

## The role of ACE inhibitor in reducing persistent proteinuria in nephrotic syndrome

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### ABSTRACT

**Background** Patients with persistent proteinuria are at risk for progression to end-stage renal failure. Angiotensin converting enzyme inhibitor (ACEI) can decrease proteinuria in nephrotic syndrome (NS) patients with persistent proteinuria. The aim of this study was to evaluate the effectiveness of ACEI (enalapril) in reducing proteinuria in NS.

**Methods** This study was conducted as a randomized double blind clinical trial with crossover design on persistent proteinuria NS patients who visited Cipto Mangunkusumo Hospital from December 2000 until July 2001. Twenty patients were enrolled in this study. Ten patients received enalapril 10 mg/day for 8 weeks and ten patients received placebo. Angiotensin converting enzyme inhibitor was considered effective if proteinuria was reduced for at least 50%.

**Results** The patients aged between 2-16 years with a mean of 11.3 years and consisted of 16 boys and 4 girls with a ratio of 4:1. Urine protein and creatinine ratio (Up/Uc) was used to evaluate proteinuria. In the ACEI group, the mean value of proteinuria increased from 5.6 (95%CI 1.1;2.2) to 6.7 (95%CI 0.3;13.2) ( $p=0.721$ ), although it decreased in five patients. Decreased proteinuria to 50% or more was found in 2 out of 10 patients in the enalapril group while in the placebo group it was found in 3 out of 10, but this difference was not statistically significant ( $p=0.5$ ). Systolic blood pressure decreased significantly ( $p=0.0185$ ) from 107 mmHg (95%CI 101.1;112.9 mmHg) to 103 mmHg (95%CI 96.2;109.8 mmHg) although still in normal range.

**Conclusions** The efficacy of enalapril in reducing proteinuria could not be evaluated yet. A further study with greater sample and longer observation is needed [Paediatr Indones 2002;42:243-248].

**Keywords:** ACE inhibitor, enalapril, nephrotic syndrome, persistent proteinuria.

Proteinuria in nephrotic syndrome (NS) results in hypoalbuminemia, hyperlipidemia, edema, and ascites. The severity of proteinuria constitutes a risk factor to progression of renal disease.<sup>1</sup> Angiotensin converting enzyme inhibitor (ACEI) can reduce proteinuria either in normotensive or hypertensive state.<sup>2</sup> Taguma *et al* showed that ACEI reduced proteinuria in diabetic patients with overt nephropathy and azotemia.<sup>3</sup> ACEI could safely effect a 60% to 70% reduction in urinary protein excretion in patients with persistent proteinuria caused by a variety of renal diseases.<sup>1</sup>

Urinary protein to creatinine ratio used to evaluate the severity of proteinuria has a normal value in a range of 0.2-0.5 depending on age. In nephrotic proteinuria this ratio could exceed 1.8.<sup>3-5</sup>

This study was conducted to evaluate the effectiveness of ACEI (enalapril) in reducing proteinuria in NS.

### Methods

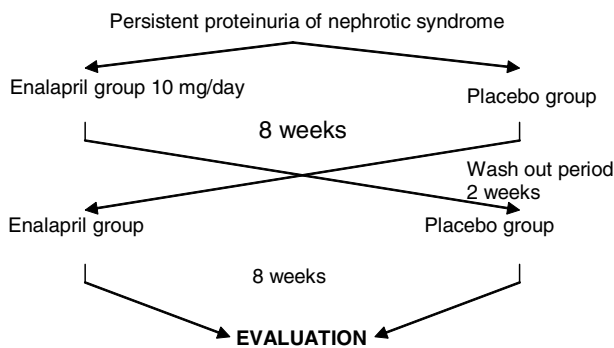
This study was a randomized double blind clinical trial with crossover design in persistent proteinuria NS patients who visited Cipto Mangunkusumo hospital

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from December 2000 until July 2001. Twenty patients were enrolled in this study. Members of each group were randomly selected and each patient acted as a control to him/herself. In the first part, ten patients were treated with enalapril and ten patients received placebo. Then in the second part, after a 2-week wash out period, these groups were changed where patients previously treated with enalapril now were given placebo and vice versa. The diagram of this study is shown in **Figure 1**.



