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Effect of Captopril on Heavy Proteinuria in Patients with Various Glomerular Diseases

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The effect of captopril on proteinuria was evaluated in twenty patients with various glomerular diseases excreting heavy proteinuria (>3.0 g/day). Captopril in a daily dose of 37.5 mg was administered orally three times a day to all patients and they were followed for eight weeks. Twenty-four hour urinary excretion of protein, creatinine, sodium, selective protein index (SPI), and blood chemistry including serum electrolytes were measured every two weeks. Twenty-four hour urinary protein excretion per gram creatinine started to fall within two weeks of captopril administration and became nearly stable after four weeks of therapy ($p<0.05$). Mean 24-hour urinary protein excretion decreased significantly from a pretreatment value of 9.0 ± 6.0 gm/gm of cr. to 4.4 ± 3.5 gm/gm of cr. after eight weeks of captopril treatment. The serum albumin level increased progressively at six and eight weeks after the captopril treatment period and was significantly higher than the pretreatment value ($p<0.05$). The decrease in proteinuria did not coincide with a fall in blood pressure or any changes in creatinine clearance. We conclude that captopril does have a significant antiproteinuric effect in patients excreting heavy proteinuria with various glomerular diseases. However, the long term therapeutic efficacy and any renal protective effect of this drug remain to be proven.

Key Words: Captopril, proteinuria, glomerular disease

Various glomerular diseases and diabetic nephropathy frequently manifest nephrotic syndrome, which results from the consequences of an increased permeability of the glomerular capillary filters to protein. By definition, these changes show heavy proteinuria, hypoalbuminemia, edema and hyperlipidemia. The great majority of cases with minimal change nephrotic syndrome manifesting minimal structural changes on light microscopy are well responsive to corticosteroid and/or cytoxan treatment, whereas in other glomerular diseases the response to drug therapy is, in general, very disappointing. In patients with nephrotic range proteinuria, clinicians frequently experience many kinds of complications due to side effects of drugs and/or due to the consequences of prolonged heavy proteinuria. In order to prevent these kind of complications, it is important to select a drug which reduce proteinuria effectively and has few side effects in clinical practice.

Recently, Taguma *et al.* (1985) demonstrated that captopril, an orally active angiotensin converting enzyme inhibitor, has an antiproteinuric effect in azotemic diabetics with heavy proteinuria. They suggested that captopril might directly influence the permeability of the glomerular capillary wall and casuse a decrease in intrarenal hypertension, which contributes to the reduction of urinary protein excretion. In 1977, Bohrer *et al.* suggested that proteinuria induced by angiotensin II could be explained, in large part, by hemodynamic factors. Yoshioka *et al.* (1986) also showed that a partial renal vein constriction caused a marked reduction in glomerular plasma flow rate and rises in glomerular transcapillary hydraulic pressure difference and

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efferent arteriolar resistance. These changes were associated with a marked increase in urinary protein excretion. Infusion of saralasin largely normalized these urinary protein excretions despite continued renal vein constriction. This result also supports the hypothesis that the antiproteinuric effect of saralasin could be explained by hemodynamic factors of glomerular capillaries.

The antiproteinuric effect of captopril was first described by Herlitz *et al.* (1984) in systemic lupus erythematosus patients with an advanced stage of glomerulonephritis. In 1987, Lagrue *et al.* also showed an antiproteinuric effect of captopril in patients with various primary glomerular diseases. They observed an antiproteinuric effect similar to that described by Herlitz *et al.* (1984) and this effect appeared independent of the histological type of glomerulonephritis. The present study was undertaken to determine whether captopril would reduce urinary protein excretion similarly in patients with various glomerular diseases excreting heavy proteinuria.

PATIENTS AND METHODS

Patients

Twenty patients with various glomerular diseases and heavy proteinuria were selected from among those who gave informed consent to this study at the renal clinic of Severance Hospital and Yongdong Severance Hospital, Yonsei University Medical Center. They ranged in age from 25 to 71. Underlying causes of proteinuria were as follows; Six had membranous glomerulonephritis, five had chronic glomerulonephritis, four had IgA nephropathy, three had membranoproliferative glomerulonephritis, one had minimal change nephrotic syndrome, and one had lupus nephritis (Table 1). All studies were performed during hospitalization and/or during out-patient clinic visits.

