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Original Article

COMPARATIVE STUDY OF KANAMYCIN AND CAPREOMYCIN ON SERUM POTASSIUM LEVEL OF MULTIDRUG RESISTANCE TUBERCULOSIS PATIENTSAT A HOSPITAL IN BANDUNG, INDONESIA

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ABSTRACT

Objective: Kanamycin and capreomycin are the second lines injectable ant tuberculosis used in therapy regimen of multidrug resistance tuberculosis (MDR TB) in Indonesia. Both have effects on serum potassium levels and cause hypokalemia. The aim of this study is to compare and evaluate the effects of kanamycin and capreomycin on serum potassium levels of MDR TB patient.

Methods: This was a retrospective and concurrent cohort study with intention-to-treat analysis on MDR TB patients during 2014 at Dr. Hasan Sadikin General Hospital Bandung, Indonesia. The patients were divided into two groups, one group received kanamycin regimen. Meanwhile, the other group received capreomycin regimen. Serum potassium level, the incidence of hypokalemia and the classification of its severity were compared monthly for five months of the therapy.

Results: In the first two months, capreomycin significantly decreased serum potassium level stronger than kanamycin (2.95 mEq/l vs. 3.82 mEq/l, P<0.001 in the first month and 2.85 mEq/l vs. 3.81 mEq/l, P<0.001 in the second month). Before five months, the number of enabled patients to follow up decline which is caused by hypokalemia in capreomycin group was60.0% while in kanamycin group is 0.0%.

Conclusion: Capreomycin has a stronger effect on decreasing serum potassium level compared to kanamycin, and it causes hypokalemia.

Keywords: Second line Injectable Antituberculosis, Adverse Drug Reaction, Hypokalemia.

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INTRODUCTION

Multidrug resistance tuberculosis (MDR-TB), defined as an infection caused by *Mycobacterium tuberculosis* strain which is resistant to both isoniazid and rifampicin, still be a problem of eradication of tuberculosis (TB). World Health Organization (WHO) mentioned that in 2013 the prevalence of MDR TB was estimated 3.6% of new cases and 20.2% of the case handled in the wide world, whereas in Indonesia the number of MDR TB cases is 1.9% of new cases and 12% of retreatment. Indonesia belongs to 27 countries with the highest MDR TB burdens [1].

MDR TB treatment uses, at least, four antituberculosis to which the *Mycobacterium tuberculosis* isolate is still sensitive including second-line injectable antituberculosis. All second-line injectable drugs are bactericidal and related to several potentials of adverse effect. The second line injectable drug used in therapy regimen is kanamycin, capreomycin, and amikacin. Kanamycin is a second-line injectable drug used in standard regimen in Indonesia. On the other hand, a review article by Caminero [2] hypothesizes that capreomycin as the first choice of second-line injectable drug in MDR TB therapy.

Kanamycin and capreomycin, classified as aminoglycoside group and cyclic polypeptide, have a disturbance effect on the electrolyte. It has been reported that the use of aminoglycoside and capreomycin causes the increase in renal electrolyte wasting, including potassium, magnesium, and calcium. Electrolyte disturbance particularly hypokalemia is related to several significant morbidities such as tetany, seizures, and cardiac arrhythmia [3]. Hypokalemia case undergone by MDR TB patients in the previous research was mentioned of 32% and 33.2% [4,5]. Therefore, serum potassium level is one of the most significant parameters in relation to the patient safety.

The aim of the study is to compare and evaluate the effects of kanamycin and capreomycin on serum potassium level of MDR TB patients at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia.

