections, particularly methicillin-resistant Staphylococcus Aureus (MRSA) [1,2]. It was found that the prevalence of highly-resistant MRSA has increased in Malaysia [3]. Rapid increase in microbial resistance and frequent under-dosing issues have led to the importance of achieving targeted $AUC_{24}$ and trough concentrations of vancomycin. Vancomycin is a narrow therapeutic index drug that requires serum concentration monitoring to ensure the level is within the therapeutic range for effective and non-toxic treatment [4]. High vancomycin doses and elevated trough serum concentrations were found to increase the rates of nephrotoxicity [5] and ototoxicity especially in the elderly [6]. The steady-state vancomycin trough serum concentration of more than 15 mg / L was associated to increased nephrotoxicity incidence as high as 30% to 35% but was not found to improve treatment outcomes and mortality [5].

The trough serum concentration has been used as a practical mean of vancomycin monitoring. Trough monitoring is recommended for seriously ill patients who require high



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vancomycin doses to achieve trough serum concentrations of 15 - 20 mg / L [7]. Besides, trough monitoring is also recommended in patients with unstable kidney functions undergoing dialysis, morbidly obese or have fluctuating volumes of distribution [4,7]. Another method of vancomycin monitoring is the 24-hour area under concentration-time curve ($AUC_{24}$) monitoring [8]. The goal of 24-hour area under concentration-time curve / minimum inhibition concentration (AUC / MIC) as recommended by the current guideline is 400 -600 mg*hr / L, assuming MIC as 1 mg / L using the broth microdilution [8]. The $AUC_{24}$ goal can be achieved with trough serum concentrations of less than 15 mg / L in most cases. A meta-analysis was conducted to evaluate the effectiveness of $AUC_{24}$-based target and concluded that $AUC_{24}$ / MIC > 400 could reduce mortality rates by 53% and reduce treatment failures by 61% [9]. Besides, a quasi-experimental model including 1280 patients found that $AUC_{24}$-guided dosing was associated with lower trough level, hence lower nephrotoxicity [10].

Several guidelines recommended vancomycin doses of 15 - 20 mg / kg, with doses calculated using actual body weight and administered every 8 - 12 hours for most patients with normal kidney functions [4,7]. Vancomycin doses should be adjusted in patients with kidney diseases based on their creatinine clearances. However, the standard weight-based vancomycin doses according to the kidney functions might not achieve the targeted $AUC_{24}$ and trough serum concentrations [11,12].

Seeing the importance of achieving the targeted trough and $AUC_{24}$ level of vancomycin for effective treatment, a more accurate vancomycin dose determination should be based on pharmacokinetic parameters from the local population. The pharmacokinetic parameters required including elimination rate constant ($K_e$), half-life ($t_{1/2}$), volume of distribution ($V_d$) and vancomycin clearance ($Cl_{vanco}$). However, there was a lack of local studies done to characterise the vancomycin pharmacokinetic parameters. Thus, this study aimed to explore the pharmacokinetic parameters among Malaysian adults in Penang with different kidney functions. With this study findings, more local population-targeted pharmacokinetic parameters according to various degrees of kidney functions can be used for the vancomycin dosing.

## METHOD

This was a retrospective, single-centered study conducted in the Clinical Pharmacokinetics Department, Penang General Hospital. This study obtained ethical approval on 23 April 2018 from the Medical Research and Ethics Committee (MREC), Ministry of Health of Malaysia (Approval number: NMRR-18-362-40029 (IIR)). The ethical approval allowed the retrospective data collection of the patients' old records from 1 January 2016 to 31 December 2017. The Clinical Pharmacokinetics Department provided the therapeutic drug monitoring (TDM) services to monitor the serum concentration of narrow therapeutic index drugs for the optimatisation of individuals' dose regime. The procedures of TDM include obtaining and analysing the patients' blood samples, interpreting the serum concentrations and providing suggestions on the dose regime. There are several terminologies used in the TDM services. Sampling time is the designated time to obtain the patient's blood for serum drug concentration monitoring. $C_{pre}$ level and $C_{post}$ level are the serum drug concentrations obtained at a specific time before and after the drug is served, respectively. $C_{max}$ (peak) level is the maximum serum drug concentration after an hour of the end of infusion to allow the complete distribution phase of vancomycin [13]. Whereas, $C_{min}$ (trough) level is the minimum serum drug concentration just before the next dose is served.