Study protocol and methods

All patients adhered to a dietary regimen of 3-5 gm sodium chloride per day. A protein intake of 60 to 80 gm/day had been advised to patients from at least 1 month prior to the start of the study. The sodium and protein content of the diet were not changed during the entire study period. A control period of two to four weeks was observed in all patients prior to administration of captopril until they became stabilized in urinary protein excretion and renal functions. Oral captopril in a daily dose of 37.5 mg was administered three times a day to all patients and they were followed for eight weeks. Serum sodium, potassium, chloride, BUN, creatinine, total protein, albumin, and cholesterol were measured every two weeks. Twenty-four hour urinary protein, creatinine, and sodium excretions and the selective protein index (SPI) were also measured every two weeks. All the measurements were performed at the clinical laboratory and central laboratory of this hospital. Blood pressure was measured with a standard mercury sphygnomanometer. Measurements were performed in triple after 10 minutes of supine rest. The mean of three readings, never having a range more than 10 mmHg, was recorded. Serum electrolytes, BUN, creatinine, total protein, albumin, and cholesterol were measured by standard auto-analyzer technique. Urinary protein was determined by the biuret method. SPI was calculated by the clearance ratio of the IgG to that of the albumin. Statistical analysis was performed using the paired t-test, with a confidence p level of <0.05 being considered significant. Data were given as mean $\pm$ SD, unless otherwise indicated.

Table 1. Age and sex distribution, and underlying cause of nephropathy in patients treated by captopril

Underlying causes	No. of patient (male, female)	Age (mean $\pm$ SD)
Membranous nephropathy	6(5, 1)	44.8 $\pm$ 4.4
Chronic glomerulonephritis	5(3, 2)	49.2 $\pm$ 18.2
IgA nephropathy	4(3, 1)	33.5 $\pm$ 11.6
Membranoproliferative glomerulonephritis	3(1, 2)	43.0 $\pm$ 8.2
Minimal change nephrotic syndrome	1(1, 0)	27.0
Lupus nephritis	1(0, 1)	29.0

RESULTS

Effect of captopril on urinary protein excretion, serum albumin and creatinine clearance

Twenty-four hour urinary protein excretion expressed as gm protein per gram of urinary creatinine, serum albumin and creatinine clearance are shown in Figure 1 at each period of captopril administration, i.e.; 2 weeks prior to captopril, 0, 2, 4, 6, and 8 weeks of captopril administration. Twenty-four hour urinary protein excretions after 4, 6, and 8 weeks of captopril treatment were significantly lower than pretreatment values ($p<0.05$) (Table 2, Fig. 1). The urinary protein excretion decreased in most patients within 2 weeks of captopril administration and became stable after 4 weeks (Fig. 1). Concomitant to these substantial reductions in urinary protein excretion, serum albumin levels of the patient at 6 and 8 weeks after captopril periods rose significantly ($p<0.05$)(Table 2, Fig. 1). Captopril induced reduction of urinary protein excretions and elevation of serum albumin levels were observed without any changes in creatinine clearance

