

Antiproteinuric effect of captopril in a patient with lupus nephritis and intractable nephrotic syndrome

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Abstract

A 22 year old woman presented with lupus nephritis, hypertension, and intractable nephrotic syndrome. Albumin and furosemide given intravenously was ineffective. Captopril administered in a daily dose of 62.5 mg was associated with a reduction in proteinuria from 28 g/24 hours to 11.5 g/24 hours over 10 weeks, resulting in a weight reduction of 16 kg. This was achieved with relative preservation of renal function. Captopril should be considered in the treatment of intractable proteinuria in patients with lupus nephritis, or when cytotoxic drugs are refused, because of its efficacy and relative safety. Captopril should, however, be used as an adjunct and not as a substitute for standard treatment.

Reduction of proteinuria by angiotensin converting enzyme (ACE) inhibitors has been described in primary renal diseases,¹ diabetes mellitus,² and other secondary renal diseases such as lupus nephritis, Wegener's granulomatosis, etc.^{3,4} There have only been a few reports of such treatment in patients with lupus nephritis and proteinuria.^{4,5} Experience with ACE inhibitors in severe nephrotic syndrome is limited. We report a case of lupus nephritis and intractable nephrotic syndrome in which captopril treatment resulted in a reduction in proteinuria and a substantial improvement of generalised oedema.

Case report

A 22 year old woman was admitted to hospital in January 1989 owing to progressive dyspnoea of two weeks' duration and intractable anasarca over the past six months, during which her weight had increased from 52 to 68 kg. The patient was known to have had systemic lupus erythematosus (SLE) with renal disease for the past seven years. A kidney biopsy specimen taken in 1983 had shown severe diffuse proliferative glomerulonephritis. She had been treated with corticosteroids and methylprednisolone pulses and then prednisone in doses according to the degree of disease activity. Azathioprine had been given orally for several months and discontinued owing to hair loss. The patient refused to take cyclophosphamide. Plasmapheresis was attempted in 1985 but was stopped after three sessions for technical reasons. Serum creatinine concentrations increased from 195-230 $\mu\text{mol/l}$ five months before admission to 293-319 $\mu\text{mol/l}$ two months before admission. Heavy proteinuria, ranging from 10

to 15 g/24 hours, was noted with a deterioration in kidney function. This was accompanied by hypoproteinaemia (albumin 18-22 g/l) and weight gain of 16 kg, leading to severe generalised oedema. Furosemide, taken orally, 200 mg a day, had no influence on the fluid retention. Hypertension was observed in 1985 and was treated with atenolol 50 mg a day and nifedipine 20 mg twice daily.

On admission generalised oedema was present and the patient weighed 68 kg. Blood pressure was 170/100 mmHg, pulse 80 a minute, and temperature 37°C. The patient had severe facial distortion—'moon-face', periorbital oedema, and mild alopecia. The second heart sound was accentuated. A 2/6 systolic murmur was heard over the apex and aortic area. There was dullness and bronchial breathing in the lung bases. The abdominal wall was tight and oedematous, and there were signs of ascites. The legs and ankles were severely swollen, with several bullae containing clear serous fluid. The fingernails showed severe trophic changes.

Her haemoglobin concentration was 91 g/l. Creatinine 250 $\mu\text{mol/l}$, blood urea nitrogen 13.3 mmol/l, total protein 44 g/l, albumin 18 g/l, calcium 1.6 mmol/l, phosphorus 3.1 mmol/l, cholesterol 6.34 mmol/l. The blood picture was otherwise normal. Analysis of the urine showed a proteinuria of 28 g/24 hours and a few hyaline casts. Antinuclear factor was 1/80; anti-DNA 16.6% (normal <20%), C3 620 mg/l (normal 700-1760 mg/l), C4 420 mg/l (normal 160-450 mg/l). Lupus erythematosus cells were observed.

Chest x ray picture showed mild cardiomegaly and moderate pleural effusions. An abdominal ultrasound scan showed ascites and swollen kidneys—11 cm each. There were no signs of renal vein thrombosis. Renal biopsy was considered too risky because of the oedema and was therefore deferred.

