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Iindividualized dose of Vancomycin for Patient's with Chronic Kidney Disease at a Government Hospital in Padang, West Sumatra, Indonesia

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ABSTRACT

Vancomycin is a narrow therapeutical index antibiotic used to treat a number of bacterial infections. This glycopeptide antibiotic is indicated for the medication of severe life-threatening infections by gram positive bacteria insensitives to other antibiotics. It is almost completely eliminated unchanged by renal. Vancomycin has potential toxic characteristic in patients with renal dysfunction. The aim of the study was to examine individualized dose of vancomycin in patients with chronic kidney disease at internal ward in a government hospital Padang. Computation of dose following pharmacokinetics dosing method. The research was arranged by observational retrospective method analyzed from 58 patient's medical record during January 2015 – April 2016. 43 patients (74.1%) of chronic kidney disease were medicated using vancomycin. Patients of chronic kidney disease on stage of 2, 3, 4 and 5 were 12, 15, 6 and 10, respectively. Clearance of vancomycin in patients with chronic kidney disease on stage of 2, 3, 4 and 5 were 3.06 ± 0.4, 1.88 ± 0.28, 0.88 ± 0.21, and 0.58 ± 0.15 L/h, respectively. The elimination half-life of this drug on chronic kidney disease stage 2, 3, 4 and 5 patients were 9.65 ± 2.09, 14.11 ± 2.89, 24.48 ± 5.44, and 51.27 ± 17.16 h, respectively. While accumulation factor in patients with chronic kidney disease on stage of 2, 3, 4 and 5 were 0.33 ± 0.12, 0.50 ± 0.1, 0.67 ± 0.09, and 0.49 ± 0.006, respectively. Results showed that 30.23% patients received exceed dose based on pharmacokinetic dosing method calculation.

Keywords: vancomycin, individualized dose, pharmacokinetic, renal dysfunction.

INTRODUCTION

Kidneys is an important organ in controling body fluids, electrolyte balance, removal of metabolic waste, and drug elimination from the body. Dysfunction of of kidneys can alter the pharmacokinetics of drugs, especially drugs that predominantly eliminated by kidneys [1].

Patients with chronic kidney disease (CKD) need an adjustment individual dose. Dose monitoring on patients with chronic kidney disease is advocated to avert acute kidney injury and its associated high morbidity, mortality and health care costs [2]. Failing in calculation of sufficient dose of drugs in this population can cause intoxication or inappropriate therapeutic response, leading to treatment failure. The approach of individualized drug dose will assure an optimal therapy [3].

Pharmacokinetically, vancomycin almost completely eliminated as parent drug in the urine, mainly by glomerular filtration (≥ 90%). Due to elimination characteristic of vancomycin, renal impairment is the paramount diseases that alter the pharmacokinetics of vancomycin [4]. Vancomycin clearance decreases proportionally with the decline of creatinine clearance (CrCl). Therefore, creatinine clearance of vancomycin can be used in calculation of vancomycin dose adjustment [5].

Vancomycin is one of antibiotics with narrow therapeutic index and great pharmacokinetic variability [4]. In impaired renal function, dose of this antibiotic is adjusted based on creatinine clearance. It should be considered of target dose of vancomycin in the therapeutic range to improve the effectiveness and minimize the potential toxic effects of the drug [6].

The principle of therapeutic management on patients can be determined based on clinical pharmacokinetics science. Pharmacokinetics concept aims are to design individual dosage regimen, optimize the therapeutic response on treatment, and minimize side effects [4]. To achieve optimal drug requires understanding not only the absorption, distribution and elimination of drug, but also the kinetics process [7].

Research on dose adjustment of narrow therapeutic drug for patients with renal impairment have been performed at several hospitals in Indonesia. One study conducted at Hospital Dr. Moewardi Surakarta in the period September-November 2007 showed 16.1% of the dose of antibiotics is not adjusted in patients with renal failure [8]. Related research has also been carried out on patients with heart and renal dysfunction in Hospital Dr. Sardjito, Yogyakarta in the period January 2010 – March 2011. 11 female and 4 male patients were treated using digoxin with doses exceeding the maximum levels of digoxin [9].