A TDM service will be offered upon physicians' request by filling an official TDM request form to monitor patient's serum drug concentration. The TDM request form has several sections including patient's profile, clinical summary and diagnosis, as well as patient's condition. Besides, the form also includes the indication for TDM request, latest lab results and concurrent medications. Lastly, the form has the information of the drug to be monitored as well as pharmacist's assessment and recommendation. In the section of patient's profile, the patient's name, age, weight, height, gender, ward, identity card (IC) number, race and the date of admission are required. Meanwhile, for the clinical summary and diagnosis section, the patient's currently diagnosed disease has to be filled in. The patient's condition section has several choices to be selected (if necessary) including edema, dialysis, liver disease, burn, dehydration and others. Besides, the indication for TDM request section has options of therapeutic monitoring, suspected toxicity, non-compliance and others. The latest lab results include the blood urea, sodium, potassium, serum creatinine, serum albumin levels, as well as culture & sensitivity results. The section on the monitored drug includes the dose, dosing interval, the starting date of the drug, the date and time of last dose served. Furthermore, the section also has infusion times and the sampling times including pre-sampling time and post-sampling time. Lastly, the pharmacist's assessment and recommendation section will document the serum concentration of the analyzed drug and the pharmacist's recommendation to the physicians in-charged.

This study included patients aged 18 years old and above who had been treated with intravenous (IV) vancomycin. Patients with incomplete TDM request forms, underwent dialysis and with $C_{post}$ levels obtained less than an hour from the end of vancomycin infusion time were excluded. Besides, samples which did not achieve targeted range of $C_{max}$ and $C_{min}$ were excluded from the study because they could be contributed by

incorrect sampling time and administration error. A patient screening checklist was specifically designed to screen for patients who fulfilled the inclusion criteria while a data collection form was used to collect the patient's information from the TDM request forms.

The patient's personalized vancomycin pharmacokinetic parameters were manually calculated for all patients using the formulae listed below (Eq. 1 - 2) [14], (Eq. 3 - 12) [15] and (Eq 13 - 15) [16].

The creatinine clearance, CrCl using the measured serum creatinine (SrCr) level was calculated using the Eq. 1 and 2.

Eq. 1:
Male CrCl = $\frac{(140-Age)\ x\ Body\ weight}{72\ x\ SrCr}$

Eq. 2:
Female CrCl = $\frac{(140-Age)\ x\ Body\ weight}{72\ x\ SrCr} x\ 0.85$

*CrCl in ml / min, age in years, body weight in kg and serum creatinine in mg / dL.

Various body weights were used for Cockcroft-Gault equation [16]. Underweight patients used the actual body weight (ABW) while patients of normal weight used the ideal body weight (IBW) (Eq. 3 and 4) [15]. For overweight, obese, and morbidly obese patients, adjusted body weight (Adj. BW) was used (Eq. 5) [15].

Eq. 3:
Male IBW (kg) = 50 kg + 0.9 (Height in cm - 152)

Eq. 4:
Female IBW (kg) = 45.5 kg + 0.9 (Height in cm - 152)

Eq. 5:
Adj. BW (kg) = IBW (kg) + 0.4 [ABW (kg) – IBW (kg)]

The elimination rate constant, $K_e$ was computed using Eq. 6.

Eq. 6:
$K_e = \frac{\ln(\frac{Co}{C})}{t}$

*$K_e$ in $hr^{-1}$; $C_o$ is the initial concentration in mg / L; C is the concentration at any time after the initial concentration in mg / L; t is the time interval in hours between the $C_o$ and C.

The half-life is calculated using Eq. 7.

Eq. 7:
$t_{1/2} = \frac{\ln 2}{Ke}$

*$t_{1/2}$ in hours (hr)
The values of maximum serum drug concentration ($C_{max}$) and minimum serum drug concentration ($C_{min}$) were computed using the formulae (Eq. 8 - 10) from the available measured $C_{pre}$ and $C_{post}$ levels.
*$C_{max}$ in mg / L; $t_{post}$ = the time interval in hours between $C_{max}$ and $C_{post}$

Eq. 8:
$C_{max} = C_{post} e^{Ke\ x\ tpost}$

*$C_{max}$ = $C_{post}$ in mg / L if the post-sampling time is exactly 2 hours from the start of vancomycin infusion
*Therapeutic range for $C_{max}$ = 20 – 40 mg / L [15,16]

Eq. 9:
$C_{min} = C_{pre} e^{-Ke\ x\ tpre}$

*$C_{min}$ in mg / L; $t_{pre}$ = the time interval in hours between the $C_{pre}$ and $C_{min}$
*Therapeutic range for $C_{min}$ = 10 – 20 mg / L [15,16]

Or

Eq. 10:
$C_{min} = C_{max}\ e^{-Ke\ (T-2)}$

*(T - 2) is the time difference in hours between the $C_{max}$ and $C_{min}$ levels. Two hours are deducted because the $C_{max}$ can only be achieved after two hours of vancomycin infusion initiation.