**Figure 1.** Diagram of clinical study

The exclusion criteria were bilateral renal artery stenosis or unilateral in a single kidney.<sup>7</sup> Persistent proteinuria was defined as the existence of protein in every urine sample within 3 months, which did not response to steroid and cytostatic therapy.<sup>8</sup> Before receiving any treatment, every patient underwent physical and laboratory tests of serum albumin, creatinine, alanine aminotransferase, cholesterol levels and a peripheral blood cell count. Routine urine assays and urinary protein-creatinine ratio (Up/Uc) were performed. Patients were followed-up every two weeks for eight weeks. Dosage of enalapril was 10 mg/day given as a single dose for 8 weeks. Urine sample was collected using the midstream method on the first voided urine in the morning. ACEI was considered effective if proteinuria was reduced for at least 50%. GFR was calculated using the patients' height and serum creatinine concentration with Schwartz's formula.<sup>9</sup> At least 80% or more medicine taken was used to evaluate the good compliance of the patient confirmed by filling the diary card supervised by the parents. Patients were dropped out from the study when any side effects appeared, relapse of NS, or when patients refused to continue the study. Sample size was

calculated by hypothesis test of mean difference for dependent variable to 24 patients. Statistical analysis used to evaluate the comparison of the pre- and post-treatment values included a paired student t test, Wilcoxon rank sum test and Mann-Whitney test. Results were considered statistically significant if the p value was less than 0.05. All results were provided as mean  $\pm$  95% CI. The protocol was approved by the ethics committee of the Department of Child Health and informed consent was obtained from each patient signed by the parent or guardian.

## Results

During the study period from December 2000 – July 2001, 20 patients were enrolled in this study. The age of the patients ranged between 2 – 16 years with a mean of 11.3 years. The patients consisted of 16 boys and 4 girls with a ratio of 4:1. Patients aged more than 10 years constituted the biggest proportion of the persistent proteinuria NS included in this study. **Table 1** shows that both groups were compatible regarding the age at study, age at diagnosis, and duration of having NS or persistent proteinuria. Two patients were dropped out due to relapse of NS, one patient had a relapse after receiving enalapril and the other after placebo treatment.

There was no difference in clinical pictures of the subjects at the beginning of the study, which included number of edema, nutritional status, and blood pressure level in both groups. At the beginning of this study, the neutrophyl count in the enalapril group was significantly lower compared to that in the placebo group, but there were no differences in other laboratory parameters in both groups (Table 1).

The mean value of proteinuria at the beginning compared to at the end of the treatment increased but the difference was not statistically significant. Before treatment the mean level of urinary protein to creatinine ratio was 5.6 (95%CI -1.1;2.2) and after treatment was 6.7 (95%CI 0.3;13.2). However, in five patients the proteinuria decreased.

The efficacy of enalapril to reduce proteinuria to 50% or more was found in 2 patients and 3 patients in the enalapril and the placebo group, respectively, but the difference was not statistically significant.

Enalapril decreased the mean systolic blood

**TABLE 1.** CHARACTERISTIC OF THE SAMPLE AND BASELINE OF LABORATORY DATA AT THE BEGINNING OF THE STUDY

Characteristic and Baseline of Laboratory Data	Enalapril Mean (95%CI)	Placebo Mean (95%CI)
Age at study (year)	11.4 (8.2;14.7)	11.2 (7.7;14.7)
Age at diagnosis of NS (year)	5.5 (2.6;7.7)	5.1 (3.4;7.7)
Duration of NS (month)	75.9 (40.3;111.5)	74.7 (37.9;111.4)
Duration of persistent proteinuria (month)	35.4 (13.1;57.7)	34.7 (11.9;57.5)
Urinary protein/creatinine ratio	5.6 (-1.1;+12.2)	10.3 (-0.5;+21.0)
Serum albumin (g/dl)	3.8 (2.8;4.7)	3.7 (2.8;4.5)
Serum cholesterol (mg/dl)	204.4 (135.9;272.81)	213.5 (174.1;252.9)
Serum creatinine (mg/dl)	1.3 (0.45;2.2)	1.7 (0.4;3.0)
GFR (ml/min/1.73 m <sup>2</sup> )	92.8 (58.9;130.6)	81.8 (43.4;120.3)
Neutrophil (%)	63.2 (52.6;73.7)	76.6 (71.2;82.0)
ALT (mU/ml)	9.6 (5.6;13.7)	8.4 (6.4;10.4)