MATERIALS AND METHODS

This was a retrospective and concurrent cohort study with intention-to-treat analysis on MDR TB patients at MDR clinic Dr. Hasan Sadikin General Hospital Bandung, Indonesia. All adults' pulmonary MDR-TB patients who start MDR-TB therapy with kanamycin standard regimen or capreomycin regimen during 2014 were identified from the list of MDR clinic registration. Kanamycin standard regimen and capreomycin regimen differ only at second-line injectable used which is combined with levofloxacin, ethionamide, cycloserine and pyrazinamide. The patients excluded such as un compliance patients, pregnant women, HIV-positive patients, patients with the history of second-line injectable antituberculosis treatment, and patients with renal impairment, alcohol or drug consumption and agents which affect serum potassium level such as insulin, angiotensin converting system (ACE) inhibitor, angiotensin II receptor blocker, non-steroidal anti-inflammatory drug (NSAID), diuretic, amphotericin B, corticosteroid, β2-agonis, and potassium supplement).

All patients involved in the study were divided into two groups, which were kanamycin regimen and capreomycin regimen. Initial demographic and clinical characteristics data of all patients were recorded such as age, gender, initial body weight, previous antituberculosis treatment history, comorbidities and smoking status. Initial serum potassium level before the treatment or baseline was also recorded. The patients were followed and monitored monthly for their serum potassium level for five months of the therapy. Each month the serum potassium level was recorded and analyzed statistically. The serum potassium level under 3.6 mEq/l was classified in regard to the severity of hypokalemia into *mild*(3.1-3.5 mEq/l), *moderate*(2.6-3.0 mEq/l), and *severe* (<2.5 mEq/l) [6].

The sample size of each group was calculated of 11 patients in each group. In the calculation, it was selected the power of 80%, the significance level (α) was 0.05 and based on the previous research it was assumed that the proportion of hypokalemia incidence in kanamycin group and capreomycin group was 10% and 68%, respectively [3].

The consent of the regular data use was obtained from Department of Education and Training at Dr. Hasan Sadikin General Hospital Bandung. The ethical approval for the study was obtained from Research and Ethical Committee of Dr. Hasan Sadikin General Hospital Bandung.

Statistical analysis

Statistical analysis employed SPSS software version 22. Initial demographic and clinical characteristics were analyzed using independent sample *t*-test for continues data with normal distribution, Mann-Whitney test for continues data with normal distribution, and χ^2or Fisher's *exact test* for categorical data. Mean serum potassium comparison levels each month with baseline value was analysed using paired *t*-test while the comparison between groups used independent sample *t*-test. The comparison of the number of hypokalemia incidence and the classification of its severity between groups were analyzed using Fisher's exact test. P<0.05 was considered statistically significant difference.

RESULTS

Distribution of patients

Total of 137 patients received MDR TB treatment during the study; 65 patients were excluded (fig. 1) and the remaining 72 patients were involved in the study. 53 patients were as kanamycin standard regimen receivers, and 19 patients were as capreomycin regimen receivers.

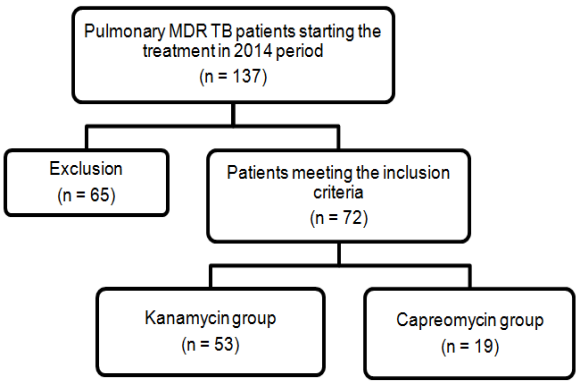

Fig. 1: Diagram of the study population included in the analysis

Initial demographic and clinical characteristic of patients

Initial demographic and clinical characteristic of each group are presented in table 1. Distribution of mean age, gender, mean initial body weight, the history of previous antituberculosis treatment, comorbidities, and smoking status were not significantly different from both groups. Antituberculosis was given based on the body weight per kg of the patient as shown in table 2.

