Transpl Int (1993) 6: 213–217

Transplant International

Effect of enalapril on proteinuria after kidney transplantation

Krzysztof Rell, Jacek Linde, Maria Morzycka-Michalik, Zbigniew Gaciong, Mieczysław Lao

Transplantation Institute, Warsaw Medical Academy, 59 Nowogrodzka Street, PL-02-006 Warsaw, Poland

Received: 25 August 1992/Received after revision: 17 November 1992/Accepted: 23 November 1992

Abstract. We studied the effect of enalapril, an inhibitor of angiotensin-converting enzyme (iACE), on proteinuria and renal function in recipients of renal allografts. Twenty-two patients with post-transplant nephrotic syndrome were treated with incremental doses of enalapril for 1 year. Urinary protein excretion decreased after 2 months of treatment from a mean of 8.9 g/day (range 4.0–18.9 g/day) to 4.5 g/day (range 0.4–10.0 g/day; $P < 0.01$) and remained significantly low for the rest of the study. However, in the same period, creatinine clearance did not change significantly; it went from 47.8 ml/min (range 17.1–110.3 ml/min) before treatment to 44.2 ml/min (range 16.5–88.5 ml/min) after 2 months of iACE therapy. Analysis of individual data showed that there was a significant reduction in proteinuria in 14 of the 22 patients and that the rate of deterioration of renal function did not increase in 17 of the 22 patients. We did not observe any serious side effects of enalapril administration. The results of our study prove that iACE can be used safely and effectively to reduce post-transplant proteinuria.

Key words: Kidney transplantation, proteinuria, enalapril – Proteinuria, kidney transplantation, enalapril – Enalapril, kidney transplantation, proteinuria

Introduction

Persistent proteinuria develops in up to 30% of all long-term kidney allograft recipients [3, 6, 7, 11, 24] and frequently progresses to nephrotic syndrome. The causes of transplant proteinuria have been attributed to recurrent or de novo glomerulonephritis, "allograft glomerulopathy", chronic rejection, renal vein thrombosis, nephrosclerosis (diabetic or hypertensive), and reflux nephropathy [2, 3, 6–8, 11, 19, 24]. The appearance of severe proteinuria is often associated with accelerated graft loss [3, 24]. Moreover, severe proteinuria contributes to morbidity as a result of the development of edema and of protein and caloric malnutrition.

Recently, it has been suggested that proteinuria per se accelerates the progression of kidney failure by direct glomerular damage and/or secondary mechanisms, such as hyperlipidemia and hypercoagulability [5]. Therefore, one may expect that even a nonspecific reduction in proteinuria may protect residual glomeruli. Inhibitors of angiotensin I converting enzyme (iACE) effectively reduce protein excretion in primary and secondary glomerulonephritis in humans [13, 16, 17, 22, 23] and in animals with induced glomerular injury [15, 18].

In renal transplant recipients, iACE are used with great caution because of the risk of induction of acute renal failure. This complication is usually associated with renal artery stenosis [14] but can also result from diffuse vascular changes caused by cyclosporin immunosuppression [1, 20] and chronic rejection [10, 21].

We studied a group of long-term renal allograft recipients with nephrotic syndrome. Patients were treated with enalapril in incremental doses to achieve a significant reduction in proteinuria. The safety and efficacy of enalapril therapy were evaluated.

Materials and methods

Out of all long-term recipients of renal cadaveric allografts, we selected 22 consecutive patients with proteinuria greater than 4 g/day of at least 3-month duration. Their clinical data are presented in Table 1. Patients remained on the same immunosuppressive regimen throughout the entire period of the study. The cyclosporin dose was adjusted to obtain trough levels in whole blood between 80 and 150 ng/ml, as determined by radioimmunoassay using monoclonal antibody (Sandoz, Basel, Switzerland).

Before treatment with enalapril, the presence of renal stenosis was ruled out in all patients on the basis of normal Doppler ultrasound examination or normal angiography, and diuretics were temporarily withdrawn. After the first (2.5 mg) dose of enalapril, subsequent doses were gradually increased over a period of 1 month until a reduction in proteinuria was achieved or serious side effects

Correspondence to: K. Rell

Table 1. Patient characteristics. Values represent mean ± SD

Male	16
Female	6
Age (years)	30 ± 9.3
Number of HLA mismatches	3.0 ± 1.1
Interval (months) between transplantation and the appearance of proteinuria > 4 g/day	18.3 ± 13.2
Immunosuppression:	
Prednisone + azathioprine	7
Prednisone + cyclosporin + azathioprine	15
Allograft biopsy:	
Membranous	6
Mesangiocapillary	2
Crescentic	1
Chronic rejection without glomerular changes in light microscopy[a]	2
Undifferentiated glomerulonephritis	4
No changes in light microscopy	5
Nondiagnostic	2