The elimination of vancomycin is slower on patients with renal insufficiency [4]. Dose of vancomycin is needed to adjust individually on patients with impaired renal function because of diminish in elimination of drug by the kidneys and prolong the half-life of drug. Dose of vancomycin can be estimated pharmacokinetically to achieve the optimal therapy, safe and effective, especially in patients with chronic kidney disease. This study used data from medical records of patients and calculated individual dose based on pharmacokinetic dosing method [4].

MATERIALS AND METHODS

This cross-sectional design was conducted using medical record data from January 2015 to April 2016 at internal ward in a government hospital in Padang, Indonesia. Inclusion criteria were data collected from medical record of patients who treated with vancomycin, and has creatinine clearance values ≤89 mL/min. Exclusion criteria were data medical record of patients who have creatinine clearance values ≥90 mL/min.

Operational Definitions

Appropriate dose: if the vancomycin dose adjusted based on the calculation of pharmacokinetic dosing method uses data creatinine clearance values [4]. Inappropriate dose: if the vancomycin dose is not adjusted based on the calculation of pharmacokinetic dosing method uses data creatinine clearance values [4]. Chronic kidney disease: classification of chronic kidney disease, according to The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI). Nephrotoxic: increased concentrations of serum creatinine (SCr) greater than 0.5 mg/dL the baseline value of serum creatinine or 50% decrease in creatinine clearance [10].

Research Instruments

Patients creatinine clearance values can be calculated using the Cockcroft-Gault equation [4]. Individualized dose measured are dosing and interval based on pharmacokinetic dosing method [4].

Data Collection

Data were collected from patient's medical records. Data used are age, body weight, height, serum creatinine values, dosage and interval of vancomycin, the duration of vancomycin used. Pharmacokinetic individual dose calculations dosing method are calculated by the formula [4]:

(1) Estimation of vancomycin clearance

Cl = 0.695 (CrCl) + 0.05 where Cl is vancomycin clearance in mL/min/kg and CrCl is creatinine clearance in mL/min/kg.

(2) Estimation of vancomycin volume of distribution
The average volume of distribution for vancomycin is 0.7 L/kg.
(3) Estimation of vancomycin elimination rate constant (k_e) and half-life ($t_{½}$)
k_e = Cl /V. The elimination rate constant (k_e) in hours^{-1}.
$t_{½} = 0.693/k_e$.. Half-life ($t_{½}$) in hours.
(4) The equation used to calculate individual dose regimens
$\tau = (\ln Css_{max} - \ln Css_{min})/k_e$
$D = Css_{max} V (1 - e^{-ke\tau})$
τ within hours, D in mg.

Assessment Instruments
Calculated dose adjustment based on pharmacokinetic dosing method were compared with the dose received by patients at internal ward in a government hospital in Padang, Indonesia.

Data Analysis
Data are presented as the mean and standard deviation (SD) when normally distributed. Otherwise, the median and interquartile range (IQR) were used. Data analyzed by Wilcoxon sign rank test. The entire analysis was performed with a suitable statistical soft ware.

RESULTS AND DISCUSSION

The objective of individualized dose for patients with chronic kidney disease medicated with vancomycin in a government hospital in Padang was for monitoring of vancomycin dosage regimen to prevent the possibility of drug accumulation. In this study, 58 patients were treated using vancomycin during the period January 2015 – April 2016. Based on inclusion criteria, 43 patient data is used as the subject of research. Gender distribution of the 43 patients were 17 male (39.5%) and 26 female patients (60.5%). The number of patients treated with vancomycin at age 20-44, 45-64, and older than 65 years were 6 (13.9%), 18 (41.9%), and 19 (44.2%), respectively.