Table 1: Initial demographic and clinical characteristic

	Kanamycin group (n = 53) n (%)	Capreomycin group (n = 19) n (%)	P-value
Age (y)[a]	36.17+11.88	37.32+10,15	0.710
Gender			
Female	20 (37.7)	6 (31.6)	0.632
Male	33 (62.3)	13 (68.4)	
History of Antituberculosis			0.501
None	1 (1.9)	0 (0.0)	
Category I	15 (28.3)	5 (26.3)	
Categoy 2	1 (1.9)	2 (10.5)	
Category 1 and 2	36 (67.9)	12 (63.2)	
Comorbid			
None	49 (92.5)	16 (84.2)	0.204
Diabetes	2 (3.8)	2 (10.5)	
Hypertension	0 (0.0)	1 (5.3)	
Chronic Hepatitis	2 (3.8)	0 (0.0)	
Initial Body Weight (kg)[a]	44.20+7.78	47.0+11.61	0.417
Smoking status			
Ex-smoker	33 (62.3)	12 (63.2)	>0.999
Current smoker	1 (1.9)	0 (0.0)	
Never	19 (35.8)	7 (36.8)	

[a]mean+SD

Table 2: Dose of Antituberculosis drug used

	Dose (mg)/Body weight (kg)/d			
Body weight (kg)	**<33 kg**	**33-50 kg**	**51-70 kg**	**>70 kg**
Kanamycin	15-20	750	1000	1000
Capreomycin	15-20	750	1000	1000
Ethionamid	15-20	500	750	1000
Levofloxacin	7.5-10	750	750	1000
Cycloserine	15-20	500	750	1000
Pirazynamide	20-30	1500	1500	2000

Table 3: Mean serum potassium level comparison each month with baseline value in kanamycin group

	Time (m)					
	Baseline	**1**	**2**	**3**	**4**	**5**
Patients	53	53	48	44	41	38
Serum potassium levels (mEq/l) [a]	4.27+0.55	3.82+0.53	3.81+0.55	3.75+0.52	3.75+0.66	3.86+0.41
Difference	-	0.45	0.46	0.52	0.52	0.41
P-value	-	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*

[a]mean+SD

Table 4: Mean of serum potassium level comparison each month with baseline value in capreomycin group

	Time (m)					
	Baseline	**1**	**2**	**3**	**4**	**5**
Patients	19	19	11	6	3	2
Serum potassium levels (mEq/l) [a]	4.06+0.47	2.95+0.72	2.85+0.65	3.18+0.91	3.75+1.46	3.86+1.06
Difference	-	1.11	1.21	0.88	0.31	0.20
P-value	-	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*

[a]mean+SD

Mean serum potassium level comparison

Mean serum potassium level comparison at baseline and each month showed a significant decline in serum potassium level for the first month until the fifth month of therapy in both groups (table 3 and table 4).

Comparison between two groups (table 5), the average serum potassium level in capreomycin group was significantly lower than kanamycin group (2.95 mEq/lvs.3.82 mEq/l, P<0.001 in the first month and 2.85mEq/l vs. 3.81 mEq/l, P<0.001 in the second month). The incidence of hypokalemia (table 6) in the first two months in both groups also showed a significant difference. Capreomycin group showed higher incidence compared to kanamycin group (89.5% vs. 28.3%, P<0.001 in the first month and 81.8 % vs. 29.2 %, P<0.001 in the second month). The severity of hypokalemia classification in the first month among capreomycin group was dominated by *mild* and *moderate* (36.8%), whereas kanamycin group was dominated by *mild* (22.6%). In the second month, capreomycin group was dominated by *mild* hypokalemia (54.5%), whereas kanamycin group was dominated by *mild* hypokalemia (20.8%).

