A Review of Vancomycin Population Pharmacokinetic Studies in Adult Critically Ill Patient

Eko Setiawan
Clinical Pharmacy Division – Department of Pharmacy
Faculty of Pharmacy – Mahidol University
Bangkok, Thailand

Centre for Medicine Information and Pharmaceutical Care
Faculty of Pharmacy – University of Surabaya
Surabaya Indonesia

Abstract — Background Efficacy of vancomycin, the most recommended anti-MRSA antibiotics, was best represented with AUC\textsubscript{24}/MIC>400 which was greatly determined by pharmacokinetic (PK) and pharmacodynamics parameters. Giving a standard dose of vancomycin to any populations with deviated pharmacokinetic parameters, as found in the critically ill population, will impact on the achievement of AUC\textsubscript{24} and MIC coverage. Objective This review was conducted to investigate the profile of critically ill adult PK parameters and examine the effects of the different PK parameters to the achievement of AUC\textsubscript{24} and maximum MIC coverage. Method Literature search was conducted using PubMed and Trip Database from the database inception to July 2012. Published articles which present the critically ill population PK equation model will be included in the review. Reference case analysis will be used to calculate the PK parameters, AUC\textsubscript{24}, and maximum MIC coverage. Result There were 5 critically ill adult population PK studies met the inclusion criteria. Each study shows specific PK equation model for Vd and CL. Only 4 studies were included in the reference case analysis. Result from reference case analysis for the Vd and CL were: 69L, 58.8L, 104.04L, 49.2L; and 4.29L/h, 5.12L/h, 3.586L/h, 3.19L/h, consecutively. The AUC\textsubscript{24} (in mg.hr.L\textsuperscript{-1}) and maximum MIC of MRSA strain (in mg/L) that still could be covered by giving standard dose of vancomycin were: 466.2, 390.63, 557.72, 626.96; and 1.16, 0.98, 1.39, 1.56. While, the Vd, CL, AUC\textsubscript{24}, and maximum MIC of MRSA resulted from general population equation model calculation were 37.2L, 2.6L/h, 769.23mg.hr.L\textsuperscript{-1}, and 1.92mg/L. Conclusion Giving standard dose of vancomycin to the critically ill population yielded a lower achievement of total AUC\textsubscript{24} leading to lower MIC of MRSA strain that still could be covered. Close monitoring and dose adjustment, if needed, should be given to ensure the achievement of desired target treatment.

Keywords—vancomycin; population pharmacokinetic study; critically ill

I. INTRODUCTION

Methicillin-resistant Staphylococcus aureus (MRSA) is a common pathogen found in the hospital setting [1-4]. Compared with the methicillin-susceptible strain, infection caused by MRSA usually result in higher mortality rate [5-7]. There are several independent mortality risk factors for patient who are infected with MRSA, and one of the most prominent risk factors is an intensive care unit (ICU) admitted [8]. Severe condition is not the only reason for higher mortality found in this setting. Inappropriate used for antimicrobial treatment, either empirical and definite antibiotic therapy, also plays as a major determinant factor in the final patients’ outcome [8-15]. Inappropriate used with antibiotics doesn’t limiting only to the erroneous choice of antibiotics but also the failure to achieve target treatment.

Vancomycin has long been used as the gold-standard in the management of MRSA infection. Nowadays, there is a great interest of using vancomycin to treat MRSA infection due to higher rates of treatment failure, especially in the case of infection caused by vancomycin minimum inhibitory concentration (MIC) MRSA strain, even still in the range of susceptibility breakpoint as classified by the Clinical and Laboratory Standards Institute (CLSI), i.e. ≤2mg/L [16-23]. Further analysis found that patients who achieved area under the plasma drug concentration and time curve for 24h/minimum inhibitory concentration (AUC\textsubscript{24}/MIC) >400 had a higher percentage of clinical success compared with those who didn’t achieve it [18,24,25]. Therefore, this pharmacokinetic-pharmacodynamic (PK-PD) index has been used as the target treatment of vancomycin in MRSA infection. This desired target treatment will totally depend on the AUC for 24h, which were greatly determined by the pharmacokinetic (PK) parameter of patients, and the distribution of MIC data.

