The Effect of the Use of Anti-Hypertensive Agents Lisinopril and Fosinopril with Different Degrees Renal Excretion on Renal Function in Hypertension with Mild to Moderate Renal Failure

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ABSTRACT

The aim of this study was to investigate the effect of antihypertensive agents with different degrees of renal excretion lisinopril(L) eliminated in the kidney and fosinopril(F), only 50% of which is eliminated through the kidney on renal function in hypertension patients with mild to moderate renal failure.

Materials and methods: Patients were divided into two groups. The first group was given F 10 mg/day and the second group was given L 10 mg/day. Groups were divided randomly, and drugs were given for 6 weeks each night at 8.00 p.m. The hypertension status of each subject was determined from systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mg/dl. Subjects were both male and female, with an age range of 18 – 65 years old.

Results: The results from the creatinine examination of the 10 mg F group was (3.06 ± 0.97) mg/dl after drug use, which showed no decrease in renal function. The difference was insignificant (p=0.17). The 10 mg L group the creatinine level was (3.22 ± 0.17), where as in the 10 mg L group the creatinine level was (3.22 ± 0.75) mg/dl before the use of the drug and (4.11 ± 2.14) mg/dl after the use of the drug respectively. There was no worsening of the renal function, which did not differ significantly (p=0.11). There was a significant difference (p < 0.05) in the creatinine level of the 10 mg F and 10 mg L groups. The serum creatinine level before and after treatment did show any significant changes at 6 week. However, the serum creatinine profile over 6 week was more significant in the F group than in the L groups.

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INTRODUCTION

Hypertension always accompanies renal failure/dysfunction. It is estimated that 85% of all renal failures are accompanied by hypertension,[1,2] thus further decreasing renal function to the point of increasing morbidity and mortality. Thus, special attention and management is necessary, especially in the administration of anti-hypertensive agents (AHA). As we know, several kinds of AHA have different elimination pathways, such as lisinopril, which is completely eliminated through the kidneys, while Fosinopril is partially eliminated through the kidneys and partially eliminated through the liver.[3,7]

Several studies demonstrate that in patients with renal dysfunction, AHAs that are completely eliminated through the kidneys would accumulate and increase renal workload, which consequently requires dose adjustment,[8] while AHAs that are not completely eliminated through the kidneys are more reno-protective. However, there has been no specific study to proof this. Thus, we decided to prove whether an AHA with that is completely eliminated through the kidneys (lisinopril) could reduce renal function, compared to an AHA that is not completely eliminated through the kidneys (fosinopril). This study is conducted on hypertension patients with mild to moderate renal failure, based on serum creatinine levels.

MATERIALS AND METHOD

Each patient that participated this study was given an explanation on all related aspects and was asked to fill in an informed consent form. Patients were classi-

fied into two groups: Group I receiving 10 mg of fosinopril/day (Acenor-M, BMS), and Group II receiving 10 mg of lisinopril per day (Zestril, Zeneca).

Hypertension was based on a systolic blood pressure of 140 mmHg or more and/or a diastolic blood pressure of 90 mmHg or more, while mild to moderate renal failure was based on a serum creatinine level of 2-4 mg/dl. Subjects were 18-65 years of age, male and female. Patients who had previously received AHAs were discontinued from therapy for 2 week and given placebo capsules for 2 weeks. All medications that could increase blood pressure and disturb renal function may not be administered. Patients that are included in the study were all patients with mild to severe hypertension that suffered from mild to moderate renal failure.

Patients excluded in this study were those who suffer from secondary hypertension, obstructive nephropathy, disorder of cerebral blood vessels, angina pectoris, heart decompensation, diabetes mellitus, and all patients that invariably required ACE-I, such as post MCI, etc., and those with renal failure with a decrease in creatinine level of more than 25% of original findings, as well as the presence of side effects such as uncontrollable cough, angiodema, etc.

Medications were administered at 8 p.m. Western Indonesian Time. In the case of hypertension crisis/severe hypertension, and other necessary conditions, patients may receive Ca-antagonist or other groups of AHAs that are safe for the kidneys. This study was conducted using a prospective, randomized, open, blind-end, method.