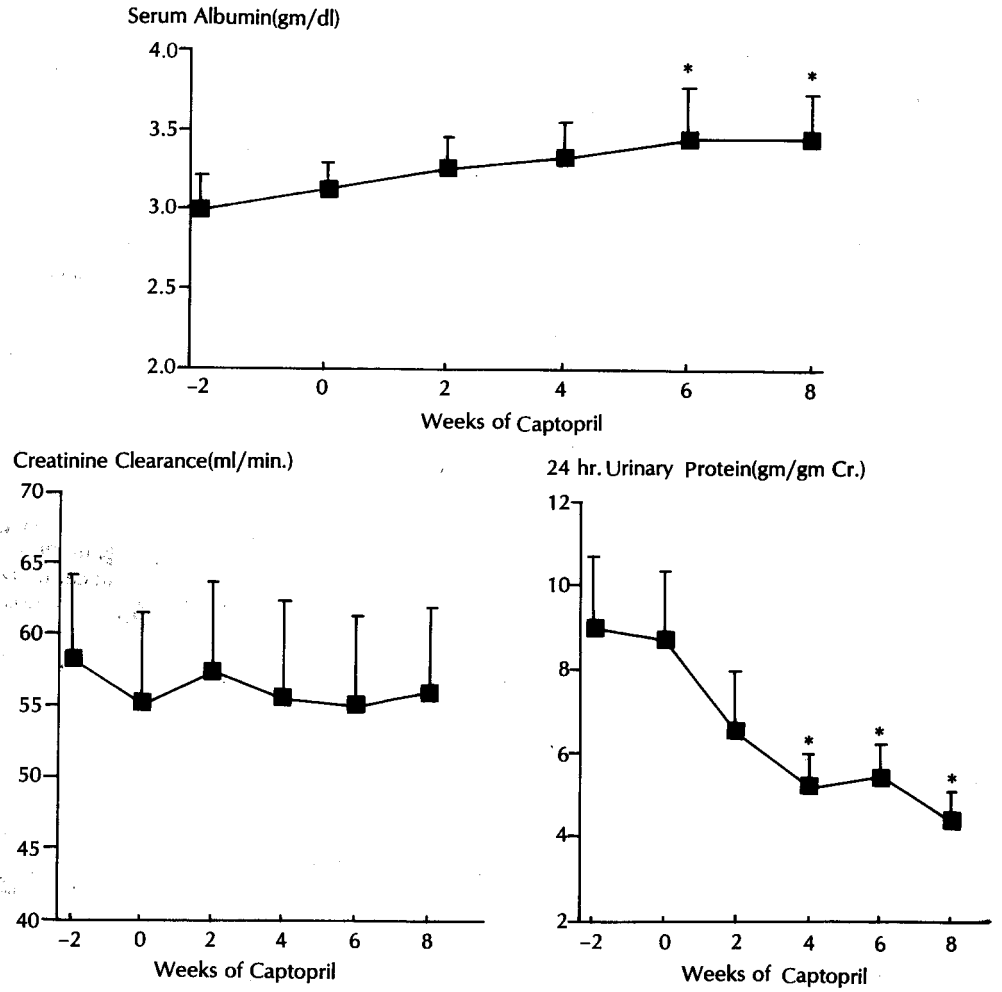

Fig. 1. *Effect of captopril on serum albumin, creatinine clearance and urinary protein excretion.*
**: $p<0.05$, compared to before captopril*
Data are mean ± SEM.

during the captopril administration (Table 2, Fig. 1).

Effect of captopril on urinary sodium excretion and blood pressure

As shown in Fig. 2, there were no significant changes in the urinary sodium excretion, systolic and diastolic blood pressure of the patients during the period following captopril administration ($p < 0.1$)(Table 2). This finding suggests that captopril is safely administered without lowering blood pressure to patients who have various glomerular diseases without hypertension. Also, we didn't observe any clinically significant side effects during the captopril

Table 2. Twenty four hour urinary protein excretion and other clincial features before and after captopril administration

	Before captopril	After captopril (8 weeks)
24 hour urine		
protein (gm/gm of Cr.)	9.0± 6.0	4.4± 3.5*
sodium (mEq)	186.6± 59.2	142.4±53.3
Serum		
creatinine (mg/dl)	1.96± 1.5	1.98± 1.4
albumin (gm/dl)	3.0± 0.6	3.5± 0.8*
cholesterol (mg/dl)	273.0±110.9	218.2±49.9
Creatinine clearance(ml/min)	58.3± 24.9	56.0±24.3
Blood pressure(mmHg)		
systolic	136.7± 10.0	125.0±11.8
diastolic	88.0± 6.3	81.0± 8.8