Critically ill population is one populated with the deviated physiologic condition compared with the general population. The different physiological condition leading to the differences in PK parameter profile [26-30]. The most affected PK parameters in this population are volume of distribution (Vd) and clearance (CL) that might impact on vancomycin blood concentration [28,29,31]. Lower blood concentration over time for 24h will result in lower AUC\textsubscript{24}, and as the consequences, without any appropriate dose adjustment, the higher MIC strain might not be covered. Infection that not treated with adequate AUC\textsubscript{24} is classified as inappropriate used of antibiotics. As already mentioned
above, this practice will put the patients to the higher risk of treatment failure.

Not many studies reported the exact figure of PK parameters in critically ill population. Rapidly changing of physiologic conditions found among this population makes valuing PK parameters even more complex. One of the most proposed methods in valuing PK parameters is population PK study. The population PK study defined as quantitative assessment of typical PK parameters, and the between-individual and residual variability in drug absorption, distribution, metabolism, and excretion [32]. The advantage by using this method is the ability to identify the source of variability in the PK parameters for certain populations. Population PK study presents an equation model for certain PK parameters, \( y_i = f(x_i, \theta_i) + e_i \), where \( y_i \) is observed data that is intended to identify, \( f \) is a specified function for predicting, \( e_i \) is the measurement of error, and \( \theta_i \) is an individual true parameter. From this equation model, it is shown that variability exists among individual in the population will not be ignored and, therefore, will result a prediction as close as the real condition. The equation model was established by adding a factor that known to influence the PK parameters one by one to the certain basic equation model. Factor that giving significantly contributed to the equation model will be retained in the final equation model. Studies have shown single value of PK parameters, without using any equation model in calculation, usually ignore the variability exist between individual and, therefore, didn’t classify as population PK study. This study aims to investigate the population PK studies conducted in the critically ill adult patients and examine the effects of different PK parameter profile to the achievement of AUC\(_{24}\) and maximum MIC value of MRSA whether it can be covered by giving a standard dose of vancomycin. Reference case analysis, using the specific characteristic of the patient, will be used to calculate the PK parameter, AUC\(_{24}\) and maximum MIC coverage.

II. MATERIALS AND METHOD

A. Definition

Critically ill patient in this study is defined as a patient with acute impair in one or more vital organ systems such that there is a high probability of imminent or life threatening deterioration in the patient’s condition [33]. By this definition, critically ill patient will not only limited implied to those who are admitted in the ICU department. Septic, trauma, post-surgical, burn and cancer patients are usually classified in this population [26-28]. Patient with age ≥17 year old are considered as an adult patient. One gram of vancomycin every 12h considered as a standard dose of vancomycin. Variables in the population PK study mean any factors that influence the values of PK parameters.

B. Literature search

PubMed and Trip Database were used to identify all vancomycin population PK studies conducted in the critically ill adult patients. A literature search was conducted from the database inception in July 2012 using several search terms, including: “vancomycin” AND “population pharmacokinetic study” or “critically ill” or “population pharmacokinetic” or “malignancy” or “cancer” or “burn” or “renal function” or “surgical” or “post-surgical” or “intensive care unit”. Follow-up of reference lists of relevant articles also has been done to an extent the searching method of the original article.

C. Study selection

All population PK studies conducted in adult critically ill patients published in English language will be included in this review. A study that included non-critically ill population or child population in the establishment of the population PK equation model, in vitro modelling, non-renal elimination modelling, and study just reported the pharmacokinetic parameters or didn’t clearly present the pharmacokinetic equation model will be excluded from the review. In order to be included in the reference case analysis, the study should clearly present the value of all variables used in the equation model.

D. Reference-case

Sixty year old male patient, weight 60kg, height 160cm, with normal serum creatinine 0.8mg/dL will be used as a reference case, either for critically ill population and general population, to calculate PK parameters for each population PK equation model. After derived PK parameters, AUC\(_{24}\) will be calculated and then used to analyse maximum MIC value of MRSA strain that still can be covered by using standard dose of vancomycin. Pharmacokinetic parameters, AUC\(_{24}\), and maximum MIC value calculated from equation model of critically ill population will be compared with ones of general population.