[a] Nine patients with dominant glomerular lesions also had concomitant chronic rejection

developed (hypotension, rise in serum creatinine). Serum creatinine and 24-h protein excretion were measured immediately before treatment, on the day after enalapril was started, and then on every outpatient visit (at least once monthly). The results of proteinuria and serum creatinine were also collected for the period of 12 months before the treatment. Glomerular filtration rate (GFR) was expressed as a creatinine clearance predicted using the Cockcroft-Gault formula [12]. For each patient the values of daily proteinuria and creatinine clearance were plotted versus time. An example of calculations for one of the patients is shown in Fig. 1. The rate of renal functional deterioration was determined for each patient by computerized derivation of the slope from the linear plot of creatinine clearance-versus-time. In the same way, changes in urine protein excretion were calculated for each patient. Values of a slope on the creatinine clearance-versus-time plot and the daily proteinuria-versus-time plot were compared in the period before and during enalapril therapy using the Mann-Whitney test.

Values of proteinuria and serum creatinine at the different times during the study in the iACE-treated patients were compared with repeated measures analysis of variance (ANOVA). Differences between rates were analyzed with the chi-square test.

Results

In the study group proteinuria greater than 4 g/day was detected 18.3 months (range 0.9–40.6 months) after transplantation. Enalapril was introduced after 6.7 months (range 3.3–22.4 months) after the development of proteinuria greater than 4 g/day. After administration of the first dose of enalapril, urine output decreased in two patients. Furosemide was immediately resumed and this was followed by increased urine production. One of these patients required a single ultrafiltration treatment to reduce fluid overload. The enalapril administration was continued and the serum creatinine level did not change in either patient.

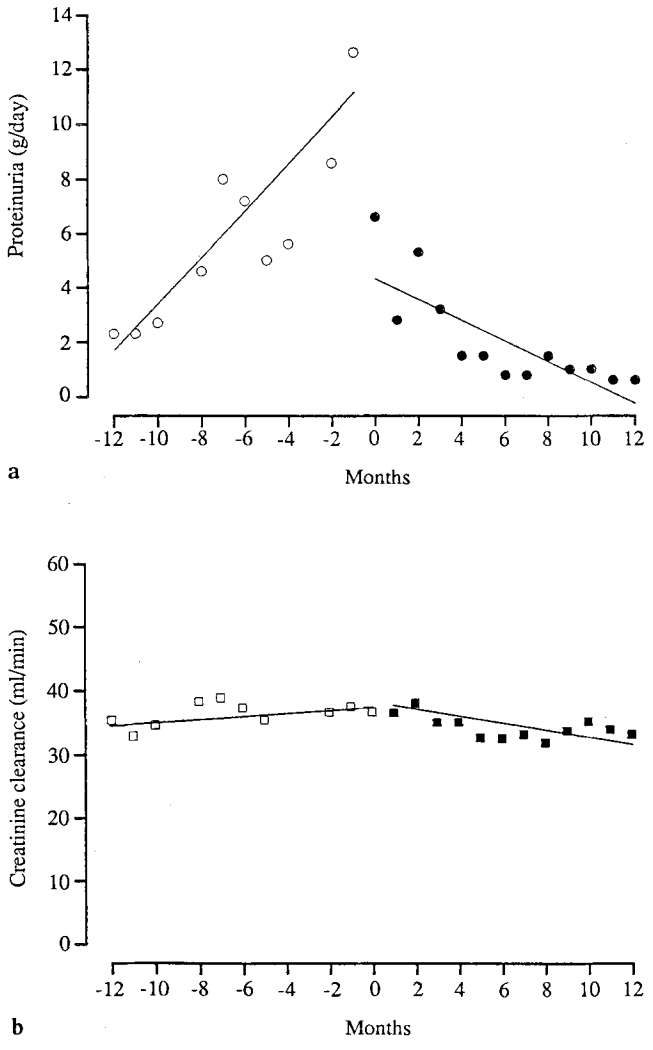

Fig. 1. Values of daily proteinuria (**a**) and predicted creatinine clearance (**b**) in a patient before and during enalapril treatment. Each *circle* or *square* represents a single measurement. Linear plots of creatinine clearance and daily proteinuria versus time are depicted. The values of the slopes of the plots of proteinuria-versus-time are 0.0078 and −0.0029 for the time before and while on enalapril ($P < 0.01$), respectively. The corresponding values of the slopes of the plots of creatinine clearance-versus-time are 0.19122 and −0.20379 (NS)