The volume of distribution, $V_d$ is calculated using Eq. 11.

Ep. 11:
$V_d = \frac{(\frac{Dose}{t'})\ (1-e^{-ket'})}{Ke\ [Cmax-(Cmin\ e^{-ket'})]}$

*$V_d$ in L / kg; dose in mg; t' = infusion time in hours

The vancomycin clearance ($Cl_{vanco}$) is computed in Eq. 12.

Ep. 12:
$Cl_{vanco} = K_e V_d$

*$Cl_{vanco}$ in L / hr

For adult patients older than 18 years old, vancomycin is excreted almost 100% renally. Hence, the vancomycin clearance is equivalent to creatinine clearance ($Cl_{vanco}$ = CrCl) [15].

The $AUC_{24}$ is computed using the formulae (Eq. 13 - 15) [16].

Eq. 13:
$AUC_{inf} = t'\ x\ \frac{(Cmax + Cmin)}{2}$

Eq. 14:
$AUC_{elim} = \frac{(Cmax - Cmin)}{Ke}$

Eq. 15:
$AUC_{24} = (AUC_{inf} + AUC_{elim})\ x\ \frac{24}{T}$

*All the AUCs in mg*hr / L; T is the dosing interval in hours.
*Therapeutic range for $AUC_{24}$ = 400 – 600 mg*hr / L [17].

The data were then transferred into IBM SPSS Statistics Version 27.0 for data analysis. Descriptive analysis was done to describe the demographic and clinical characteristics of the patients. The data of creatinine clearance and vancomycin clearance were initially tested for normality. As the data was not normally distributed, all the data was presented as medians and interquartile ranges (IQR). Besides, Wilcoxon signed rank test was used to test for the difference between the creatinine clearance and vancomycin clearance. The p-value of less than 0.05 showed the results were significantly different.

## RESULT

A total of 26 patients were included in this study. Nearly three-quarters of patients were male (73.1%). Most patients aged above 50 years old (46.2%) with mean age of 49.42 (± 18.97) years. Majority of the vancomycin-treated patients were from hematological ward (34.6%) and orthopedic ward (23.1%). Out of 26 patients, 46.2% were Malay while 34.6% were Chinese. The mean ABW for patients was 63.00 (± 11.06) kg. Specifically looking at the ABW/IBW ratio, 34.6% patients were more than 1.0 while 26.9% of patients were less than 1.0. More than half of the patients (53.8%) were treated with vancomycin empirically. Whereas, quite a number of patients (34.6%) were treated for MRSA. Most patients were diagnosed with neutropenic sepsis (42.3%) and bone abscess (15.4%). Slightly more than half of the patients have serum creatinine less than 0.7 mg / dL (50.9%) as well as creatinine clearance of 80 ml/min and above (54.4%). The median number of TDM checking per individual is 1.0 (IQR: 1.0 - 3.0) (Table I.).

Most patients had the vancomycin doses of 1000 mg (45.6%) and 750 mg (36.8%), respectively. About half (49.2%) of the patients had doses of 7.5 - 12.5 mg / kg while only 14.0% patients were using the higher doses of 17.6 - 23.0 mg / kg. Most patients had the dosing interval of 12-hourly (42.1%) and 8-hourly (40.4%). A total of 38.6% patients had the total daily dose in the range of 1501 - 2250 mg of vancomycin. One-third of patients (33.3%) had a total daily dose of 36.0 - 50.0 mg / kg. Most patients (96.5%) had their vancomycin administered in an hour of infusion. Majority patients had the pre-sampling time of 0.5 hours before the dose (91.2%) and post-sampling time of 2.0 hours after the initiation of vancomycin infusion (91.3%) (Table II). The median for total daily dose was 34.72 mg/kg and it resulted in the median $C_{max}$ of 26.00 mg / L, $C_{min}$ of 14.20 mg / L and $AUC_{24}$ of 412.08 mg*hr / L (Table III).