Pharmacokinetic parameters for critically ill population will be calculated using each equation model derived from studies found in the literature search. While, for general population will be calculated using equations listed below. The first PK parameter should be calculated was \( K_e \) [34].

\[ K_e = (0.00083 \times CL_{cr}) + 0.0044 \]  

(1)

\( K_e \) stands for elimination rate constant (h\(^{-1}\)); and \( CL_{cr} \) stands for creatinine clearance (mL/min).

Creatinine clearance (\( CL_{cr} \)) will be calculated using Cockcroft and Gault’s equation [35,36]. This equation also used for \( CL_{cr} \) calculation in the critically ill population equation model.

\[ CL_{cr} = [(140-\text{age}) \times \text{weight}] / (72 \times S_{cr}) \]  

(2)

\( \text{Age} \) (year); weight used in this equation should be ideal body weight (IBW; in kg); \( S_{cr} \) stands for serum creatinine (mg/dL) [35,36].

IBW = 50kg + (2.3kg) each inch of height over 5 feet  

(3)

To convert height from cm to inch, this equation will be used:

\[ \text{Height in cm} / 2.54 \]  

(4)

The second PK parameter should be calculated was Vd [34].

\[ Vd = 0.62L/kg \times TBW \]  

(5)

Vd stands for volume distribution (L).

The third PK parameter, clearance of vancomycin, was calculated by multiplying the first and second PK parameters [34-36].
CL = $K_v \times V_d$ (6)  

CL stands for vancomycin clearance (L/h).

After getting clearance for vancomycin, then AUC$_{24}$ can be calculated by using [37]:

$$AUC_{24} = \text{total daily dose of vancomycin/CL}$$ (7)

Maximum MIC of MRSA strain that can still be covered, will be calculated by using the following equation:

Maximum MIC of MRSA strain = $AUC_{24}/400$ (8)

III. RESULTS

A total of 74 studies was identified during the literature search. And finally there were 21 adults critically ill population studies retrieved for more detailed evaluation and only 5 studies met the inclusion criteria. Details of the study flow presented in the figure 1. Most studies used intermittent infusion of vancomycin with the mean dose between 1,000mg-1,500mg. Dose adjustment was usually conducted based on the patient’s renal function. Number of blood concentration sampling at least 3 per patient in these studies. Only study conducted by Robert, et al, used continuous infusion and didn’t inform the number of sampling per patient.

Population PK studies

There were 5 population PK equation models derived from different critically ill populations, including: post Cardiothoracic surgery patients ($n=1$), hematological malignancy patients ($n=1$), all ICU patients ($n=3$) [38-42]. Complete population PK equation models were presented in the table 1. Studies that didn’t present the peripheral Vd means that they used one-compartment model in their analysis. Symbol 0 used in the equation model represented the estimate for PK parameter. The objective function value (OFV) was used in all studies as a criteria whether certain variable should be retained in the final equation model or should be rejected. In the first process, where the basic equation model was added with variable one by one, the OFV difference between basic equation model and added variable equation model should be at least 3.84 (with degree of freedom = 1). And for the second process, a backwards elimination process where each variable was fixed to zero value, the OFV difference should be at least 6.63. Each model also reported interindividual and residual variability.

Reference case analysis

Four critically ill population studies were used in the reference case analysis [38-41]. Even though present the population PK equation model, study conducted by Robert, et al, did not show the value of 0 (both $\theta_t$ and $\theta_0$) in the equation model. They just reported the final estimation of each pharmacokinetic parameter. Therefore, this study was not included in the reference case analysis. Table II presented the Vd and CL of vancomycin in critically ill population as well as AUC$_{24}$ calculation and maximum MIC still can be covered by giving a standard dose of vancomycin.