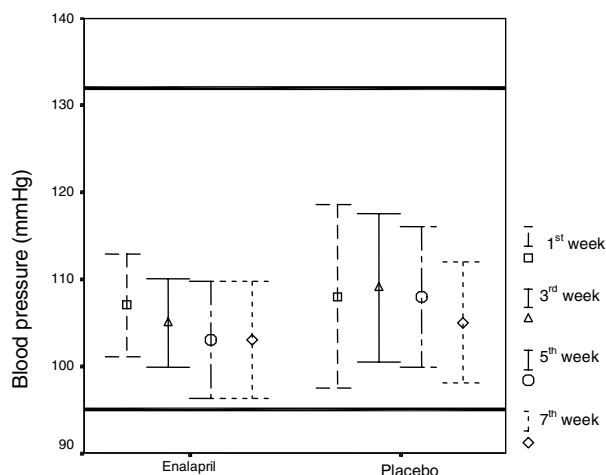
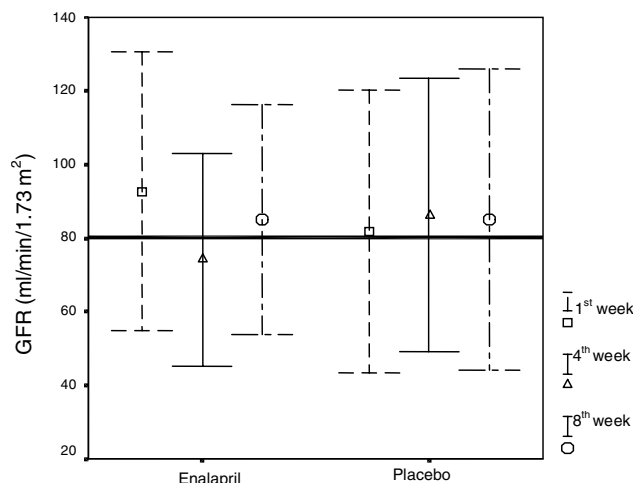
pressure from 107 mmHg (95%CI 101.1;112.9) to 103 mmHg (95%CI 96.2;109.8) although remained within normal limit. **Figure 1** shows the decrease of systolic blood pressure in the enalapril group that was statistically significant ( $p=0.0185$ ) and this simultaneously influenced the GFR temporarily (Figure 2). But the diastolic blood pressure did not decrease significantly.

**Figure 2** shows the effect of enalapril and placebo on GFR level. The GFR decreased in the 4<sup>th</sup> week of enalapril treatment but not statistically significant ( $p=0.290$ ), and increased again in the following weeks. This effect did not appear on the placebo group.

Enalapril is well-known to induce neutropenia but it was not found in this study. Serum albumin level

seemed to increase in the enalapril group, while not in the placebo group although this difference was not significant. In the enalapril group the mean serum albumin level was 3.8 g/dl (95%CI 2.8;4.7) increased to 3.9 g/dl (95%CI 3.1; 4.8), while in the placebo group it was 3.7 g/dl (95%CI 2.8;4.5) decreased to 3.4 g/dl (95%CI 2.6;4.3).

There was no increase of serum cholesterol level in the enalapril group. The increase of serum cholesterol level was more prominent in the placebo group but was not statistically significant. In the enalapril group the mean serum cholesterol level was 204.4 mg/dl (95%CI 135.9; 272.8), slightly increased to 207.3 g/dl (95%CI 158.6; 256) and in the placebo group it was 213.5 mg/dl (95%CI 174.1; 252.9), increased to 241 g/dl (95%CI 145; 338.2).