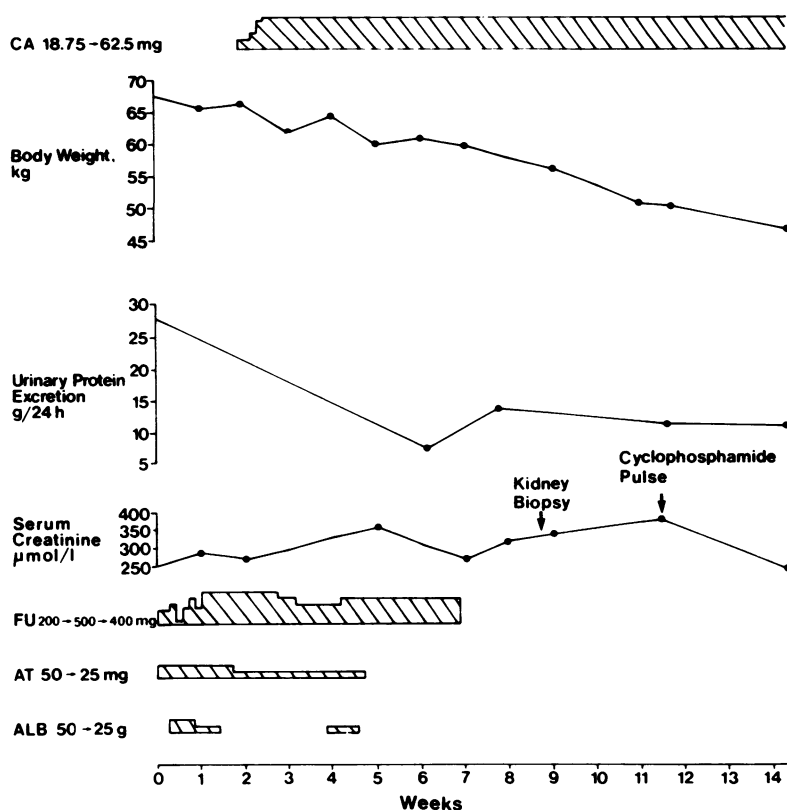
The figure summarises the changes in body weight, proteinuria, and serum creatinine concentrations during the 12 weeks as an inpatient, and the drugs given during that period. Additional treatment comprised nifedipine 40 mg a day and prednisone 10 mg a day. It is evident that two weeks of treatment with salt free albumin and intravenous furosemide in doses up to 500 mg a day had no effect on body weight.

Thirteen days after admission captopril was given, starting with 18.75 mg a day and increasing to 62.5 mg a day after four days. She received that dose for 10 more weeks. Intravenous furosemide 300-400 mg a day in continuous drip over 12 hours was given until the seventh hospital week and then stopped.

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Effect of captopril on body weight, urinary protein excretion, and serum creatinine. CA=captopril; FU=furosemide; AT=atenolol; ALB=albumin.

Atenolol was discontinued after five weeks. The patient lost 16 kg, of which 6.5 kg was lost during the 35 days of concurrent treatment with furosemide and the other 9.5 kg subsequently. There was a considerable reduction in the anasarca, leaving only leg oedema.

Urinary protein excretion decreased from 28 g/24 hours at admission to 7.5, 13.2, and 11.5 g/24 hours in the sixth, eighth, and twelfth week, respectively. Serum albumin concentrations rose from 18 g/l to 25–26 g/l. Blood pressure did not change during treatment and was usually about 170/100 mmHg. Serum creatinine concentration rose to 328–381 µmol/l during the fourth hospital week after a febrile illness, returned to baseline concentrations of 266–310 µmol/l, and rose again in the ninth week to about 355 µmol/l. Creatinine clearance was 10 ml/minute on admission, and 8 ml/minute after 12 weeks.

Once the oedema had begun to reduce a kidney biopsy specimen was taken, during the ninth week; this showed diffuse proliferative glomerulonephritis. By this time the patient had given her approval for cyclophosphamide pulses, which were begun in the thirteenth week of her stay. Two weeks later the serum creatinine concentration had fallen to 239 µmol/l, albumin 28 g/l, creatinine clearance 13.8 ml/minute, and urinary protein excretion was 10.8 g/24 hours. Body weight further decreased to 46 kg. After the second pulse, the creatinine concentration decreased to 168 µmol/l.