Valuse are mean±S.D

*: $p<0.05$, compared to before captopril

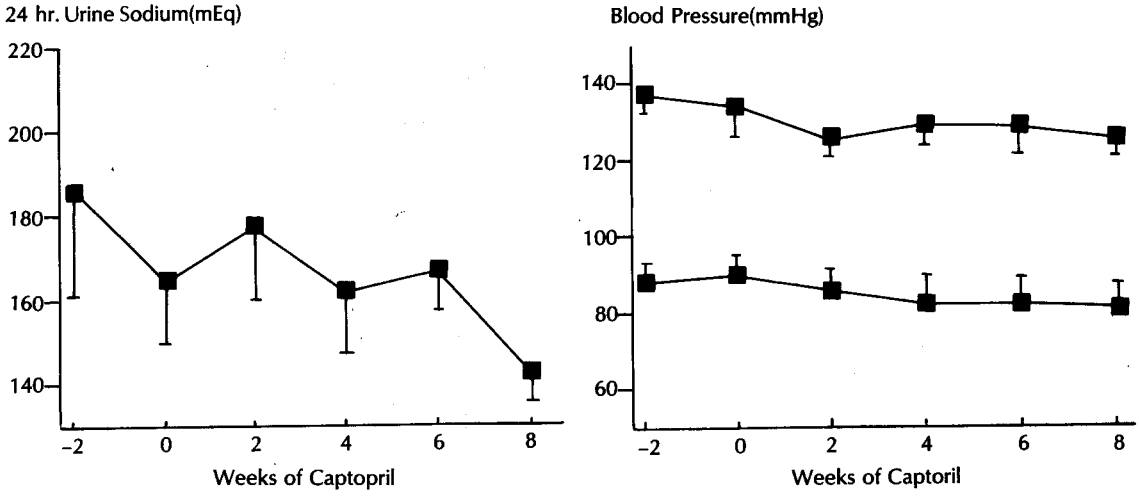

Fig. 2. *Effect of captopril on urinary sodium excretion and blood pressure. No significant changes between before control and captopril periods Data are mean±SEM.*

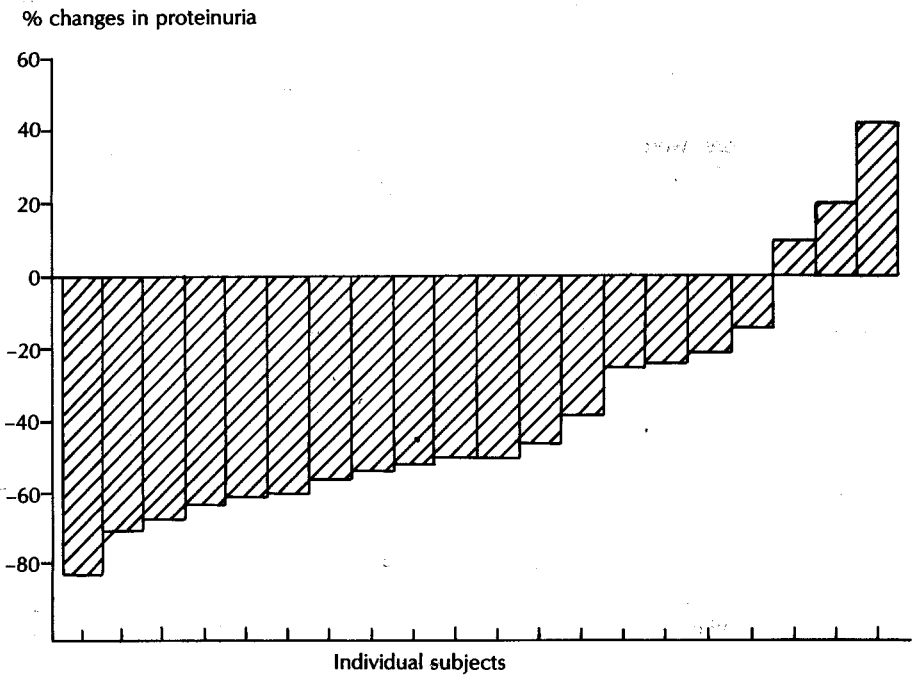

Fig. 3. *Percent changes in urinary protein excretion 8 weeks after captopril therapy in 20 individual subjects.*

administration period in these patients with heavy proteinuria.

Percent changes in urinary protein excretion

Captopril does have a significant antiproteinuric effect in subjects excreting heavy proteinuria from various glomerular diseases, reducing protein excretion 50% or more in 11 out of 20 patients (Fig. 3). We also observed increased proteinuria in 3 out of 20 subjects. The long term therapeutic value of captopril on the antiproteinuric effect remains to be determined because of the exacerbation of proteinuria in some cases.

Effect of captopril on selective protein index (SPI)

SPI, obtained by the clearance ratio of the IgG to that of the albumin, was evaluated to find out the effect of captopril on the shift of glomerular permselectivity. As shown in Fig. 4, there were no significant changes in SPI between pre and post captopril periods ($p>0.1$). This finding leads us to the notion that changes in membrane permselectivity were not significantly altered during captopril therapy but further evaluation of this aspect through examination of a larger sample will be needed.