Table 5: Mean serum potassium level comparison each month between two groups

Time (m)	Group	Patients	Lowest serum potassium levels (mEq/l)	Serum potassium levels (mEq/l)	P-value
Baseline	Kanamycin	53	3.1	4.27+0.54	0.098
	Capreomycin	19	3.2	4.04+0.48	
1	Kanamycin	53	2.5	3.82+0.53	<0.001*
	Capreomycin	19	1.6	2.95+0.72	
2	Kanamycin	48	2.7	3.81+0.55	<0.001*
	Capreomycin	11	2.0	2.85+0.65	
3	Kanamycin	44	2.3	3.75+0.57	Statistical analysed did not performed
	Capreomycin	6	<1.5	3.18+0.91	
4	Kanamycin	41	2.2	3.75+0.66	
	Capreomycin	3	2.3	3.05+1.46	
5	Kanamycin	38	2.6	3.86+0.55	
	Capreomycin	2	2.3	3.05+1.06	

Table 6: Incidence and severity of hypokalemia comparison between two groups

Time (m)	Group	Patients	Not Hypokalemia n (%)	Hypokalemia n (%)	Severity classification			P-value
					Mild	*Moderate*	*Severe*	
Baseline	Kanamycin	53	50 (94.3)	3 (5.7)	3 (5.7)	0 (0.0)	0 (0.0)	0.184
	Capreomycin	19	16 (84.2)	3 (15.8)	3 (15.8)	0 (0.0)	0 (0.0)	
1	Kanamycin	53	38 (71.7)	15 (28.3)	12 (22.6)	2 (3.8)	1 (1.9)	<0.001*
	Capreomycin	19	2 (10.5)	17 (89.5)	7 (36.8)	7 (36.8)	3 (15.8)	
2	Kanamycin	48	34 (70.8)	14 (29.2)	10 (20.8)	4 (8.4)	0 (0.0)	<0.001*
	Capreomycin	11	2 (18.2)	9 (81.8)	0 (0.0)	6 (54.5)	3 (27.3)	
3	Kanamycin	44						
	Capreomycin	6	Statistical analysed did not performed					
4	Kanamycin	41						
	Capreomycin	3						
5	Kanamycin	38						
	Capreomycin	2						

Table 7: Declining number of enabled patients to follow up in two groups

Reasons	Kanamycin group (n = 53) n (%)	Capreomycin group (n = 19) n (%)
Related to hypokalemia	0 (0.0)	11 (60.0)
Changed to kanamycin regimen and received potassium supplement	0	3
Received potassium supplement	0	7
Died	0	1
Unrelated to hypokalemia	8 (15.1)	2 (10.0)
Received medications influence serum potassium levels	8	2
Unknown	7 (13.2)	4 (20.0)
Decided to stop MDR TB treatment	6	3
Died	1	1

Declining number of patients

Statistical analysis could not be performed in the next three months because the number of enabled patients to follow-up among capreomycin group decreased smaller than the limit of samples needed. The reason of the declining number of patients observed was the patients could not continue the treatment or did not meet the inclusion criteria anymore due to either related or unrelated to hypokalemia (table 7). The declining number of patients observed related to hypokalemia such as patients turned to use kanamycin regimen, to receive potassium supplement, and passed away due to arrhythmia. The number of patients declines related to hypokalemia was 60.0% patient in capreomycin group.

DISCUSSION

MDR-TB can be cured by an appropriate combination of antituberculosis agents. Several factors should be considered when determining the appropriate agents including the availability of the agents, the rationality of the drug use, the resistance profile of the patient, the history of drug use, the cost of therapy, and the possibility of toxic adverse events [2]. This study compared the effects of kanamycin and capreomycin in the use of MDR-TB therapy regimen on serum potassium level in order to evaluate the safety parameter related to the adverse effect.

