Original Article

Long-Term Renoprotective Effect of Combination Therapy with Prostaglandin E1 and Angiotensin-Converting Enzyme Inhibitor in Patients with Chronic Renal Failure

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Angiotensin-converting enzyme inhibitors (ACE-I) have a renoprotective effect in patients with chronic renal failure. Prostaglandins (PGs) have also been shown to ameliorate renal impairment. Although these two have different mechanisms—ACE-I reduces intraglomerular pressure by dilating the efferent arterioles, while it is thought that PGs may increase intraglomerular pressure—coadministration of these drugs may have an additive effect. Administration of a PG with an ACE-I might have an additive effect on chronic renal failure. However, there have been no studies on the efficacy of such a combination therapy. This study was conducted to determine whether combination therapy with PGE1 and an ACE-I might have a long-term benefit on chronic renal failure. Sixty patients with chronic renal disease receiving an ACE-I in advance were assigned to receive an ACE-I alone or an ACE-I plus PGE1. Blood pressure, blood chemistry, urinary protein excretion, and the changes in the reciprocal of serum creatinine ($\Delta 1/\text{Cr}$) were monitored once monthly for an average of 36.5 months. In patients treated only with an ACE-I, the progression of renal failure did not change with time. In contrast, the decline of renal function was significantly reduced with the combination therapy. The renoprotective effect of the combination therapy was not exerted by reduced proteinuria or by decreased blood pressure. PGE1 may reinforce the renoprotective effects of ACE-I to prevent the progression of chronic renal failure. (*Hypertens Res* 2005; 28: 733–739)

Key Words: chronic renal failure, angiotensin-converting enzyme inhibitor, prostaglandin

Introduction

Angiotensin-converting enzyme inhibitors (ACE-I) are now widely used to treat patients with chronic renal failure because of their renoprotective effects (1). The beneficial effect of ACE-I on renal impairment is mainly caused by the dilatation of the efferent arterioles, which leads to a reduction of intraglomerular pressure and subsequent decrease in pro-

teinuria, but is also partly due to the reduction of whole body blood pressure (2).

Prostaglandins (PGs) have also been used to treat many clinical conditions, including renal diseases. Over the last decade, one PG in particular, PGE1, has been shown to have substantial renoprotective effects. For example, PGE1 has been reported to ameliorate the renal damage after renal ischemia *via* its vasodilatory action (3), lipo-PGE1 has been shown to improve the renal impairment caused by glomerulo-

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Table 1. Characteristics and Clinical Data of the Two Treatment Groups

	PGE1 admission		<i>p</i> value
	A (–)	B (+)	
Age (years old)	54±3	59±3	0.138
No. (male, female)	32 (15,17)	28 (16,12)	0.431
Body weight (kg)	55.0±1.7	55.2±1.6	0.927
Period			
Total	37±4	36±4	0.947
Before admission	18±2	20±3	0.750
After admission	19±2	17±2	0.175
Renal disease			
Glomerular	29	27	0.373
Non-glomerular	3	1	
DM	5	12	0.021*
Non-DM	27	16	
ACE gene			
I (%)	76.7	77.3	0.960
D (%)	53.3	68.2	0.286
ACE-I			
Temocapril	9	15	
Enalapril	4	2	
Benazepril	3	2	
Alacepril	8	4	
Lisinopril	1	2	
Imidapril	7	1	
Delapril	0	1	
Cilazapril	0	1	
PGE1 (μg)	(–)	51.3±4.2	

No. (male, female): number and gender of patients; period: observation period (month). ACE, angiotensin-converting enzyme; ACE-I, ACE inhibitor; PGE1, prostaglandin E1 (alprostadil alfadex); DM, diabetes mellitus; I and D, insertion/deletion polymorphism of ACE gene. Data are shown as total number or mean±SEM. Statistical analysis was performed using nonparametric analysis with Mann-Whitney test. **p*<0.05.

nephritis (4), and PGE1 was reported to decrease the proteinuria and histological changes in glomerulonephritis as well as to reduce the immune deposition in this disease. These renoprotective outcomes are probably due to the anti-inflammatory and anti-proliferative effects of PGE1. In another study, levels of circulating immune complex were reduced by PGE1 administration in patients with collagen diseases (5). PGE1 has also been shown to reduce severe proteinuria in patients with lupus nephritis nonresponsive to steroid and cyclophosphamide therapy (6). More recently, several reports have demonstrated that PGE1 attenuated the progression of diabetic nephropathy (7). In addition to conferring renoprotection in renal diseases, PGE1 has been shown to ameliorate the renal dysfunction caused by drugs (8) or surgery (9), including renal transplantation (10). While the above studies were mostly related to the acute phase of renal damage,