A total of 57 samples for TDM checking were collected from the 26 patients. The overall median for elimination rate constant ($K_e$) is 0.091 $hr^{-1}$. Increment of Ke was observed with the increasing trend of creatinine clearance. For patients with low creatinine clearance between 35 - 59 ml / min, the median $K_e$ was 0.680 $hr^{-1}$. Whereas, the median $K_e$ for patients with creatine clearances of more than 100 ml / min was raised to 0.115 $hr^{-1}$. The overall median for $t_{1/2}$ was 7.62 hours. Longer $t_{1/2}$ of vancomycin was observed with lower creatinine clearance. The median $t_{1/2}$ of 10.20 hours was the longest for patients with creatinine clearances of 35 - 59 ml / min. Meanwhile, the median $t_{1/2}$ of 6.01 hours was observed among patients with creatinine clearance of more than 100 ml / min. The overall median $V_d$ observed were 57.43 L and 0.90 L / kg, respectively. The $V_d$ decreased with decreasing creatinine clearances. The median $V_d$ was found to be 62.41 L or 1.13 L / kg in patients with creatinine clearances more than 100 ml / min and it dropped to 40.43 L or 0.68 L / kg among those with creatinine clearances between 35 - 59 ml / min (Table IV).

**Table I. Demographic and clinical characteristics of study population**

| Patients' Demographic | N (%) | Patients' Demographic | N (%) |
|---|---|---|---|
| ***Gender*** | | ***Culture and Sensitivity Results*** | |
| Male | 19 (73.1) | Empirical | 14 (53.8) |
| Female | 7 (26.9) | MRSA | 9 (34.6) |
| ***Age group*** | | Enterococcus | 1 (3.8) |
| 20 - 30 | 5 (19.2) | MRCONS | 1 (3.8) |
| 31 - 40 | 5 (19.2) | Rhodococcus | 1 (3.8) |
| 41 - 50 | 4 (15.4) | ***Diseases*** | |
| 51 - 65 | 6 (23.1) | Neutropenic sepsis | 11 (42.3) |
| > 65 | 6 (23.1) | Bone abscess | 4 (15.4) |
| ***Wards*** | | Osteomyelitis | 2 (7.7) |
| Haematology | 9 (34.6) | Sepsis | 2 (7.7) |
| Orthopaedic | 6 (23.1) | Diabetic ulcer | 1 (3.8) |
| Cardiothoracic | 3 (11.5) | Perforated colon | 1 (3.8) |
| Medical | 3 (11.5) | RVD | 1 (3.8) |
| GICU | 2 (7.7) | Others | 4 (15.4) |
| Surgical | 2 (7.7) | ***Serum Creatinine (mg/dL)*** | |
| Oncology | 1 (3.8) | > 1.0 | 6 (10.5) |
| ***Ethnic Group*** | | 0.7 - 1.0 | 22 (38.6) |
| Malay | 12 (46.2) | < 0.7 | 29 (50.9) |
| Chinese | 9 (34.6) | ***Creatinine clearance (ml/min)**** | |
| Indian | 4 (15.4) | 35 - 59 | 13 (22.8) |
| Others | 1 (3.8) | 60 - 79 | 13 (22.8) |
| ***Actual Body Weight*** | | 80 - 99 | 8 (14.0) |
| 40 - 50 | 4 (15.4) | >100 | 23 (40.4) |
| 51 - 60 | 6 (23.1) | ***Blood Urea Nitrogen (mmol/L)*** | |
| 61- 70 | 9 (34.6) | 1.0 - 2.5 | 12 (21.1) |
| 71 - 80 | 7 (26.9) | 2.6 - 3.5 | 12 (21.1) |
| ***ABW/IBW*** | | 3.6 - 5.0 | 17 (29.8) |
| More than 1.2 | 3 (11.5) | 5.1 - 6.5 | 7 (12.3) |
| 1.1 - 1.2 | 6 (23.1) | > 6.5 | 9 (15.8) |
| 1.0 | 2 (7.7) | ***Number of TDM checking per Individual*** | |
| Less than 1.0 | 7 (26.9) | 1 | 15 (57.7) |
| Unknown | 8 (30.8) | 2 | 4 (15.4) |
| | | 3 | 3 (11.5) |
| | | More than 3 | 4 (15.4) |