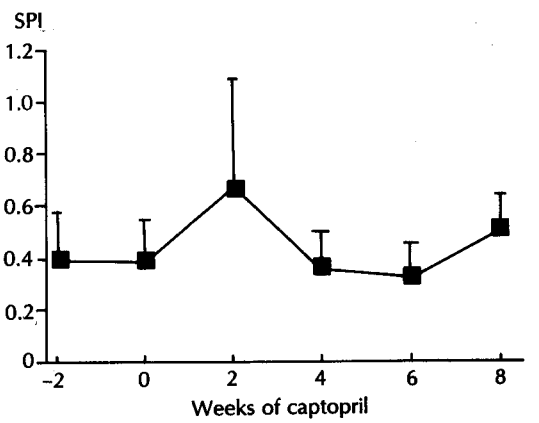

Fig. 4. *Effect of captoril on selective protein index(SPI).*
n: Number of subjects
No significant changes between control and captopril periods
Data are mean ± SD.

DISCUSSION

Captopril, originally known as SQ 14225, is an orally active potent competitive inhibitor of angiotensin converting enzyme (ACE), and was used as an effective antihypertensive agent in various types of hypertension. Gavras *et al.* (1978) reported the first clinical trial of this new drug that promised a different approach to the treatment of hypertension. This drug inhibits the formation of angiotensin II (A-II) from angiotensin I (A-I). A fall in plasma A-II concentration and the consequent decrease in aldosterone biosynthesis decreases vascular smooth muscle contraction, lessens sodium retention and contracts intravascular volume. Renin and angiotensin II are known to induce proteinuria in experimental animals (Pickering and Prinzmetal 1940; Addis *et al.* 1949; Sellers *et al.* 1952; Eisenbach *et al.* 1975) and there are some evidences that renin induces proteinuria in human beings, especially in associated with hyperreninemia, hypertension, and renal artery stenosis (Berlyne *et al.* 1964; Montoliu *et al.* 1979; Kumar and Shapiro 1980; Eiser *et al.* 1982; Vea *et al.* 1987). In addition, reduction of proteinuria was documented intermittently during ACE inhibitor therapy in patients with hypertension and proteinuria (Simon *et al.* 1983; Bauer and Jones 1984; Reams and Bauer 1986; Parving *et al.* 1988; Takeda *et al.* 1980). Recently there were some reports on the therapeutic values of ACE inhibitor for proteinuria in various renal diseases (Herlitz *et al.* 1984; Taguma *et al.* 1985; Anderson *et al.* 1986; Heeg *et al.* 1987; Lagrue *et al.* 1987; Vea *et al.* 1987). In 1984, Herlitz *et al.* observed that renal function improved in 64% of systemic lupus erythematosus patients with an advanced stage of glomerulonephritis on long term captopril therapy and mean proteinuria decreased from 4.5 gm/day before captopril to 2.7 gm/day after captopril treatment. In 1985, Taguma *et al.* also demonstrated marked reduction of proteinuria in 10 azotemic diabetics. They observed that urinary protein decreased promptly within two weeks and the decrease in proteinuria did not coincide with a fall in systemic blood pressure or in the blood glucose concentration. These findings suggested that captopril caused a decrease in intrarenal hypertension, which contributed to the reduction of urinary protein excretion. In our study, urinary protein excretions were significantly diminished in 17 out of 20 patients with various glomerular disease, and among them, 11 patients showed a more than 50% decrease in proteinuria (Fig. 3). These findings are similar to Taguma *et al.* (1985) in the aspect of the antiproteinuric effect of captopril. Heeg *et al.* in 1987 showed that the ACE inhibitor lisinopril effectively reduces blood pressure and proteinuria in patients with various renal diseases. Lagrue *et al.* in 1987 also demonstrated an antiproteinuric effect of captopril similar to that described by Herlitz *et al.* (1984) and Taguma *et al.* (1985) and this effect appeared independent of the histological type of glomerulonephritis. However, a control study with a larger sample is needed to confirm the antiproteinuric effect of ACE inhibitors and to define which patients could benefit from this treatment.