The mean value of daily proteinuria was 8.9 g/day (range 4.0–18.9 g/day) at the beginning of enalapril therapy; it started to decrease gradually thereafter, reaching a mean nadir of 2.9 g/day (range 0.8–6.6 g/day) after 6 months. The reduction in protein excretion was statistically significant starting in the 3rd month of treatment and it remained significantly low for nine consecutive months during the study (Fig. 2). The mean dose of enalapril throughout this period was 14.4 mg/day (range 2.5–20 mg/day).

For 14 patients, the slope on the daily proteinuria-versus-time plot was significantly lower during enalapril therapy than the corresponding value from the control period before enalapril administration. The effect of enalapril on protein excretion did not differ according to the immunosuppressive therapy. Reduction in proteinuria was observed in 10 out of 15 recipients who were on a triple drug

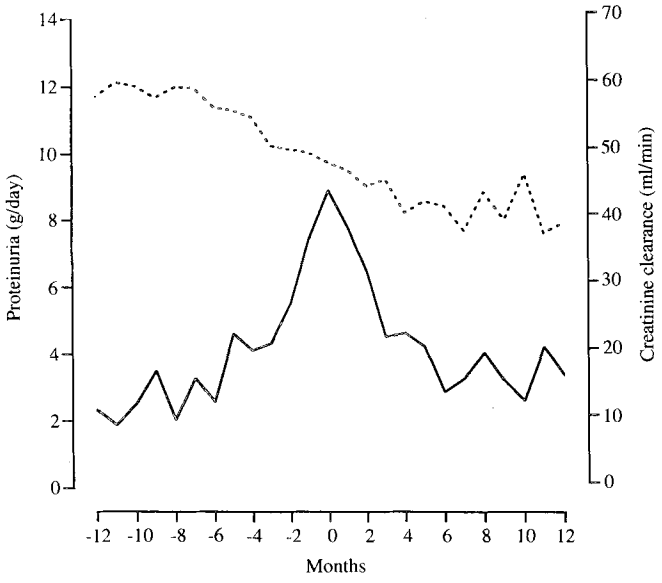

Fig. 2. Mean daily proteinuria (—) and creatinine clearance (---) in patients ($n = 22$) before and during enalapril treatment

regimen (prednisone + cyclosporin + azathioprine) and in 4 out of 7 patients who did not receive cyclosporin. In 7 patients there was no change in daily proteinuria and in 1 case a significant increase in proteinuria was noted (Fig. 3).

During 2 years of the study, the mean estimated creatinine clearance decreased steadily from 58.6 ml/min (range 16.5–99.0 ml/min) 12 months before treatment to 47.8 ml/min (range 17.1–110.3 ml/min) on the day before administration of enalapril, down to 38.7 ml/min (range 16.5–72.1 ml/min) after 12 months of therapy ($P < 0.05$; repeated measures ANOVA; Fig. 2). The rate of deterioration of renal function, determined as a mean value of slopes on the creatinine clearance-versus-time plot, was not different in the periods before and 12 months after administration of enalapril (-0.614 ± 2.848 vs -1.681 ± 2.546; $P = 0.32$). After 2 months of enalapril therapy, when daily proteinuria significantly decreased from 8.9 g/day (range 4.0–18.9 g/day) to 4.5 g/day (range 0.4–10.0 g/day; $P < 0.01$), mean creatinine clearance was similar to the value on the day immediately before initiation of the drug: 44.2 ml/min (range 16.5–88.5 ml/min) vs 47.8 ml/min (range 17.1–110.3 ml/min; $P = 0.18$).