Table 2. Changes in Blood Pressure, Proteinuria and Renal Function in the Two Treatment Groups

	ACE-I±PGE1		
	A(–)	B (+)	<i>p</i> value
BP (mmHg)			
Pre SBP	143±3	141±4	0.379
Post SBP	134±4	134±3	0.939
Post – Pre	–9±3	–7±3	0.754
{ <i>p</i> }	{0.001}	{0.019}	
Pre DBP	76±2	74±2	0.446
Post DBP	71±2	71±2	0.886
Post – Pre	–5±2	–4±2	0.647
{ <i>p</i> }	{0.002}	{0.025}	
U-TP (g/day)			
Pre U-TP	1.6±0.2	3.0±0.4	0.011*
Post U-TP	1.3±0.2	2.4±0.4	0.069
Post – Pre	–0.4±0.2	–0.4±0.3	0.613
{ <i>p</i> }	{0.050}	{0.183}	
Renal function			
S-Cr (mg/dl)	2.6±0.3	3.2±0.3	0.091
PreΔ1/Cr	–15.4±4.3	–26.3±5.5	0.018*
PostΔ1/Cr	–12.7±2.7	–13.1±3.4	0.935
Post – Pre	3.0±2.0	13.0±3.0	0.003*
{ <i>p</i> }	{0.284}	{0.002}	

BP, blood pressure; SBP, systolic BP (mmHg); DBP, diastolic BP (mmHg); U-TP, daily urinary protein excretion (g/day); S-Cr, serum creatinine concentration at admission; Δ1/Cr, slope of reciprocal of serum creatinine per month ($\times 10^{-3}$ dl/mg/month). Data are shown as mean±SEM. Statistical analysis was performed using paired *t*-test or nonparametric analysis with Mann-Whitney test. **p*<0.05.

administration of PGE1 has also been reported to prevent the development of chronic renal failure, although the observation period in this study was short (11).

These renoprotective effects of PGE1 are probably exerted by an anti-platelet effect, improvement of renal hemodynamics, an anti-proliferative effect on smooth muscle cells, and protection of endothelial cells by suppression of inflammatory cytokines. However, PGE1 are also known to increase intraglomerular pressure by dilatation of the afferent arteries, which may contribute to the progression of chronic renal failure. This could be the reason for the small number of reports showing a long-term beneficial effect of PGE1. In contrast, ACE-I reduces the intraglomerular pressure by dilating the efferent arterioles, which prevents the progression of chronic renal failure. Numerous reports have demonstrated the beneficial outcomes of treatment with either a PGE1 or an ACE-I, as discussed above. However, no report has addressed the effectiveness of combination therapy using both compounds. We hypothesized that combination therapy with a PGE1 and an ACE-I would confer greater protection against renal dysfunction than either ACE-I or PG monotherapy, and would do

so without increasing intraglomerular pressure. This study was designed to investigate whether combination therapy with PGE1 and an ACE-I (PAC therapy) could slow the progression of chronic renal failure more effectively than ACE-I monotherapy.

Methods

Study Population

From January 1995 to April 2002, 60 patients admitted to our hospital division for evaluation and management of renal disease, were enrolled in this prospective study. All patients were already using an ACE-I and none of the patients had ever received PGs until this study. After admission, all patients were fully explained about our study and 32 patients chose only continuous ACE-I treatment (group A). Twenty-eight patients agreed to receive PGE1 administration in addition to ACE-I treatment (group B). The kinds and doses of ACE-I were not changed throughout the study. The renal functions of all patients were evaluated before, during and after the admission. Informed consent was obtained orally from all patients after an adequate explanation of the study.