Table 1. Demographic and clinical data patients with chronic kidney disease at internal ward in a government Hospital in Padang, Indonesia

Demographic and clinical data	Number and percentage
Total number of data patients during the study period	58
Number of patients with chronic kidney disease	43 (74.1%)
Male	17 (39.5%)
Female	26 (60.5%)
Age (years) median (IQR)	63 (52 – 70)
Weight (kg) median (IQR)	57 (50 – 60)
SCr: serum creatinine (mg/dL) median (IQR)	1.4 (0.9 – 3.1)
CrCl: creatinine clearance (mL/min) median (IQR)	39.97 (17.0 – 60.5)
CrCl 60–89 mL/min	12 (27.9%)
CrCl 30–59 mL/min	15 (34.9%)
CrCl 15–29 mL/min	6 (13.9%)
CrCl <15 mL/min	10 (23.3%)

Results showed that vancomycin was used on 43 patients who had tested positive of culture bacteria with pathogenic bacteria Methicillin-resistant *Staphylococcus aureus* (MRSA) and antibiotic sensitivity testing with vancomycin. MRSA bacteria found in the throat swab, sputum, and pus were 19 (44%), 16 (37%), and 8 patients (19%), respectively. Vancomycin is a first-line therapy in infectious diseases caused by bacteria MRSA and there is the list of drugs on Indonesia National Formulary 2015 for national health insurance patients [11].

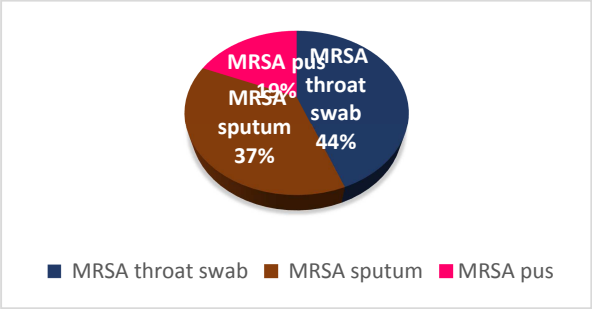

Figure 1. The diagram of pathogenic bacteria MRSA

Cockcroft-Gault and Salazar-Corcoran equations in calculation of creatinine clearance values were implemented and suitable for 39 and 4 patients, respectively. Distribution of the number and percentage of patients based on creatinine clearance values of 60-89, 30-59, 15-29, and < 15 mL/min were found in 12, 15, 6, and 10 patients, respectively or in percentage were 34.9, 13.9, 27.9, and 23.3%, respectively.

Table 2. The value of CrCl patients and stages of CKD

Stage of CKD	Cockcroft-Gault Median (IQR)
Stage 2	65.1 (62.8 – 74.0)
Stage 3	41.5 (37.4 – 43.7)
Stage 4	22.3 (18.4 – 24.3)
Stage 5	11.0 (7.31 – 13.02)

Vancomycin pharmacokinetic parameters can be computed from calculated creatinine clearance values.

Table 3. Pharmacokinetic parameters

Pharmacokinetic parameters	Stage 2	Stage 3	Stage 4	Stage 5
Clearance of vancomycin (L/h)				
Mean ± SD	3.06 ± 0.40	1.88 ± 0.28	0.88 ± 0.21	0.58 ± 0.15
Volume of distribution (V) (L)				
Mean ± SD	41.65 ± 10.07	37.52 ± 5.24	36.98 ± 4.39	40.18 ± 5.30
Elimination rate constant (k_e) (h^{-1})				
Mean ± SD	0.076 ± 0.016	0.051 ± 0.011	0.025± 0.008	0.015 ± 0.004
Elimination half life ($t_{½}$) (h)				
Mean ± SD	9.65 ± 2.09	14.11 ± 2.89	24.48 ± 5.44	51.27 ± 17.16
Accumulation factor (f)				
Mean ± SD	0.33 ± 0.12	0.50 ± 0.1	0,67 ± 0,09	0.49 ± .01
Accumulation index (R)				
Mean ± SD	1.53 ± 0.29	2.07 ± 0.42	3.2 ± 0.8	1.99 ± 0.02

Vancomycin is an antibiotics with narrow therapeutic index and has potential risk of side effects such as nephrotoxicity and ototoxicity [12]. Ttherefore, it is necessary for individual dose adjustment to patients with chronic kidney disease [13]. Vancomycin is excreted 90% in the kidney by glomerular filtration. Vancomycin clearance reduced proportionally with decreased creatinine clearance [4].