* Creatinine clearance calculated by using vancomycin clearance

The overall median creatinine clearance of 101.61 ml / min (IQR: 66.64 - 151.02 ml / min) was significantly different from the vancomycin clearance of 84.26 ml / min (IQR: 61.94 - 123.03 ml / min). When analysing patients with the serum creatinine between 0.7 - 1.0 mg / dL and more than 1.0 mg /dL, no significant differences were observed between the creatinine clearance and vancomycin clearance. However, significant difference was observed between creatinine clearance (median

= 147.33 ml / min) and vancomycin clearance (median = 114.49 ml / min), respectively in patients with serum creatinine less than 0.7 mg / dL (Table V).

**Table II. Dosing regime, dosing interval, infusion hours and sampling time**

| Description | N (%) | Description | N (%) |
|---|---|---|---|
| ***Dose (mg)*** | | ***Total daily dose per kg (mg/kg)*** | |
| 500 | 9 (15.8) | 15.0 - 25.0 | 13 (22.8) |
| 600 | 1 (1.8) | 26.0 - 35.0 | 17 (29.8) |
| 750 | 21 (36.8) | 36.0 - 50.0 | 19 (33.3) |
| 1000 | 26 (45.6) | 51.0 - 67.0 | 8 (14.0) |
| ***Dose per kg (mg/kg)*** | | ***Infusion hours (hours)*** | |
| 7.5 - 10.0 | 14 (24.6) | 1.0 | 55 (96.5) |
| 10.1 - 12.5 | 14 (24.6) | 0.5 | 1 (1.8) |
| 12.6 - 15.0 | 10 (17.5) | 1.5 | 1 (1.8) |
| 15.1 - 17.5 | 11 (19.3) | ***Pre-sample hours (hours)*** | |
| 17.6 - 23.0 | 8 (14.0) | 0.50 | 52 (91.2) |
| ***Dosing Interval (hours)*** | | 0.33 | 2 (3.5) |
| 12 | 24 (42.1) | 0.42 | 1 (1.8) |
| 8 | 23 (40.4) | 0.67 | 1 (1.8) |
| 6 | 10 (17.5) | 1.50 | 1 (1.8) |
| ***Total daily dose (mg)*** | | ***Post-sample hours (hours)*** | |
| 1000 - 1500 | 15 (26.3) | 2.00 | 52 (91.2) |
| 1501 - 2250 | 22 (38.6) | 2.50 | 3 (5.3) |
| 2251 - 4000 | 20 (35.1) | 2.67 | 1 (1.8) |
| | | 3.00 | 1 (1.8) |

**Table III. Dosage of vancomycin, peak and trough serum vancomycin concentrations, and AUC levels**

| Description | Median | IQR |
|---|---|---|
| Dose | 750 mg | 750 - 1000 |
| Dose per kg | 13.16 mg / kg | 10.14 - 16.40 |
| Dosing interval | 8 hours | 8 - 12 |
| Total daily dose | 2250 mg | 1500 - 3000 |
| Total daily dose per kg | 34.72 mg / kg | 26.79 - 48.68 |
| $C_{max}$ | 26.00 mg / L | 23.20 - 30.25 |
| $C_{min}$ | 14.20 mg / L | 12.24 - 16.04 |

## DISCUSSION

This study compares the creatinine clearances estimated using serum creatinine level and vancomycin clearance, respectively. A significant difference was observed between these two clearances for patients with serum creatinine level of less than 0.7 mg / dL. Slightly more than half of the patients having low serum creatinine level of less than 0.7 mg / dL which can be associated with muscle dystrophy [18]. The muscle dystrophy can be possibly due to old age, being bedridden and malnourished from prolonged hospital stay. Since creatinine is the metabolism product of muscle, the decreased muscle mass in these patients will cause low creatinine production [18]. Serum creatinine is eliminated mainly through the glomerular filtration. Thus, it has been used as an estimation of glomerular filtration rate termed as the creatinine clearance [14]. The low serum creatinine will overestimate the creatinine clearance. Hence, a more accurate estimation of creatinine clearance which is not dependent on the serum creatinine should be used. This can be achieved by using the vancomycin clearance ($Cl_{vanco} = K_eV_d$) derived from individualised serum vancomycin concentrations [15]. If the vancomycin clearance showed no significant difference with the calculated creatinine clearance, thus, the serum creatinine value is considered valid for creatinine clearance estimation. This study revealed no significant difference between the clearances in patients with the serum creatinine of more than 0.7 mg / dL. Therefore, serum creatinine value exceeding 0.7 mg / dL can be used for patient's creatinine clearance estimation.