Blood pressure was evaluated using Nova-standard sphygmomanometers in resting and standing positions. Before the evaluation, patients were requested to rest for 5 minutes for evaluation in a resting position and for 1 minute for evaluation in a standing position. Blood pressure evaluation in a resting position was conducted 3 times. The mean blood pressure value during the second and third measurement was used as the blood pressure value in a resting position. The patient's blood pressure during standing was only examined once. Blood pressure was evaluated at weeks –2, -1, 0, and so forth every week until the last week of the study (6 weeks).

Creatinine clearance test was conducted using the 4-hour method. Patients were asked to fast at night for approximately 10 hours, until they were examined in the morning (at approximately 8 a.m.). In the morning before the examination, the patient was asked to empty their bladders (urinate) until their bladder was completely empty, and then they were requested to drink 250 ml of water. They were requested to empty their bladder every 60 minutes and were given 200 ml of water every 60 minutes until 4 hours. Blood and urine samples were taken to check the creatinine clearance test. The value is determined using the following formula:

$$CC = \frac{\text{Urinary creatinine level (a)}}{\text{Blood creatinine level (b)}} \times \frac{\text{4-hour urine volume (L)}}{240}$$

$$CC = \frac{a \times c}{240\ b}$$

Creatinine evaluation was conducted according to Jafre reaction using a spectronic device (MILTONROY). Examination of renal proximal tubule function was conducted by examining uric acid reabsorbtion by evaluating uric acid excretion using the uric acid clearance to creatinine clearance ratio, as follows:

The patient was advised to undergo a low purine diet since one day prior to the examination. The patient's urine is collected for 24 hours. Urine and blood samples were taken for evaluation. The ratio is determined using the following formula:

$$\text{Ratio} = \frac{\text{Uric acid clearance}}{\text{Creatinine clearance}}$$

Evaluation was conducted using the calorimetric enzymatic method with a Vitalab Selectra instrument. The following laboratory analysis was also conducted on all study subjects: routine blood check, urinalysis, ureum and creatinine levels, uric acid level, blood electrolyte levels, lipid profile, blood sugar level, as well as calcium, phosphor, magnesium levels, using standard methods and instruments.

STATISTICAL TRIAL

The collected data was presented as mean value $\pm$ standard deviation and SEM, and was statistically analyzed using the unpaired t-test using Microstat software. A value of $p < 0.05$ is considered statistically significant.

RESULTS

Serum creatinine levels prior to administration of 10 mg of lisinopril and 10 mg of fosinopril were (3,22 ± 0,75) and (3,06 ± 0,62) respectively, which is not significantly different (p=0,3). (Table 1 and Figure 2).

Serum creatinine levels after administration of 10 mg of fosinopril demonstrated a reduction at each point of observation, compared to the serum creatinine levels of subjects that received 10 mg of lisinopril, which demonstrated an increase. There was a statistically significant difference in creatinine levels of the 10 mg of fosinopril group and the 10 mg of lisinopril group (p < 0,05). (Table 1 and Figure 2)

Creatinine clearance prior to the administration of 10 mg of fosinopril (53,86 ± 28,5) and lisinopril (66,30 ± 25,67) did not demonstrate a statistically significant difference (p=0,16) (Table 2 and Figure 3).

Creatinine clearance before and after the administration 10 mg of fosinopril did not demonstrate a significant change, while before and after the administration of 10 mg of lisinopril there was a reduction in creatinine clearance. The difference in creatinine clearance after the administration of 10 mg of fosinopril and after the administration 10 mg of lisinopril was not statistically significant (p=0,26) (Table 2 and Figure 3).

The ratio of uric acid clearance to creatinine clearance prior to the administration of 10 mg of fosinopril (0,069 ± 0,03) and 10 mg of lisinopril (0,15 ± 0,15) was not statistically different (p=0,067) (Table 3 and Figure 4).

The ratio of uric acid clearance to creatinine clearance before and after the administration of 10 mg of fosinopril did not demonstrate any significant change, just as that before and after the administration of 10 mg of lisinopril. The difference between the group treated with 10 mg of fosinopril and the group treated with 10 mg of lisinopril in the ratio of uric acid clearance to creatinine clearance was statistically significant (p < 0,05) (Table 3 and Figure 4).