On patients with chronic kidney disease stage 3 the half lifes were 14.11 ± 2.89 hours, longer than normal patients. Similarly for patients with kidney disease stage 4 and 5 the half life of drug were 20.43 ± 5.44, and 51.27 ± 17.16 hours, respectively. The elimination half life of vancomycin in normal renal patients are 3-13 hours with the average 6 hours [14], while other researcher reported about 8 hours [15].

About 34 patients (79.07%) received dose of vancomycin were 2x1000mg/day and 8 patients (18.60%) with dose of

1 x 1000 mg/day, 1 patient (2.33%) with dose of 2 x 500 mg/day. 30.23% patients received dose exceeding individual dose vancomycin calculated following pharmacokinetic dosing method. The usual dose of vancomycin in adult patients with normal renal function is 2 grams/day with administration of 1 g every 12 hours as an intravenous infusion over 1 - 2 hours. In general the responses seen in 48 to 72 hours at a sensitive infection [14]. Vancomycin elimination is slower in patients with renal impairment, therefore vancomycin dosage adjustment is required for patients with decreased kidney function. Vancomycin accumulation can occur if the dose is not modified based on the level of renal impairment [16].

In patients with chronic kidney disease stage 3, average individual dose should be 768.3 ± 92.7 mg, with an interval of 14.1 ± 2.89 hours. While the administered dose for these patients were 2x1000 mg/day in 12 patients, and 3 patients receive dose of 1x1000mg/ day. Average individual dose for ppatients with chronic kidney disease stage 4 should be 702.9 ± 95.9 mg with interval of 24.5 ± 4.97 hours. While the administered dose for these patients were 2 x 1000 mg / day in 5 patients, and 1 patient with a dose of 1 x 1000 mg/day.

Average individual dose for patients with chronic kidney disease stage 5 should be 794.22 ± 125.08 mg with intervals of 51.3 ± 17.18 hours. While the dose given 2x1000 mg/day in 9 patients, and 1 patient with a dose of 2x500 mg/day.

Table 4. Calculation of individualized dose vancomycin based on pharmacokinetic dosing method

No	Criteria of CKD	Before		After		p
		D (mg)	τ (h)	D (mg)	τ (h)	
1	Stage 2 (n = 12) IQR Median Mean ± SD	 1000 – 1000 1000 1000 ± 0	 12 - 24 12 16 ± 5.91	 850.5 –1049.5 936.19 965.1 ± 134.1	 12 – 12 12 12.6 ± 1.73	0.239
2	Stage 3 (n = 15) IQR Median Mean ± SD	 1000 – 1000 1000 1000 ± 0	 12 – 12 12 14.4 ± 4.97	 702.1 – 846.7 769.8 768.3 ± 92.7	 11.5 – 16 15 14.1 ± 2.89	0.182
3	Stage 4 (n = 6) IQR Median Mean ± SD	 1000 – 1000 1000 1000 ± 0	 12 – 12 12 14 ± 4.90	 619.5 – 767.8 693 702.9 ± 95.9	 22.5 – 28 26 24.5 ± 4.97	0.028
4	Stage 5 (n = 10) IQR Median Mean ± SD	 1000 – 1000 1000 950 ± 158.11	 12 – 12 12 12 ± 0	 711.9 – 861.4 754.6 794.22 ± 125.08	 38.75 – 60.75 44.5 51.3 ± 17.18	0.005

Note:D = maintenance dose; τ = interval dose; p analyzed by Wilcoxon sign rank test