The administration of vancomycin infusion in most patients was over an hour. This is crucial as rapid infusion of vancomycin can contribute to the development of red man syndrome which include hypotension and maculopapular rash on the face, trunk, neck and upper extremities. Hence, vancomycin should be administered over at least 60 - 90 minutes of infusion to prevent this side effect [1]. Another issue of rapid administration of vancomycin is thrombophlebitis which is the development of blood clots in the veins, causing inflammation. The blockage in the veins will cause leakage of vancomycin during administration, hence the body will not acquire the full dose of vancomycin. It would then contribute to subtherapeutic vancomycin treatment. Meanwhile, most patients had their blood samples taken correctly after two hours of starting vancomycin infusion. This is to allow complete vancomycin distribution phase after an hour of post-infusion [13]. If taken before two hours from the start of vancomycin infusion, the true serum vancomycin concentration is not reflected. Hence, the post-sampling levels taken will be falsely high due to incomplete distribution.

Creatinine clearance will influence the vancomycin pharmacokinetic parameters particularly the elimination rate constant ($K_e$). Elimination rate constant is the fraction or percentage of the total amount of drug in the body removed per unit time. It is the function of clearance and the volume of distribution [19]. The normal range of creatinine clearance is 85 - 135 ml / min [18]. The median creatinine clearance in our study was 101.61 ml / min, which was within the normal range [20]. This study showed better kidney functions will produce a greater $K_e$. A North Carolina study with better kidney functions of high mean creatinine clearance (161.6 ml / min) gave a greater $K_e$ (0.141 $hr^{-1}$) [19] when compared to the present study's $K_e$ (0.091 $hr^{-1}$).

The half-life ($t_{1/2}$) of vancomycin is influenced by creatinine clearance. Half-life is the time taken for the total plasma drug concentration in the body to reduce to half of the initial plasma drug concentration. The $t_{1/2}$ of vancomycin is inversely proportional to the creatinine clearance [20]. The $t_{1/2}$ of 7.62 hours from our present study was slightly longer than the general Caucasian population $t_{1/2}$ which was between 6 - 7 hours [15]. Besides, the $t_{1/2}$ in our present study was also longer

than the North Carolina study with the $t_{1/2}$ of 6.5 hours [19]. This might reflect the vancomycin $t_{1/2}$ was shorter in Malaysian population compared to the Caucasians. Furthermore, the prolonged $t_{1/2}$ in this study could also be contributed by kidney impairment with a total of 22.8% patients having the creatinine clearances of less than 60 ml / min. Hence, vancomycin was cleared from the body slower.

**Table IV. Vancomycin pharmacokinetic data according to creatinine clearance**

| Creatinine clearance* (ml / min) | $K_e$ ($hr^{-1}$) Median (IQR) | Half-life (hours) Median (IQR) | $V_d$ (L) Median (IQR) | $V_d$ (L / kg) Median (IQR) |
|---|---|---|---|---|
| † Overall (n = 57) | 0.091 (0.067 - 0.116) | 7.62 (5.99 - 10.39) | 57.43 (44.01 - 73.62) | 0.90 (0.68 - 1.22) |
| 35 - 59 (n = 13) | 0.680 (0.460 - 0.910) | 10.20 (7.65 - 15.02) | 40.43 (32.43 - 55.48) | 0.68 (0.53 - 0.86) |
| 60 - 79 (n = 13) | 0.079 (0.061 - 0.107) | 8.77 (6.50 - 11.35) | 48.03 (39.20 - 65.89) | 0.84 (0.66 - 0.99) |
| 80 - 99 (n = 8) | 0.085 (0.069 - 0.093) | 8.22 (7.44 - 10.14) | 63.74 (57.78 - 80.83) | 1.11 (0.90 - 1.63) |
| > 100 (n = 23) | 0.115 (0.091 - 0.172) | 6.01 (4.02 - 7.62) | 62.41 (50.08 - 88.39) | 1.13 (0.82 - 1.39) |