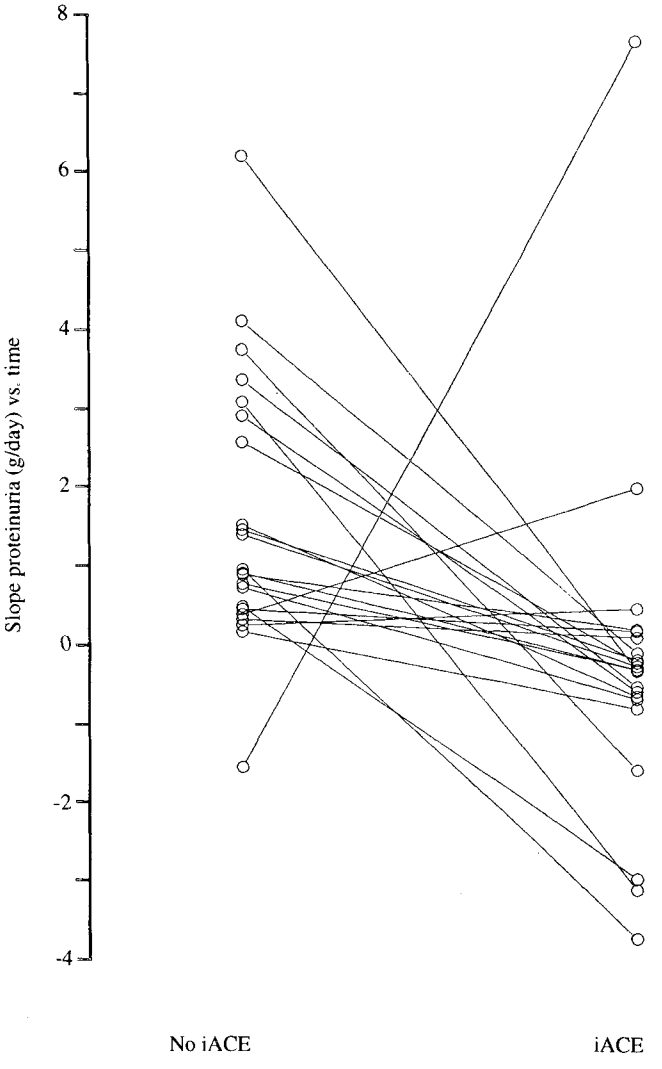

Fig. 3. Effect of treatment with enalapril on daily proteinuria. Each *circle* represents a value of a slope ($\times 10^{-2}$) on proteinuria-versus-time plot for a single patient before and during therapy

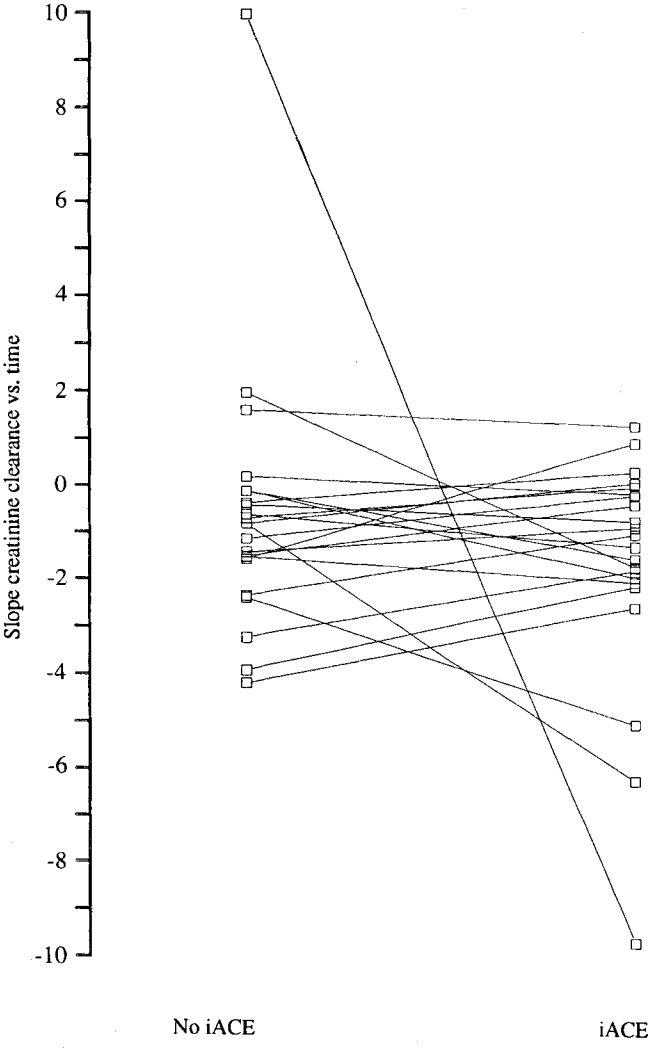

Fig. 4. Effect of treatment with enalapril on creatinine clearance. Each *square* represents a value of a slope on creatinine clearance-versus-time plot for a single patient before and during therapy

