RESPONSE TO THE FUROSEMIDE TEST MAY PREDICT THE EFFECTS OF DELAPRIL ON RENAL FUNCTION IN PATIENTS WITH CHRONIC RENAL INSUFFICIENCY

YOSHIHIRO FUJII, TADASHI KISHIMOTO and KAZUHIRO DOHI
First Department of Internal Medicine Nara Medical University
Received September 4, 1997

Abstract: **Background**: It is not clear whether the administration of an angiotensin-converting enzyme (ACE) inhibitor consisitently slows the progression of disease in patients with renal disease. We investigated the usefulness of the furosemide test in predicting the efficacy of delapril, an ACE inhibitor, in patients with chronic renal insufficiency.

Methods: Delapril (7.5 mg to 15 mg) was administered daily to 24 patients with chronic renal insufficiency as indicated by a serum concentration of creatinine (Scr) between 1.2 mg/dl and 3.0 mg/dl. Patients were classified into improved, unchanged, and worsened groups based on the effect of delapril on the Scr. We measured the following parameters before the administration of delapril for a mean of 9 months blood pressure, Scr, urinary protein excretion, urinary sodium excretion, and changes in the renin and aldosterone response (the PRA ratio and PAC ratio) to a furosemide test.

Results: Renal function was improved in 6 patients, unchanged in 8 patients, and worsend in 10 patients after delapril treatment. Urinary protein excretion was decreased, but not significantly, in all three groups. No significant differences in baseline parameters were observed among the groups before treatment. The PRA ratio was significantly higher in the group showing improvement vs. the groups showing either no improvement or a worsening of renal function.

Conclusions: Delapril tended to reduce the urinary excretion of protein in patients with chronic renal insufficienty. However, delapril did not consistently reduce the rate of decline in glomerular filtration rate. The protective effect of this drug on renal function appeared to be related to the renin response to furosemide test.

Index Terms

angiotensin-converting enzyme inhibitor, furosemide test, plasma renin activity, renal insufficency

INTRODUCTION

Hypertension is both a cause and a result of chronic renal disease, and is an important contributor to renal disease progression. In animals with experimentally induced renal disease, the administration of angiotensin-converting enzyme (ACE) inhibitors normalizes the glomerular capillary hydraulic pressure by reducing efferent arteriolar resistance and reduces the glomerular-capillary permeability to proteins, thus diminishing the severity of proteinuria and preventing the development of glomerulosclerosis[1-4]. ACE inhibitors appear to reduce the

severity of overt proteinuria, irrespective of the underlying renal disease[5-7], and to reduce the rate of decline in the glomerular filiration rate, irrespective of the degree of blood pressure control[8]. However, ACE inhibitors may occasionally induce renal insufficiency. The glomerular filtration rate is maintained by the angiotensin II-mediated efferent arteriolar constriction, which sustains the glomerular capillary hydraulic pressure. A reduction in the efferent arteriolar tone induced by ACE inhibitors may reduce glomerular capillary hydraulic pressure, reducing the glomerular filtration rate[9,10]. Whether ACE inhibitors are consistently protective in humans has not been clarified. Some studies have suggested that ACE inhibitors protect renal function in patients with renal disease[11-14]. However, others have reported that ACE inhibitors do not maintain the glomerular filtration rate in patients with chronic renal insufficiency[15,16]. We investigated factors that predict the effect of delapril, an ACE inhibitor, on renal dysfunction in patients with mild renal insufficiency.

METHODS

Patients

We studied 24 Japanese patients aged 24 to 80 years, 18 men and 6 women with chronic renal insufficiency caused by chronic glomerulonephrits or nephrosclerosis who had a serum concentration of creatinine (Scr) of 1.2 to 3.0 mg/dl. We excluded patients who had received corticosteroids, nonsteroidal antiinflammatory drugs, or immunosuppressive drug, and patients with renovascular hypertension, malignant hypertension, a history of a myocardial infaction or cerebrovascular accident in the 6 months preceding the study, congestive heart failure, non-insulin-dependent diabetes mellitus, collagen disease, obstructive uropathy, cancer, an allergic reaction to an ACE inhibitor, and pregnancy. Chronic glomerulonephritis was diagnosed in 19 patients and nephrosclerosis in 5 patients, based on examination of renal biopsies.

Study Design

Patients were screened for at least six months to determine the rate of decline in the 1/Scr, which roughly represents the creatinine clearance. Patients receved 7.5 mg to 15 mg of delapril with an anti-platelet agent (300 mg of dipyridamole or 300 mg of dilazep). Of the 29 patients initially enrolled in the study, 5 withdrew because of the development of an intolerable cough attributed to delapril.