Table 1. Comparison of Creatinine Levels Before and After Administration of 10 mg of Lisinopril and 10 mg of Fosinopril.

	W0	W1	W2	W4	W6	p
Lisinopril	3,22 ± 0,75	3,37 ± 0,91	3,34 ± 1,06	3,67 ± 1,69	4,11 ± 2,14	0,11
Fosinopril	3,06 ± 0,62	3,22 ± 0,39	3,10 ± 0,51	2,94 ± 0,60	2,75 ± 0,79	0,17
p	0,3	0,31	0,26	0,11	0,037	

Note: W0 = Week zero, W1= the first week, W2 = the second week, W4 = the fourth week, W6 = the sixth week.

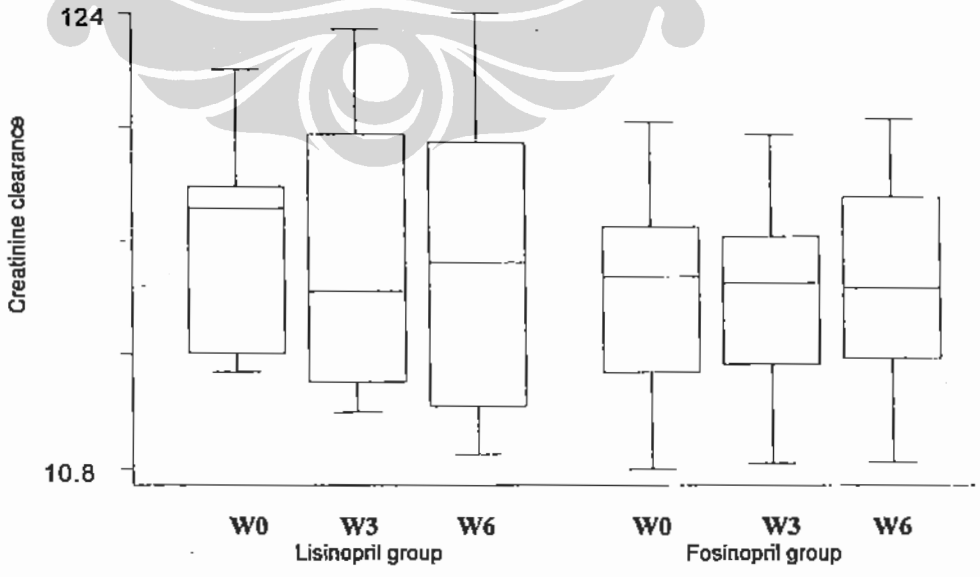


Figure 1. Box Plot of Creatinine Clearance Levels from the Lisinopril and Fosinopril Groups at Week Zero, the Third Week, and the Sixth Week.