**Figure 1.** Systolic blood pressure during the study**Figure 2.** Glomerular filtration rate during the study

## Discussion

The benefit of antiproteinuric effect of ACEI is in nature due to hemodynamic alteration. By reducing angiotensin II levels, ACEI relaxes the efferent arteriole. This decompresses the glomeruli by reducing glomerular hypertension and in turn, reduces proteinuria.<sup>10</sup> United States National Kidney Foundation (1998) reported that the decrease of proteinuria for at least 40-50% was an important therapeutic target for proteinuria cases.<sup>11</sup> Milliner *et al.* conducted a study of six children aged 12 months-11 ½ years with steroid resistant NS. They were treated with low dosage of enalapril up to 10 mg/day for 2 to 8 weeks, proteinuria decreased 52.4% based on the calculation of urinary protein to creatinine ratio (Up/Uc).<sup>1</sup> In our study, the duration of enalapril treatment was 8 weeks with a dosage of 10 mg/day. The decrease of proteinuria 350% occurred in 2 cases in the treatment group and 3 cases in placebo group. The explanation of this discrepancy could be due to several factors i.e., firstly, in our study there was a variation of dosage per kg body weight between 0.2-0.8 mg/kgBW/day, consisted of 5 children with 0.2-0.4 mg/kgBW/day, 3 children with 0.4-0.6 mg/kgBW/day and 2 children for 0.6-0.8 mg/kgBW/day. Bagga *et al* compared the consumption of low dose (0.2 mg/kgBW/day) for 8 weeks followed by 2 weeks washout period and later used high dose of 0.6 mg/kgBW/day. The result of the study was that the decrease of proteinuria in patients given enalapril of 0.6-0.7mg/BW/day was better than of 0.2 mg/BW/day.<sup>12</sup> Secondly, the time of follow-up in our study was not long enough. In some studies using different duration of treatment, the decrease of proteinuria took place in the first two months but increased when the duration was more than 2 months. Delluchi *et al* studied 13 children with enalapril for 24-84 months, 4 children had free proteinuria after 24 months.<sup>13</sup> Shiigai T *et al* found out that the decrease of proteinuria to >50% was detected after the consumption of enalapril or lisinopril for  $6.9 \pm 8.8$  months in 59 patients.<sup>14</sup> Lama G *et al* found the decrease of proteinuria in 5 out of 6 steroid-resistant NS patients in 2 years observation.<sup>15</sup> Thirdly, in our study, the amount of sample was not sufficient according to the sample size required. Sample size calculation was 24 patients

but there was only 20 patients enrolled. The insufficient sample made the decrease of the power of the study (42%).

Trachtmant and Gauthier assumed 3 factors that cause lowering of blood pressure in using ACE inhibitor.<sup>4</sup> It may be related to inhibition action on angiotensin I to angiotensin II conversion, increased circulating bradykinin levels or direct stimulation on renal prostaglandin synthesis.<sup>4</sup> Hypotension was one of the side effects of ACE inhibitor, which often happened in congestive heart failure and bilateral renal artery stenosis.<sup>7</sup> Milliner *et al* did not find significant hypotension in his study on 6 children with resistant steroid NS.<sup>1</sup> In our study the decrease of systolic blood pressure was statistically significant ( $p=0.0185$ ). Prior to enalapril therapy, mean systolic blood pressure was 107 mmHg (95%CI 101.1;112.9) and post therapy was 103 mmHg (95%CI 96.2;109.8) but this value was still in the normal range, however the mean diastolic blood pressure did not significantly decrease ( $p=0.172$ ).

Kamper *et al* concluded that enalapril could be tolerated in severe renal insufficiency (GFR 10 ml/min/1.73 m<sup>2</sup>) without progression of the disease.<sup>16</sup> Ruggenti *et al* and Thomas *et al* did not find any reduction of GFR in enalapril therapy.<sup>17-8</sup> In our study there was a decrease of mean GFR, but still remained in normal value and the decrease was not statistically significant ( $p=0.290$ ). The decrease of GFR was temporary and increased again after 8 weeks off the study.

Although it was rare (0.01%), it is necessary to evaluate the neutrophyl count in enalapril therapy to look for the side effect of neutropenia.<sup>7</sup> In this study no neutropenia was found but there was significant difference in the neutrophyl cell count between the enalapril and the placebo group.

Although there was a reverse relationship between urinary protein excretion rate and hypoalbuminemia, in persistent proteinuria state serum albumin could return to normal with or without changing in protein excretion rate.<sup>19</sup> At the beginning of this study, the mean serum albumin level was 3.8 g/dl (95%CI 2.8;4.7) in the enalapril group and was 3.7 g/dl (95%CI 2.8;4.5) in the placebo group. At the end of the study, the mean serum albumin level was 3.9 g/dl (95%CI 3.1; 4.8) in the enalapril group and 3.4 g/dl (95%CI 2.6; 4.3) in the placebo group. The increase of serum albumin level in the enalapril group was not

statistically significant.

In primary NS cases, hypercholesterolemia was more prominent in NS with minimal-change histopathology features. In general, there is a reverse correlation between serum albumin and cholesterol concentration. As the level of serum albumin becomes normal, either spontaneously or by intervention, the dysfunction of lipid lead to normal.<sup>19</sup> At the beginning of this study, the mean serum cholesterol level was 204.4 mg/dl (95%CI 135.9;272.8) in the enalapril group and 213.5 mg/dl (95%CI 174.1;252.9) in the placebo group. At the end of the study, the mean serum cholesterol level was 207.3 g/dl (95%CI 158.6; 256) in the enalapril group and 241 g/dl (95%CI 145;338.2) in the placebo group. The slight increase of serum cholesterol level in the enalapril group was not statistically significant.