![Figure 1. Study review flowchart](image_url)

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Peripheral Vd</th>
<th>Central Vd $^a$</th>
<th>Clearing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staatz, et al</td>
<td>Unstable renal function</td>
<td>-</td>
<td>1.15 L/kg</td>
<td>Inter-individual variability: 36%</td>
</tr>
<tr>
<td></td>
<td>following cardiothoracic</td>
<td></td>
<td></td>
<td>$\theta_t = 2.94$ (estimation error 3%)</td>
</tr>
<tr>
<td></td>
<td>surgery</td>
<td></td>
<td></td>
<td>$\theta_0 = 0.0209$ (estimation error 3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Residual variability: 15%</td>
</tr>
<tr>
<td>Buelga, et al</td>
<td>Haematological malignancy</td>
<td>-</td>
<td>$\theta_0 \times \text{TBW}$</td>
<td>Inter-individual variability: 37.15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$\theta_t = 0.98$ (estimation error 7.43%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>$\theta_0 \times \text{CL}_{cr}$</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>$\theta_t = 1.08$ (estimation error 2.12%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Residual variability: 3.52%</td>
</tr>
</tbody>
</table>

TABLE I. CRITICALLY ILL POPULATION PK MODEL

TABLE II. CRITICALLY ILL POPULATION PK MODEL
TABLE II

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Population PK Model</th>
<th>Parameters</th>
<th>( \text{Vd} ) (L)</th>
<th>( \text{CL} ) (L/hr)</th>
<th>AUC ( \text{v} ) (mg/hr/L)</th>
<th>Max MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stantz, et al</td>
<td>Unstable renal function</td>
<td>69</td>
<td>( \text{CLr} )</td>
<td>4.29</td>
<td>466.2</td>
<td>1.16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>following cardiothoracic</td>
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<td>surgery</td>
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</tr>
<tr>
<td>Buelga, et al</td>
<td>Haematological malignancy</td>
<td>58.8</td>
<td>( \text{CLr} )</td>
<td>5.12</td>
<td>390.63</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Llopis-Salvia,</td>
<td>ICU patients</td>
<td>104.0</td>
<td>( \text{CLr} )</td>
<td>3.586</td>
<td>557.72</td>
<td>1.39</td>
<td></td>
</tr>
<tr>
<td>et al [40]</td>
<td></td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revilla, et al</td>
<td>ICU patients</td>
<td>49.2</td>
<td>( \text{CLr} )</td>
<td>3.19</td>
<td>626.96</td>
<td>1.56</td>
<td></td>
</tr>
<tr>
<td>et al [41]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>General population</td>
<td>37.2</td>
<td>( \text{CLr} )</td>
<td>2.60</td>
<td>769.23</td>
<td>1.92</td>
<td></td>
</tr>
</tbody>
</table>

In case, no \( \text{Vd} \) peripheral presented in the model, \( \text{Vd} = \text{Vd total} \).

\( \text{CLr} \) = creatinine clearance; \( \text{TBW} \) = total body weight.

IV. DISCUSSION

This review was focused on the population PK study of adult critically ill population with specific objectives to analyze the effect of deviated PK parameters found in this population to the achievement of AUC\( _{24} \) and maximum MIC coverage by giving a standard dose of vancomycin. There was another just published review of vancomycin population PK study conducted by Marsot, et al [43]. They reported all population PK studies both in adult and pediatric populations, but didn’t analyze the effect of different PK parameter to the achievement of AUC\( _{24} \) and MIC coverage by giving a certain dose of vancomycin. Finding from current review was in accordance with the finding from a study by Marsot, et al, i.e: Vd and CL were the most intended PK parameter to be modeled. Our review presents the creatinine clearance (\( \text{CLr} \)) and body weight as an important variable for CL of vancomycin and Vd equation model, which just the same with what Marsot, et al presented in their review.