The current study showed declining serum potassium level in both groups since the first month of the therapy but the patients who received capreomycin significantly underwent declining serum potassium level greater than kanamycin receivers (2.95 mEq/l vs. 3.82 mEq/l, P<0.001 in the first month and 2.85 mEq/l vs. 3.81 mEq/l, p<0.001 in the second month). The incidence of hypokalemia was also higher in the patients receiving capreomycin than those receiving kanamycin (89.5% vs. 28.3%, P<0.001 in the first month and 81.8 %vs. 29.2 %, P<0.001 in the second month). The mechanism considered explaining this effect was stimulation of calcium-sensing receptor (CaSR) by both injectable drugs. CaSR is abasolateral receptor in the thick ascending limb of the loop of Henle, which is activated by aminoglycoside, polyvalent and cationic molecules. Capreomycin mentioned has a similar activity to an aminoglycoside. This stimulation could disrupt electrolyte transport via inhibition of four different pathways that involve Na^+, K^+,Cl^- symporter channel(NKCC2), renal outer medullary potassium channel (ROMK), Na^+, K^+-ATPase and/or paracellular diffusion. Inhibition of these transport mechanism leads to increased urinary excretion of Na^+, K^+, Mg^+, and $Ca^{2+}$and associated electrolyte disorders [7]. The stronger effect of capreomycin was assumed related to the number of amino group in its structure. It is known that capreomycin is antibiotic as a cyclic polypeptide which has many amino groups than kanamycin. The previous study reported that the potency order of several aminoglycoside was directly proportional with the number of amino group explaining the infirmity of kanamycin stimulation effect in CaSR having the least amino group compared to gentamicin, tobramycin, and neomycin (four, compared to five on gentamicin and tobramycin, and six on neomycin) [8]. The incidence of hypokalemia in capreomycin group caused several patients must change into kanamycin, unable continue the therapy without potassium supplement, and even died. This phenomenon showed that the use of capreomycin related to the higher hypokalemia potential which might cause the patients are not being able to continue the therapy and would increase the therapy cost. However, if the benefit of capreomycin use was highly required, then the monitoring of serum potassium level and preventive actions of hypokalemia must be conducted.

CONCLUSION

This study showed that the use of capreomycin in MDR-TB therapy regimen caused the declining of serum potassium level greater than the use of kanamycin significantly. Moreover, the incidence of hypokalemia was higher in the capreomycin group than kanamycin group caused several patients are not being able to continue the therapy without potassium supplement or must change into kanamycin. Monitoring serum potassium level and preventive actions of hypokalemia must be conducted in the use of capreomycin.

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CONFLICT OF INTERESTS

All authors have none to declare

REFERENCES

1. Katherine F, Annabel B, Anna D, Hannah MD, Dennis F, Inés G, *et al.* editors. Global tuberculosis report. France: WHO Library Cataloguing-in-Publication Data; 2013.
2. Jose AC, Giovani S, Alimuddin Z, Giovani BM. Best drug treatment for multi-drug-resistant and extensively drug-resistant tuberculosis. Lancet Infect Dis 2010;10:621-9.
3. Sonya S, Jennifer F, Felix A, Anne H, Keith J, Epifanio S, *et al.* Hypokalemia among patients receiving treatment for multi-drug resistant tuberculosis. Chest 2004;125:974-80.
4. Shin SS, Pasechnikov AD, Gelmanova IY, Peremitin GG, Strelis AK, Mishutin S, *et al.* Adverse reactions among patients being treated for MDR-TB in Tomsk, Rusia. Int J Tuberculosis Lung Dis 2007;11:1314-20.
5. Haregewoin B, Daniel S, Getnet Y, Tesfamariam M. Prevalence and risk factors of adverse drug reactions associated multidrug-resistant tuberculosis treatments in selected treatment centers in addis ababa ethiopia. J Tuberc Res 2014;2:144-54.
6. Helen S, Rustam R. Hypokalemia in adults. Share Care Pathology Guidelines CHISCP6; 2012.
7. Zietse R, Zoutendijk R, Hoorn EJ. Fluid, electrolyte and acid-based disorders associated with antibiotic therapy. Nat Rev Nephrol 2009;5:193-202.
8. Zuzana S, Michel B, Saiid K, Romuald M. Agonist and allosteric modulators of the calcium-sensing receptor and their therapeutic applications. Mol Pharm 2009;76:1131-44.