Although the mechanism by which captopril decreases urinary protein excretion is speculative, it is likely to be related to an interference of captopril with renin and A-II mediated effects on the kidney. In 1940, Pickering and Prinzmetal reported that urinary protein excretion augmented following renin administration to rabbits. These observations were subsequently confirmed by others (Addis *et al.* 1949; Deodher *et al.* 1964; Pessina and Peart 1972). This renin-induced proteinuria has been shown to be mimicked by infusion of A-II (Eisenbach *et al.* 1975). Evidences obtained in recent years strongly suggest that renin and A-II alter the permeability of the glomerular filter to circulating macromolecules (Deodhar *et al.* 1964; Eisenbach *et al.* 1975; Hulme and Pessina 1975). In the study by Eisenbach *et al.* (1975), A-II was found to increase the albumin content of fluid collected from the immediate postcapsular portions of the proximal tubule, leading to the conclusion that A-II indeed enhances the transglomerular passage of albumin. Hulme and Pessina (1975) also found a significant increase in the urinary clearance of intravenously infused high-molecular-weight polyvinylpyrrolidone molecules in rats treated with renin or A-II. In recent animal experiments, infusion of A-II caused a rise in urinary protein loss (Bohrer *et al.* 1977; Olivetti *et al.* 1981) and also in man, renin induced proteinuria has been described in a case of renal artery stenosis (Montoliu *et al.* 1979; Kumar and Shapiro 1980; Takeda *et al.* 1980; Eiser *et al.* 1982; Vea *et al.* 1987). In man, Kumar and Shapiro (1980) reported three cases with proteinuria and nephrotic syndrome induced by renin in patients with renal artery stenosis. They observed that correction of the stenosis by arterial bypass or nephrectomy

resulted in a rapid decrease in urinary protein excretion. These authors suggested that the proteinuria which occured in these patients was a renin or angiotensin induced phenomenon. Bohrer *et al.* in 1977 also suggested that in rats the proteinuria induced by A-II could be explained, in large part, by increased filtration fraction due to a rise in glomerular transcapillary hydraulic pressure differences. According to Yoshioka *et al.* in 1986, A-II inhibition with saralasin during continued renal vein constriction led to a reduction in glomerular capillary hydraulic pressure almost to a preconstriction level. This saralasin induced decline in glomerular hydraulic pressure was associated with a profound fall in resistance of efferent arteriole while that of the afferent arteriole remained essentially unaffected. These findings indicate that the action of captopril would be mediated by a fall in the transcapillary hydraulic pressure and the filtration fraction, alleviating the enhanced glomerular capillary plasma flow rate. In the same experiment, they showed that fractional clearances of neutral [^{125}]dextrans with large and small radii were measured and renal vein constriction caused a significant increase in fractional clearances of large dextran, but not small dextran. Saralasin infusion led to a partial return toward baseline values of fractional clearance of large dextrans. The glomerular sieving defect during renal vein constriction was attributed to an increase in the relative fluid flux thorugh a group of large nonselective pores. In the present study, the selective protein index (SPI), determining the clearance ratio of the IgG to that of the albumin, has been evaluated to investigate the extent to which glomerular size distribution is shifted but significant changes in permselectivity before and after captopril administration were not observed. This result was in agreement with Yoshioka *et al.* (1986). Heeg *et al.* (1987) showed that there was a significant positive correlation between the fall in proteinuria and comitant decrease in mean blood pressure. But Taguma *et al.* in 1985 observed a contradictory result that a decrease in urinary protein excretion after captopril did not coincide with significant changes in blood pressure. Our result was the same as Taguma *et al.* (1985): that the decrease of proteinuria didn't coincide with a fall in systemic blood pressure and the creatinine clearance determined eight weeks after captopril treatment. In our patients, the serum albumin level increased gradually, and, at six weeks after captopril therapy, it became far higher than the pretreatment value. Concerning the changes of the other clinical features including serum electrolytes, there were no statistically significant changes observed after captopril therapy. Side effects such as hypot(1985)ension, rash, neutropenia, and altered taste sensation were not observed in any cases during the study period. According to Weber (1988), when captopril was used in high doses for severe hypertension, adverse effects were noted which now with use of lower doses have virtually disappeared; a previous report by Taguma *et al.* (1985) also showed no clinically significant side effects with the same dosage of captopril as in our study. Sometimes captopril induce proteinuria of significant quantity (over 1 gm/day). Findings of membranous nephropathy on renal biopsy have been described in some of these patients (Frohlich *et al.* 1984; Case *et al.* 1980; Sturgill and Shearlock 1983; Textor *et al.* 1983). Seventy-five percent of the originally reported patients exhibiting captopril related proteinuria were receiveing daily drug doses in excess of 150 mg/day, and had a history of preexisting renal disease (Vidt *et al.* 1982; Frohlich *et al.* 1984).

In conclusion, captopril has a significant antiproteinuric effect in patients excreting heavy proteinuria from various glomerular diseases without any significant changes in renal functions, selective protein indices and blood pressure. However, further study will be needed to evaluate the long-term antiproteinuric effect of this drug.

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