Vancomycin was well characterized as a hydrophlyc drug with high molecular weight and was eliminated mainly by glomerular filtration [31,44]. By these characteristics, vancomycin will mostly distribute into the intravascular and interstitial space rather than further penetrate to the intracellular compartment. Two-compartment PK model was the best model describing PK process of vancomycin in the human body. Any condition changing the Vd and CL will greatly impact on vancomycin blood concentration profile. Since, AUC\( _{24} \) is calculated as a total of area under the plasma vancomycin concentration against time curve for 24h, any changes in blood concentration will impact on the total AUC\( _{24} \). Reference case calculation in table II has showed the same pattern of PK parameters in critically ill patients, i.e: higher Vd and faster CL compared with general population. There are some mechanisms that might contribute to the higher Vd among critically ill patient, including endothelial dysfunction leading to the increase of capillary permeability and fluid shift to the interstitial space, hypoalbuminaemia which would lowered the intravascular oncotic pressure leading to fluid shift to the interstitial space, aggresive fluid treatment used to overcome some symptoms, using special medical services like mechanical ventilation or extracorporeal membrane oxigenase, and post-surgical drainages [26-30]. While, some mechanisms that increase the CL of vancomycin usually associated with enhancement of renal blood flow. Any process increasing the renal blood flow will increase the CL of vancomycin, such as increase cardiac output found in the early phase of sepsis as a natural compensation mechanism of the human body, and using haemodynamically active drugs (HAD) like dopamine to manage some symptoms. In the other hand, any condition that decreased the renal function will also decrease the clearance of vancomycin, as can be seen in patients who developed complication or those in severe condition [26-30].

Giving a standard dose of vancomycin to general population can cover higher MIC of MRSA strain compared with the critically ill population. As shown in the table II, almost all MRSA strains classified as susceptible by CLSI guideline can be covered by giving a standard dose of vancomycin [23]. While in critically ill population, different
Moreover, higher MIC value should be compensated with higher value based on CLSI breakpoint recommendation. The value of AUC\textsubscript{24} ultimately is a determinant factor in this difference, where in Revilla, et al study, the AUC\textsubscript{24} approximately two fold higher than Buell, et al. Calculation of AUC\textsubscript{24} in this review using an equation that assumed the steady state condition already achieved, therefore CL of vancomycin will determine the achievement of AUC\textsubscript{24}. Both equation models of CL vancomycin included Cl\textsubscript{cr} as a variable with or without other variables. Since we use reference case analysis with the same Cl\textsubscript{cr} for both equation models, there should be other factors contributing to the different CL of vancomycin. The values of $\theta$, in both equations were different, i.e: 0.67 in Revilla, et al and 1.08 in Buell, et al. This difference plays as a major determinant in the total CL, since the additional variable included in Revilla, et al, i.e. age, just contribute approximately 0.7% from total CL. Different value of $\theta$ might be caused by different baseline characteristics of the patients included in both studies. All critically ill equation model included Cl\textsubscript{cr} as a variable in their models.

Body weight was the most influencing factor for Vd equation model. Equation model proposed by Revilla, et al, was the only Vd model that didn’t include the body weight as covariate. They found no significant improvement of goodness-of-fit plots when included weight in the final Vd equation model. The equation model proposed by Llopis-Salvia, et al, showed the highest Vd compared with another model. Higher Vd in this equation model correlated with two-compartment PK model applied in this study, while another model using one-compartment PK model. In two-compartment PK model, the Vd presented as a total Vd of peripheral and central compartments. In this equation model, peripheral compartment takes a major portion (75.85%) of total Vd. And another models didn’t calculate it in the total Vd. In study with main objective to determining the most appropriate loading or empirical dose, the impact of using different compartment PK model should be carefully considered.

We realize that the studies found in this review might be not all published population PK studies available, since only two database used and no any effort to search grey literature. We also didn’t pay much attention on the fluctuation of physiologic condition occurred in this population when we conducted the reference case analysis. However, due to the same pattern of PK parameters derived from accessible studies, result of this study emphasized the importance of close monitoring when prescribed standard dose of vancomycin to the critically ill patients, not only the achievement of recommended blood concentration but also vancomycin MIC of the MRSA strain. Especially in the era with increasing number of studies present the new phenomenon of shifting of vancomycin MIC of MRSA strain to the higher number even still classified as susceptible strain based on CLSI breakpoint recommendation [45–48]. The higher MIC value should be compensated with higher value of AUC\textsubscript{24} to ensure the achievement of AUC\textsubscript{24}/MIC=400. Moreover, vancomycin dose adjustment might be needed to achieve higher AUC\textsubscript{24} in this fluctuative PK profile population.

**References**