* Creatinine clearance using vancomycin clearance

† The total number of samples included for TDM checking were 57

**Table V. Comparison between creatinine clearance determined by using measured serum creatinine value and vancomycin clearance**

| Serum creatinine (mg / dL) | Creatinine clearance determined by using measured serum creatinine value (ml / min) Median (IQR) | Creatinine clearance determined by using vancomycin clearance (ml / min) Median (IQR) | Wilcoxon Signed Rank test Results |
|---|---|---|---|
| † Overall (n = 57) | 101.61 (66.64 - 151.02) | 84.26 (61.94 - 123.03) | Z = -3.810; p < 0.001 |
| > 1.0 (n = 6) | 58.87 (58.24 - 65.49) | 54.45 (50.59 - 75.35) | Z = -0.734; p = 0.463 |
| 0.7 - 1.0 (n = 22) | 73.92 (63.97 - 88.88) | 73.33 (45.74 - 94.51) | Z = -0.243; p = 0.808 |
| < 0.7 (n = 29) | 147.33 (111.08 - 200.45) | 114.49 (75.39 - 137.24) | Z = -4.400; p < 0.001 |

† The total number of samples included for TDM checking were 57

Creatinine clearance will affect the volume of distribution ($V_d$) of vancomycin. Volume of distribution is the ratio of the total amount of drug present in the body and plasma drug concentration. The population data for $V_d$ is 0.5 - 1.0 L / kg. Nevertheless, the average value of 0.7 L / kg was selected as the general vancomycin $V_d$ in clinical practice [15]. The $V_d$ of 0.9 L / kg in our study was found to be higher than the average population value. The higher $V_d$ could be due to having more elderly patients and one-third of the patients with body weights of more than IBW. This is because the $V_d$ of vancomycin is also influenced by age and body weight [21]. Our findings were consistent with a study by Ducharme et al. involving 704 patients in USA which showed the greater the age, the higher the $V_d$. The Ducharme study showed elder patients had higher $V_d$ of 54.2 L or 0.86 L / kg as compared to younger patients with lower $V_d$ of 41.7 L or 0.61 L / kg [21]. Besides, the study from Ducharme et al. also found that greater body weight will increase the Vd. Patients with greater body weight had $V_d$ of 51.6 L or 0.89 L / kg whereas patients with lower body weight had $V_d$ of 43.8 L or 0.62 L / kg [21].

A population-based pharmacokinetic data is required for several conditions. For instance, this population data is required to initiate the vancomycin therapy when there are no individualised vancomycin concentrations available [22]. Besides, such data is also utilised when the blood samples are invalid for personalised vancomycin dose determination. For example, the post-sampling blood is taken too early before the vancomycin distribution phase is complete. This will contribute to a falsely high vancomycin post-level. Furthermore, the data is also used when TDM services are not available [12]. Hence, the population-based data from this study in accordance to different degrees of creatinine clearance in Table IV. can be used in the above-mentioned conditions.

Our study consisted of majority male patients and patients with age of more than 50 years old. Besides, our study also had slightly more than one-third patients with their actual body weight more than the ideal body weight. These parameters such as the gender, age and body weight will influence the pharmacokinetic profile of vancomycin [21]. Therefore, the generalisability of the data was limited. Besides, this study was an observational retrospective study which the accuracy of the data record keeping cannot be ensured. Besides, the retrospective study design has the limitation of selection bias and information bias. Furthermore, bias will also be introduced in this study using the routine collection of clinical samples for the sampling times without a designated clear protocol.

Furthermore, the cases with $C_{max}$ and $C_{min}$ out of the targeted ranges were excluded in this study. Although inaccurate sampling times and administration could be the factors causing the concentrations to fall out of the targeted ranges, this issue may also occur with correct sampling times and administration. Hence, this exclusion step may introduce bias to the study. This

study included the three main ethnic groups of Malay, Chinese and Indian. Nevertheless, it cannot represent the whole Malaysian population since the ethnic groups indigenous to the Sabah and Sarawak were not included. Besides, this study did not include critically ill and dialysis patients.

## CONCLUSION

The Malaysian pharmacokinetic data of vancomycin have been characterised in this study for adults in Penang with varying kidney functions. This study found that both the $t_{1/2}$ and $V_d$ of vancomycin among adult patients in Penang were greater than the Caucasian-population values. There might be a difference in the pharmacokinetic data between local Penang Malaysians and Caucasians. However, the difference in the findings of this study can also be contributed by having more elderly and patients with impaired kidney functions.

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## CONFLICT OF INTEREST

There was no conflict of interest. This research did not receive any financial support from any institution.

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