From the result of this study, the efficacy of enalapril in reducing proteinuria significantly could not be evaluated yet because there were only 2 out of 10 patients who showed decreased proteinuria more than 50%. There were no side effects of hypotension and neutropenia found in this study. The decrease of mean systolic blood pressure was statistically significant in the pre and post therapy of enalapril, which influenced the GFR temporarily. Further study is necessary with sufficient amount of sample, uniform enalapril dosage and a longer observation to obtain the decrease of proteinuria in a significant amount.

## References

1. Millner DS, Morgenstern BZ. ACE inhibitors for reduction of proteinuria in children with steroid-resistant nephrotic syndrome. *Pediatr Nephrol* 1991;5:587-90.
2. Bohlen L, de Courten M, Weidmann P. Comparative study of the effect of ACE-inhibitors and other antihypertensive agents on proteinuria in diabetic patients. *Am J Hypertens* 1994;7:84S-94S.
3. Taguma Y, Kitamoto Y, Futaki G, Ueda H, Monma H, Ishizaki M, et al. Effect of captopril on heavy proteinuria in azotemic diabetics. *New Engl J Med* 1985;313:1617-20.
4. Trachtman H, Gauthier B. Effect of ACE inhibitor therapy on proteinuria in children with renal disease. *J Pediatr* 1988;112:295-8.
5. Houser M. Assessment of proteinuria using random urine samples. *J Pediatr* 1984;104:845-8.
6. Bergstein JM. A practical approach to proteinuria. *Pediatr Nephrol* 1999;13:697-700.
7. Opie LH. ACE inhibitors: side effect and contraindications. In: Opie LH, editor. *Angiotensin converting enzyme inhibitors. Scientific basis for clinical use.* 2<sup>nd</sup> ed. New York: Wiley-Liss; 1994. p. 218-27.
8. Erley CM, Harrer U, Kramer BK, Risler T. Renal hemodynamic and reduction of proteinuria by a vasodilating beta-blocker versus an ACE inhibitor. *Kidney Int* 1992;41:1297-303.
9. Schwartz GJ, Haycock GB, Edelmann CM, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics* 1976;58:259-63.
10. de Cotret PR. Proteinuria, microalbuminuria and the role of ACE inhibitors. *The Can J Diagn. Suppl* 1996;4:11-4.
11. Keane WF, Eknoyan G. Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation. *Am J Kidney Dis* 1999;33:1004-10.
12. Yoshida A, Morozumi K, Takeda A, Koyama K, Ideura T, Ikeda M, et al. The effect of enalapril on proteinuria in patients with chronic glomerulonephritis and renal insufficiency [abstract]. *Nippon Jinzo Gakkai Shi* 1993; 35:1249-52.
13. Delucchi A, Cano F, Rodriguez E, Wolff E, Gonzalez X, Cumsille MA. Enalapril and prednisone in children with nephrotic-range proteinuria. *Pediatr Nephrol* 2000;14:1088-91.
14. Shiigai T, Shichiri M. Late escape from the antiproteinuric effect of ACE inhibitors in nondiabetic renal disease. *Am J Kidney Dis* 2001;37:477-83.
15. Lama G, Luongo I, Piscitelli A, Salsano ME. Enalapril: antiproteinuric effect in children with nephrotic syndrome [abstract]. *Clin Nephrol* 2000;53:432-6.
16. Kamper AL, Strangaard S, Leysaac PP. Effect of enalapril on the progression of chronic renal failure. A randomized controlled trial. *Am J Hypertens* 1992;5:423-30.
17. Ruggenenti P, Mosconi L, Vendramin G, Moriggi M, Remuzzi A, Sangalli F, et al. ACE inhibition improves glomerular size selectivity in patients with idiopathic membranous nephropathy and persistent nephrotic syndrome. *Am J Kidney Dis* 2000;35:381-91.

18. Thomas DM, Hillis AN, Coles GA, Davies M, Williams JD. Enalapril can treat the proteinuria of membranous glomerulonephritis without detriment to systemic or renal hemodynamics. *Am J Kidney Dis* 1991;18:38-43.
19. Wila Wirya IGN. Sindrom nefrotik. In: Alatas H, Tambunan T, Trihono PP, editors. *Buku ajar Nefrologi Anak*. 2<sup>nd</sup> ed. Jakarta: Balai Penerbit FKUI; 2002. p. 381-426.