Monitoring vancomycin therapy is recommended to prevent toxicity. The level of vancomycin in blood is commonly used by peak concentration in range of 20-40 mg/L and through concentrations of 5-10 mg/L. Concentration of 15-20 mg/L is recommended for MRSA infections, including pneumonia, endocarditis, meningitis and osteomyelitis [17]. Vancomycin is reported to generate toxic at concentrations exceeding 80 µg/mL [4]. Based on pharmacokinetic calculations are 30.23% of patients using doses of vancomycin exceeding individual dose in four patients with chronic kidney disease stage 4, and 9 patients with chronic kidney disease stage 5, respectively.

Nephrotoxicity was defined as an increase 0.5 mg/dL from baseline of serum creatinine or 50% in creatinine clearance [10]. Vancomycin therapy should be administered with caution with dose reduction in patients with renal impairment, because of the possibility of increased risk of nephrotoxicity due to accumulation of the drug. This is due to reduced renal function, clearance of vancomycin is reduced, and the plasma concentration and half-life will be increased. To minimize the risk of toxicity, the dose administered should not exceed the usual dose, serum concentrations of the drug should be prescribed has been reported at regular intervals and the dose adjusted to maintain a desired concentration [18]. Use of other nephrotoxic compounds concomitantly should be avoided [19]. Use of a nephrotoxic compounds may increase approximately 35% of vancomycin toxicity. Nephrotoxicity commonly associated with vancomycin serum concentrations 80 to 100 µg/mL. Therefore kidney function tests should be performed periodically during therapy [14].

Based on laboratory results of patients increased in serum creatinine values from before using and during vancomycin therapy of three patients were 3.4, 1.8, and 0.9 mg/dL.

Initial Serum creatinine levels at the begining and during therapy in a patient were 4.3, and 7.7 mg/dL, respectively. Creatinine clearance values calculated using Cockcroft- Gault equation in this patient at the beginning and during therapy were 13.53, and 7.56 mL/min, respectively. Other patient has initial and during therapy serum creatinine level were 2.4, and 4.2 mg/dL, respectively. Based on the value of creatinine clearance calculated by Cockcroft-Gault equation at the beginning of 20.95 mL min and during therapy decrease to 11.97 mL/min. There is one patient with initial serum creatinine level of 1.5 mg/dL, to 2.4 mg/dL during therapy. Calculated creatinine clearance were 43.57 mL/min at the begining and 24.68 mL/min during therapy. However, this data could not be categorized as nephrotoxic effect of vancomycin used, because the value of creatinine in patients serum greater than the limit value of serum creatinine before and after the administration of vancomycin. This is because three patients have decreased renal function based on laboratory data of patients. One patient shows the value of serum creatinine 4.3 mg/dL and ureum serum 140 mg/dL, other patient have the value of serum creatinine 2.4 mg/dL and ureum serum 113 mg/dL, and there is one patient with serum creatinine values 1.5 mg/dL and ureum serum 50 mg/dL.

Limitations of the study

This research effort has been made and implemented in accordance with scientific procedures, however, still has limitation:

1. Most of the data in this study uses secondary data from the medical record, so the chances are recording poor and incomplete data such as weight and patient laboratory data.
2. The calculation of doses of vancomycin using an approach based on pharmacokinetic equations according to the literature. Vancomycin therapy should be monitored by serum vancomycin concentration data so that estimates of doses to achieve the target concentration of vancomycin appropriate therapy can be predicted more accurately according to the condition of each patient individually.

CONCLUSION

Based on the results of study adjustment dose vancomycin on patients with chronic kidney disease in internal ward in a government hospital in Padang, Indonesia can be concluded:

1. The number of patients using doses of vancomycin exceed individual doses as calculated by "Pharmacokinetic Dosing Method" were 30.23%.
2. Dose should be adjusted for individual dose patients with chronic kidney disease who use vancomycin in order to achieve a safe and effective therapy.

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