Blood pressure was measured every 2 weeks with a standard sphygmomanometer after patients rested in the sitting position for at least 5 min. Levels of blood urea nitrogen (BUN), Scr, and serum electrolytes and the 24-hour urinary excretion of protein and sodium were measured every 4 weeks with an autoanalyzer.

Furosemide test

Blood samples for measurement of the baseline peripheral venous plasma renin activity (PRA) and the plasma aldosterone concentration (PAC) were obtained after 30 minutes of bedrest. Furosemide (40 mg) was then injected intravenously and blood samples were again obtained after patients had remained standing for 2 hours. Changes in the renin and aldosterone response to the furosemide test are expressed as the ratio of the baseilne PRA and PAC to the

PRA or the PAC, respectively, after the furosemide test.

Evaluation of effects of delapril on renal function

Fig. 1 explains the way to evaluate the effects of delapril on renal function[17]. The rate of decline in 1/Scr was measuted before and after the administration of delapril. Renal function was classified as improved if the ratio of the declie in the 1/Scr before delapril to the decline in the 1/Scr after delapril was less than 0.6, unchanged if the ratio was more than 0.6 and less than 1.1, and worsened if the ratio was more than 1.1.

Statistical Analysis

Data are presented as the mean±SD. Results were analyzed with the Statistical Analysis System (Statview-J 4.5). Differences in renal function before and after delapril treatment were analyzed with paired t test in each group. Differences in results of furosemide test were analyzed by Fisher's exact test. A p value of <0.05 was accepted as statistically significant.

RESULTS

Renal function was improved after delapril treatment in 6 patients, unchanged in 8 patients, and worsened in 10 patients (Table 1). The mean duration of delapril treatment was 9 months. There ware no significant pre-treatment differences among groups in blood pressure, the Scr. urinary protein excretion, or urinary sodium excretion (Table 2).

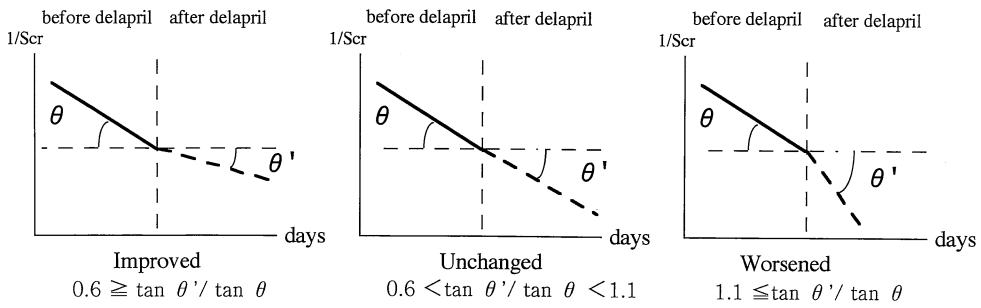

Fig. 1. Evaluation of effect of delapril on renal function.
Renal function was classified as improved if the ratio of the decline in the 1/Scr before delapril to the decline in the 1/Scr after delapril was less than 0.6, unchanged if the ratio was between 0.6 and 1.1, and worsened if the ratio was more than 1.1.

Table 1. Clinical characteristics

Characteristic	Improved (n=6)	Unchanged (n=8)	Worsened (n=10)
Male/Female	5/1	3/5	10/0
Age (years)	49±23	49±12	58±10
Disease	3 CGN	6 CGN	10 CGN
	3 nephrosclerosis	2 nephrosclerosis	

CGN=chronic glomerulonephritis

Table 2. Parameters of renal function before and after delapril treatment

Characteristic	Improved		Unchanged		Worsened	
	before	after	before	after	before	after
Systolic blood pressure (mmHg)	149±17	160±21	138±21	130±16	140±17	132±21
Diastolic blood pressure (mmHg)	86±5	87±10	87±15	80±11	85±10	81±10
Serum creatinine (mg/dl)	1.65±0.67	1.62±0.60	1.33±0.27	1.42±0.28	1.82±0.70	2.34±0.76
24-hour urinary protein excretion (g/day)	3.36±3.69	0.93±0.83	1.01±0.57	0.65±0.44	1.95±1.77	1.47±1.50
24-hour urinary sodium excretion (mEq/day)	152±85	158±50	143±75	119±87	145±68	117±55

Data are the mean±SD.