Discussion

Angiotensin converting enzyme inhibitors are newcomers in the treatment of proteinuria,¹⁻⁵

though such drugs rarely cause proteinuria by themselves.⁶ Two reports on captopril for the treatment of lupus nephritis and proteinuria have been published. Herlitz *et al* reported the influence of captopril in 11 hypertensive lupus patients, who had been treated for at least six months.⁵ Proteinuria was reduced from a mean of 4.5 g/24 hours to 2.7 g/24 hours, but there was no mention of individual proteinuria concentrations or their range. Among the eight patients in whom glomerular filtration rate was consecutively measured, there was a substantial increase in seven, by a mean of 73 (SD 34)%. It should be noted, however, that only four of the patients had a serum creatinine concentration of 250 µmol/l or above; in two of them the creatinine concentration decreased within a year, while in the other two renal function deteriorated. The authors did not comment on the correlation between a reduction in blood pressure and proteinuria. Mean (SD) daily captopril dose was 153 (31), 110 (17), and 70 (15) mg after one, six, and 12 months, respectively.

Trachtman and Gauthier studied the influence of ACE inhibitors on eight subjects (aged 5–22 years) with proteinuria that was unresponsive to standard treatment.⁴ Four of the patients had SLE and chronic glomerulonephritis. There was no evidence of flare-up of SLE during the study. The goal of the study was to reduce proteinuria, as opposed to Herlitz's trial,⁵ in which a reduction in blood pressure was the primary objective. The ACE inhibitor studied was captopril given to seven of the patients. The urinary protein:creatinine ratio decreased in all of the patients. Mean glomerular filtration rate decreased by 11%, but this was not significant. In six of the patients there was neither significant hypoalbuminaemia, nor peripheral oedema. The results in the patients with SLE were not evaluated separately.

Our case shows the beneficial effect of captopril on massive and intractable proteinuria (28 g/24 hours) in a patient with SLE, in whom diuretics and albumin were of no apparent benefit. We were able to discontinue furosemide after one month of captopril treatment, yet weight loss continued and proteinuria decreased, though still in nephrotic range.

What is the risk of ACE inhibitor treatment in patients with nephrotic syndrome, hypertension, and impaired renal function? Lagrue *et al* gave captopril (25 mg twice daily) to 10 hypertensive patients with nephrotic syndrome.¹ Seven of the patients had mild to moderate renal dysfunction (serum creatinine concentration 133–219 µmol/l). In only one was there a significant decrease in renal function after treatment. Heeg *et al* gave lisinopril to 13 hypertensive patients with proteinuria. All had impaired renal function before treatment, with creatinine clearance ranging from 10 to 56 ml/minute. Creatinine was not significantly increased after 12 weeks of treatment, but there was a significant, though mild, decrease in creatinine clearance.

Eight patients with SLE and renal dysfunction and proteinuria were given captopril for 12 months in the study by Herlitz.⁵ In five of these

serum creatinine concentrations decreased, while in three it increased, including one patient who underwent dialysis after seven months.

The effect of ACE inhibitors on renal function in hypertensive patients with renal dysfunction and proteinuria is thus not yet established. In most patients renal function is preserved or even improves, while in only a few does it deteriorate.

Blood pressure did not change significantly during treatment with captopril in the case reported here, and thus could not account for the decrease in the proteinuria. This agrees with the findings of previous reports in which the decrease in proteinuria during treatment with an ACE inhibitor exceeded the decrease in blood pressure.^{3 4}

The mechanism through which ACE inhibitors inhibit proteinuria is not fully understood. Some of the proposed mechanisms are related to the renal haemodynamics, mainly post-glomerular vasodilatation.³ Thus the effect on proteinuria is symptomatic and not curative. Angiotensin converting enzyme inhibitors, however, have other properties, one of which is immunoregulatory.⁷ This may be especially important in autoimmune renal diseases such as lupus nephritis. Herlitz *et al* showed that captopril can significantly diminish the glomerular damage and increase survival in MRL lpr/lpr mice with an SLE-like disease.⁸ A similar mechanism may occur in man, but this requires further confirmation.

In conclusion, captopril was efficient and relatively safe for the treatment of intractable nephrotic syndrome in a patient with lupus nephritis. Longer follow up and further studies are needed to establish this treatment in other patients. Until then, a cautious approach, with a stepwise increase in ACE inhibitor dose and a close follow up of renal function is advisable. This treatment does not, however, replace the standard treatment for lupus nephritis, but may be regarded as an adjunct in cases of intractable proteinuria, or when the patient refuses to take cytotoxic drugs.

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