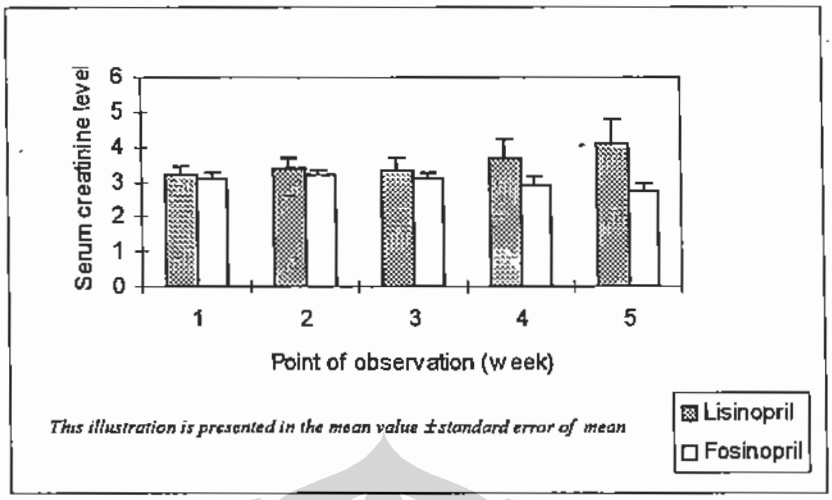
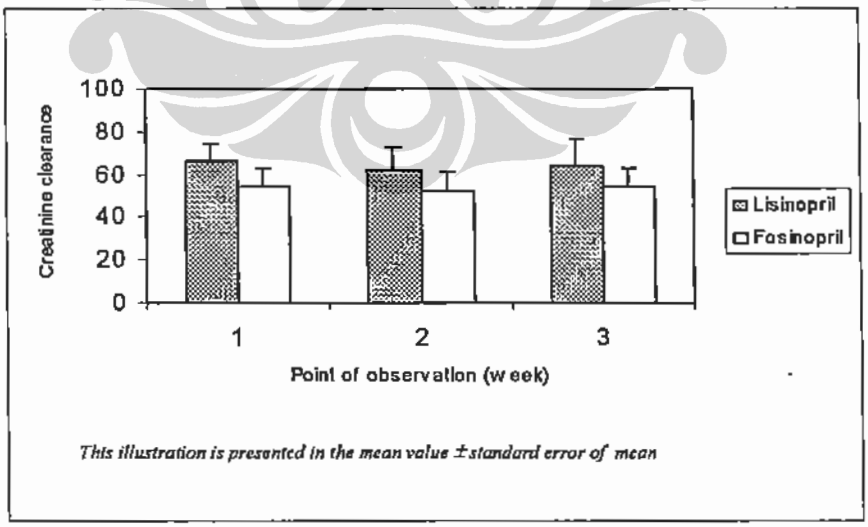


Figure 2. Comparison of Creatinine Clearance after Administration of 10 mg of Lisinopril and 10 mg of Fosinopril.

Table 2. Comparison of Creatinine Clearance After Administration of 10 mg of Lisinopril and 10 mg of Fosinopril.

	W0	W3	W6	p
Lisinopril	66,30 ± 25,67	61,98 ± 33,77	63,88 ± 39,01	0,43
Fosinopril	53,86 ± 28,52	52,68 ± 27,08	53,82 ± 28,92	0,49
p	0,16	0,25	0,26	

Note: W0 = Week zero, W3= the third week, W6 = the sixth week.



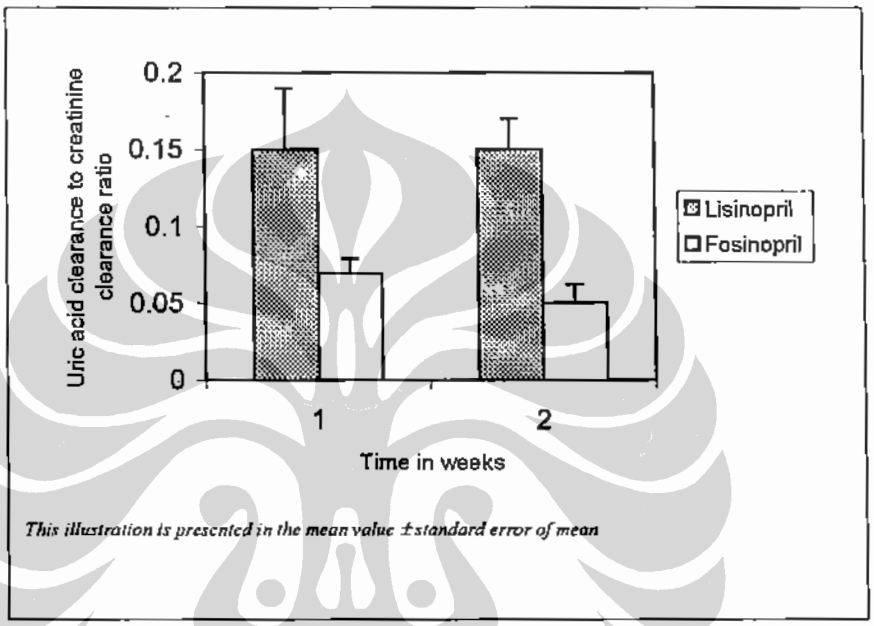
Note: W0 = Week zero, W3= the third week, W6 = the sixth week.