Analysis of the rates of deterioration of renal function in individual patients (Fig. 4) showed a significant decline in five patients. There was no difference in the mean rate of deterioration of renal function during enalapril treatment between the group of recipients with and the group without cyclosporin. However, among patients with an accelerated decline in renal function, four were receiving cyclosporin and only one was on prednisone-azathioprine immunosuppression. In two of these patients chronic rejection was found on repeated kidney biopsy and one patient experienced acute rejection. In two other patients with a steady decline in renal function, chronic rejection was diagnosed without kidney biopsy. Four of these patients returned to hemodialysis after a mean of 7.3 months (range 4.1–17.2 months) of enalapril therapy. In one patient, the allograft was removed in spite of good kidney function (88.4 μmol/l of serum creatinine) because of uncontrollable proteinuria and malnutrition.

The rest of the enalapril-treated patients showed an unchanged ($n = 9$) or decreased ($n = 8$) rate of deterioration of renal function during the enalapril treatment as compared to the period without enalapril (Fig. 4).

Of the patients studied, 17 had hypertension that was treated with hypotensive drugs. In this group of patients, after administration of enalapril, other hypotensive medications were withdrawn, or their doses tapered, to keep blood pressure unchanged. In the study group, mean arterial pressure (1/3 pulse pressure + diastolic) was 104.0 mm Hg (range 80.0–123.0 mm Hg) before treatment and 99.5 mm Hg (range 83.3–126.0 mm Hg) after 2 months of enalapril administration. Mean arterial blood pressure did not change significantly during the entire study period.

Patient survival was 100 %.

Discussion

There is general agreement that iACE should be prescribed with great caution in kidney transplant patients [1, 9, 10, 14, 21]. This group is at high risk of developing vascular changes (renal artery stenosis, diffused arterial lesions caused by chronic rejection or cyclosporin toxicity), resulting in glomerular hypoperfusion. It is assumed that under conditions of hypoperfusion, filtration is maintained by vasoconstriction of efferent arterioles secondary to the increased activity of the renin-angiotensin system. iACE block the efferent arteriolar vasoconstriction and, thereby, reduce glomerular filtration.

Before administration of enalapril, we confirmed the absence of renal artery stenosis using Doppler ultrasound examination or angiography, withdrew diuretics for 1 day, and expanded intravascular fluid volume with physiological saline. After undertaking these protective measures, we did not observe any case of acute renal failure and only two patients experienced a transient fall in urine output that responded to furosemide.

In our group of recipients, the mean creatinine clearance measured a day before initiation of enalapril therapy was significantly higher than it was after 1 year of treatment; however, it was significantly lower than the mean value 1 year before the beginning of enalapril therapy. We estimated a rate of decline in renal function as a slope of creatinine clearance-versus-time plot. The mean values of the slopes before and after initiation of therapy did not differ, thereby showing no detrimental effect of enalapril on renal function.

Analysis of individual values of a slope on the reciprocal creatinine clearance-versus-time plot shows that during enalapril therapy, significant deterioration of renal function occurred in 5 of the 22 recipients; 3 of them had features of chronic or acute rejection in biopsy and only 1 of them did not receive cyclosporin immunosuppression. Although these differences were statistically insignificant, they support previous suggestions that chronic rejection and/or cyclosporin toxicity may predispose one to deterioration of renal function during iACE therapy [1, 10, 20].

In the enalapril-treated patients, a significant fall in the mean daily proteinuria was noted after 2 months of therapy. Our data are in agreement with those of others [4] who found a decrease in post-transplant proteinuria after 4 months of iACE therapy. The same group observed a reversible reduction in GFR and a rise in serum creatinine while on iACE therapy. A decrease in GFR reduces the load of filtered proteins, decreasing the amount of protein apearing in urine. In our study we did not measure GFR directly, but we judged kidney function on predicted creatinine clearance, calculated using the Cockroft-Gault equation. In renal transplant recipients, predicted creatinine clearance correlates with measured creatinine clearance at about the same level it does with GFR measured by inulin or comparable compounds [12]. After 2 months of enalapril treatment, the mean predicted creatinine clearance did not change significantly compared to the value immediately before the therapy, but we noticed a significant fall in urine protein excretion. Therefore, it seems possible that the observed decrease in proteinuria was not secondary to a decline in kidney function. This is in accordance with data suggesting that iACE may affect the permeability of the glomerular membrane.

Our study proves that enalapril can be used safely in kidney transplant patients with nephrotic syndrome to significantly reduce proteinuria.

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