Table 3. PRA and PAC before and after the furosemide test

Characteristic	Improved		Unchanged		Worsened	
	before	after	before	after	before	after
PRA (ng/ml/hr)	1.56±0.27	6.52±4.01	1.41±0.91	4.32±2.65	2.95±3.47	4.73±6.16
PAC (pg/ml)	100.1±56.2	328.7±228.2	82.2±53.0	188.6±116.3	85.7±58.1	168.4±106.8
PRA ratio	4.00±1.86		3.27±1.08		1.64±0.42	
		*		*		
				*		
PAC ratio	3.42±1.85		2.50±1.89		2.01±0.60	

PRA=plasma renin activity, PAC=plasma aldosterone concentration
Data are the mean±SD.
*$p<0.01$

Changes in Scr and Urinary Protein Excretion

While the Scr decreased after delapril treatment in the improved group, and increased in the unchanged and worsened groups, these changes were not statistically significant (Table 2). Urinary protein excreion decreased in all 3 groups, but the changes were not significant.

Changes in the PRA and PAC

There were no significant differences among groups in the baseline PRA and PAC or the changes in PRA and PAC after delapril treatment. However, the PRA ratio was significantly higher in the improved group than in the unchanged and worsened group (Table 3). The PRA ratio was significantly higher in the unchanged group than in the worsened group. There were significant differences among groups in the PAC ratio.

DISCUSSION

Studies in animals with experimentally induced progressive renal disease or diabetic ne-

phropathy have shown the ACE inhibitors reduce glomerular injury more consistently than calcium channel blockers or the combination of hydrochlorothiazide, reserpine, and hydralazine[18]. Previous studies have also found that enalapril or lisinopril have effects on renal function in patients with chronic renal insufficiency[15,16,19]. ACE inhibitors reduce urinary protein excretion in patients with diabetes and other glomerulopathies[20-22]. The mechanism of the effect of ACE inhibitors on proteinuria is unknown. Experimental studies using micropuncture techniques have suggested that a reduction in glomerular capillary hydraulic pressure reduces proteinuria[1-3]. ACE inhibitors reduce the filtration fraction, which indicates a decrease in postglomerular vascular resistance. Thus, alterations in renal hemodynamics may be responsible for the ACE inhibitor-induced decrease in urinary protein excretion. In the present study, delapril tended to reduce urinary protein excretion in all groups with chronic renal insufficiency.

However, the effects of delapril on renal function seemed to be variable in patients with chronic renal insufficiency. Delapril did not consistently retard the loss of renal function in patients with chronic renal insufficiency. Renal function, assessed by the rate of decline in the 1/Scr, was improved in 6 of 24 patients, unchanged in 8 patients, and worsened in 10 patients. ACE inhibitors may induce acute renal insufficiency in patients with renal artery stenosis or advanced congestive heart failure, even when the systemic blood pressure remains unchanged[9-10]. These conditions are characterized by the dependence of the glomerular hydraulic pressure on angiotensin II mediated efferent arteriolar constriction. Thus ACE inhibitors may worsen renal function in patients in whom glomerular filtration is maintained primarily by angiotensin II. The present results suggest that angiotensin II mediation of the glomerular filtration rate is variable in patients with chronic renal insufficiency. There were no significant differences in blood pressure, the Scr. urinary protein excretion, and urinary sodium excretion before delapril treatment among groups in the present study, indicating that these factors were not useful for predicting the effect of delapril. There were also no significant differences in the PRA and PAC before or after the furosemide test or in the PAC ratio among groups. However, the PRA ratio was significantly higher in patients who showed improvement in renal function than in patients who showed no change or worsening of renal function. The PRA ratio was also significantly higher in the unchanged group compared with the worsened group. The release of renin is stimulated by furosemide-induced sodium depletion and the decrease in renal perfusion induced by standing. The low PRA ratio in the worsened group suggests that maintenance of the glomerular filtration rate was strongly dependent on the renin-angiotensin system in this group. The present results suggest that furosemide-induced changes in the PRA reflect the role of the renin-angiotensin system in the progression of renal disease, and may be useful for predicting the effects of delapril on renal function in patients with chronic renal insufficiency.

In conclusion, the protective effect of delapril on renal function appeared to be related to the magnitude of the renin response to the furosemide test.

REFERENCES

1) **Anderson, S., Meyer, T. W., Rennke, H. G.** and **Brenner, B. M.**: Control of glomerular hypertension

limits glomerular injury in rats with reduced renal mass. J. Clin. Invest. **76**: 612-619, 1985.