Figure 3. Comparison of Creatinine Levels after Administration of 10 mg of Lisinopril and 10 mg of Fosinopril.

Table 3. Comparison of Uric Acid Clearance to Creatinine Clearance Ratio After Administration of 10 mg of Lisinopril and 10 mg of Fosinopril.

	W0	W6	p
Lisinopril	0,15 ± 0,15	0,15 ± 0,16	0,48
Fosinopril	0,069 ± 0,03	0,05 ± 0,04	0,12
p	0,067	0,039	

Note: W0 = Week zero, W2= the second week, W6 = the sixth week.



Note. W0 = Week zero, W2= the second week, W6 = the sixth week.

Figure 4. Comparison of Uric Acid Clearance to Creatinine Clearance Ratio Levels after Administration of 10 mg of Lisinopril and 10 mg of Fosinopril.

DISCUSSION

Based on serum creatinine levels, there was a significant difference in the renal function of hypertension patients with mild and moderate renal failure after administration of 10 mg of fosinopril compared to 10 mg of lisinopril. We could conclude that 10 mg of fosinopril is better for renal function compared to 10 mg of lisinopril. This is in conformity with the fact that AHAs that are not completely eliminated through the kidneys are more renoprotective[9-13], in this case fosinopril, which is not completely eliminated through the kidneys.[14] However, administration of 10 mg of lisinopril does not turn out to aggravate renal dysfunction. If we compare the creatinine level before and after treatment, there seemed to be no significant difference (Table 1). This finding differs from several studies that state that AHAs that are completely eliminated through the kidneys would be accumulated and aggravate renal dysfunction.[2,13]

Creatinine clearance, which is another method to evaluate renal function, demonstrated a different result from that of creatinine. This study demonstrated no significant reduction in creatininee cearancc in the 10 mg of fosinopril group before and after administration of 10 mg of fosinopril (Table 2). This shows that fosinopril does not aggravate renal dysfunction, where as the creatinine clearance of the 10 mg of lisinopril group was reduced after administration of 10 mg of lisinopril, even though the reduction was not statistically significant (Table 2). Compared to the results after the administration of 10 mg of fosinopril and 10 mg of lisinopril, there is no significant difference in creatinine clearance (Table 2 and Figure 3). Such findings are not in accordance

with previous statements that AHAs completely excreted through the kidneys such as lisinopril would aggravate renal dysfunction. This could be explained by the fact that the creatinine clearance in this study prior to the administration of 10 mg of lisinopril is still within safe limits of renal function, in accordance to a statement by Hui[6] that dose adjustment is only required for creatinine clearance above 30-60 ml/minute.

The results of uric acid clearance to creatinine clearance ratio in determining the function of the renal tubules[15] demonstrated a significant difference after the administration of 10 mg of fosinopril and 10 mg of lisinopril. However, within each group, there was no significant difference before and after treatment (Table 3), which indicates that there was no reduction in the ratio of uric acid clearance to creatinine clearance.

Based on the results of the uric acid clearance to creatinine clearance ratio, we could conclude that administration of fosinopril and lisinopril has similar effects and would not reduce renal tubulus function. This is in contrary to previous statements that AHAs completely excreted through the kidneys would aggravate renal dysfunction, even though comparison between the two AHAs (lisinopril and fosinopril) demonstrated that fosinopril has a tendency to produce more satisfactory results.

From the study data, creatinine clearance, creatinine, and uric acid to creatinine clearance ratio demonstrate almost similar results. Both the fosinopril group and the lisinopril group did not aggravate renal dysfunction. The hypothesis that lisinopril, which belongs to the group of AHAs that are completely excreted through the kidneys, would aggravate renal dysfunction was not verified. However, fosinopril, which is not completely excreted through the kidneys, demonstrated a tendency to produce more satisfactory results compared to lisinopril.

CONCLUSION

Administration of 10 mg of lisinopril, which is completely excreted through the kidneys, does not aggravate renal dysfunction in hypertension patients with mild to moderate renal failure. However, fosinopril demonstrated more satisfactory results compared to lisinopril towards renal function.

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