2) **Anderson, S., Rennke, H. G.** and **Brenner, B. M.**: Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. J. Clin. Invest. **77**: 1993-2000, 1986.
3) **Meyer, T. W., Anderson, S., Rennke, H. G.** and **Brenner, B. M.**: Reversing glomerular hypertension stabilizes established glomerular injury. Kidney Int. **31**: 752-759, 1987.
4) **Zatz, R., Anderson, S., Meyer, T. W., Dunn, B. R., Rennke, H. G.** and **Brenner, B. M.**: Lowering of arterial blood pressure limits glomerular sclerosis in rats with renal ablation and in experimental diabetes. Kidney Int. Suppl. **20**: S123-S129, 1987.
5) **Heeg, J. E., de Jong, P. E., van der Hem, G. K.** and **de Zeeuw, D.**: Efficacy and variability of the anti-proteinuric effect of ACE inhibition by lisinopril. Kidney Int. **36**: 272-279, 1989.
6) **Kasiske, B. L., Kalil, R. S. N., Ma, J. Z., Liao, M.** and **Keane, W. F.**: Effect of antihypertensive therapy on the kidney in patients with diabetes: A meta-regression analysis. Ann. Intern. Med. **118**: 129-138, 1993.
7) **Kelleher, C. C.**: ACE inhibitors in the prevention and therapy of diabetic nephropathy. What is their role? Drugs **39**: 639-645, 1990.
8) **Bjorck, S., Mulec, H., Johnsen, S. A., Norden, G.** and **Aurell, M.**: Renal protective effect of enalapril in diabetic nephropathy. Br. Med. J. **304**: 339-343, 1992.
9) **Hricik, D. E., Browning, P. J., Kopelman, R., Goorno, W. E., Madias, N. E.** and **Dzau, V. J.**: Captopril-induced functional renal insufficiency in patients with bilateral renal-artery stenosis or renal-artery stenosis in a solitary kidney. N. Engl. J. Med. **308**: 373-376, 1983.
10) **Kackson, B., Matthews, P. G., McGrath, B. P.** and **Johnston, C. I.**: Angiotensin converting enzyme inhibition in renovascular hypertension: frequency of reversible renal failure [Letter]. Lancet **1**: 225-226, 1984.
11) **Mann, J. F. E., Reisch, C.** and **Ritz, E.**: Use of angiotensin-converting enzyme inhibitors for the presentation of kidney function. Nephron **55**: Suppll: 38-42, 1990.
12) **Rekola, S., Bergstrand, A.** and **Bucht, H.**: Deterioration rate in hypertensive IgA nephropathy: comparison of a converting enzyme inhibitor and beta-blocking agents. Nephron **59**: 57-60, 1991.
13) **Kamper, A. L., Strandgaard, S.** and **Leyssac, P. P.**: Effect of enalapril on the progression of chronic renal failure: a randomized controlled trial. Am. J. Hypertens. **5**: 423-430, 1992.
14) **Hannedouche, T., Landias, P.** and **Glodfarb, B.**: Randomized controlled trial of enalapril and beta blockers in non-diabetic chronic renal failure. B. M. J. **309**: 833-837, 1994.
15) **Reams, G. P.** and **Bauer, J. H.**: Effect of enalapril in subjects with hypertension associated with moderate to severe renal dysfunction. Arch. Intern. Med. **146**: 2145-2148, 1986.
16) **Heeg, J. E., de Jong, P. E., van der Hem, G. K.** and **de Zeeuw, D.**: Reduction of proteinuria by angiotensin converting enzyme inhibition. Kidney Int. **32**: 78-83, 1987.
17) **Koide, K., Koshikawa, S., Yamane, K.** and **Hidaka, S.**: Clinical evaluation of AST-120 on suppression of progression of chronic renal failure. -Multi-center, double-blind study in comparison with placebo-Clin. Eval. **15**: 527-564, 1987.
18) **Keane, W. F., Anderson, S., Aurell, M., de Zeeuw, R.** and **Pover, G.**: Angiotensin converting enzyme inhibitors and progressive renal insufficiency. Current experience and future directions. Ann. Intern. Med. **111**: 503-516, 1989.
19) **Bauer, J. H., Reams, G. P.** and **Lal, S. M.**: Renal protective effect of strict blood pressure control with enalapril therapy. Arch. Intern. Med. **147**: 1397-1400, 1987.
20) **Taguma, Y., Kitamoto, Y.** and **Futaki, G.**: Effect of captopril on heavy proteinuria in azotemic diabetics. N. Engl. J. Med. **313**: 1617-1620, 1985.
21) **Praga, M., Hernandez, E., Montoyo, C., Andres, A., Ruilope, L. M.** and **Rodicio, J. L.**: Long-term bene-

ficial effects of angiotensin-converting enzyme inhibition in patients with nephrotic proteinuria. Am. J. Kidney. Dis. **20** : 240-248, 1992.

22) **Kasiske, B. L., Kalil, R. S. N., Ma, J. Z., Liao, M.** and **Keane, W. F.** : Effect of antihypertensive therapy on the kidney in patients with diabetes : a meta-regression analysis. Ann. Intern. Med. **118** : 129-138, 1993.