Treatment Regimens

After admission, low doses of PGE1 (alprostadil alfadex; 30–60 µg/day) were administered intravenously for 2 weeks, followed by oral limaprost alfadex treatment (30 µg/day). The doses of ACE-I were not changed in either group at any point during this study. The types of ACE-I used were as follows: temocapril 1–4 mg ($n=24$), alacepril 25–50 mg ($n=12$), imidapril 2.5–5 mg ($n=8$), enalapril 2.5–5 mg ($n=6$), benazepril 2.5–5 mg ($n=5$), lisinopril 10 mg ($n=3$), delapril 15 mg ($n=1$), and cilazapril 2 mg ($n=1$). Protein and sodium chloride intake were restricted to 0.6–0.8 g/kg/day and 5–7 g/day, respectively, in all patients during and after admission. Also during admission, patients were instructed on the target caloric intake (30–35 kcal/kg/day). In diabetic patients, daily caloric intake was restricted to 30 kcal/kg/day. Daily protein and sodium intakes were monitored every month by means of 24-h urine sampling, and dietary instruction was repeated if needed.

Data Collection

Blood pressure and blood chemistry were monitored monthly throughout the study, and changes in the reciprocal of serum creatinine ($\Delta 1/\text{Cr}$) were calculated in each patient to evaluate the progression of renal failure. The pre-admission $\Delta 1/\text{Cr}$ was calculated using the pre-admission data, and the post-admission $\Delta 1/\text{Cr}$ was calculated using the data gathered after discharge. In each patient, 24-h urine was collected once a month to evaluate the urinary protein excretion. Deletion/insertion (D/I) polymorphism of the ACE gene was also ana-

lyzed as described previously (12). For statistical analysis, mean blood pressure and mean urinary protein excretions before the addition of PGE1 were calculated as the average over the 3 months before admission. Similarly, the data after the addition of PGE1 was calculated as the average value over the latest 3 months after discharge.

Statistical Analysis

Statistical evaluation was performed using a paired Student's *t*-test, or nonparametric analysis (Mann-Whitney test). Values of $p < 0.05$ were considered to indicate statistical significance.

Results

Patient Profiles

The profiles of all patients are summarized in Table 1. Thirty-one males and 29 females were entered in our study. The average age at admission was 56.1 ± 2.2 years old. The pre-administration, post-administration and total observation periods were 18.5 ± 1.8 , 18.0 ± 1.5 , and 36.5 ± 2.6 months, respectively. The average hospitalization period was 22 ± 2 days. There were no significant differences in age or gender or in the durations of the observation and hospitalization periods between the two groups. The underlying renal diseases were IgA nephropathy ($n=15$), diabetic nephropathy ($n=17$), Henoch-Schönlein purpura nephritis ($n=1$), chronic glomerulonephritis of unknown origin ($n=12$), benign nephrosclerosis ($n=4$), lupus nephritis ($n=1$), membranous nephropathy ($n=2$), membranoproliferative glomerulonephritis ($n=1$), amyloidosis ($n=1$) and other causes ($n=6$). The basic characteristics of the patients, including underlying renal diseases, were not significantly different between the two groups, with the exception that there were more diabetic patients in the PGE1 group. There was no clear trend in the distribution of ACE gene polymorphism between the two groups. Regarding diet, the protein intakes after the discharge in the monotherapy and combination therapy groups were 0.81 ± 0.05 and 0.75 ± 0.06 g/kg/day, respectively. The intakes of daily sodium chloride were 7.6 ± 0.5 and 7.5 ± 0.7 g/day, respectively. There was no significant difference in protein or sodium chloride intake between the two groups.

Blood Pressure

After the discharge, average blood pressure tended to decrease in both groups, but there was no difference in systolic or diastolic blood pressure between the two groups (Table 2). The changes in blood pressure did not correlate with the ACE gene polymorphism.

Renal Function

Serum creatinine levels were slightly lower in the ACE-I

Fig. 1. Changes in the urinary protein excretion. Group A: ACE-I (+), PGE1 (-). Group B: ACE-I (+), PGE1 (+). Mean urinary protein excretion was calculated as an average of the latest 3 months during the observation period. Urinary protein excretion before the admission was larger in group B compared to group A. There was no significant decrease in proteinuria observed in either group between before and after the discharge. Statistical evaluation was performed using paired t-test and nonparametric analysis with Mann-Whitney test. □, before; ■, after the addition of PGE1. * $p=0.011$. U-TP, urinary protein excretion.

monotherapy group, but the difference was not statistically significant. Urinary protein excretion before the admission was statistically larger in the combination therapy group (Fig. 1). This trend may have been due to the larger number of diabetic patients in this group. There was no significant difference between the pre- and post-admission proteinuria in either group.

The baseline rate of progression of renal failure before the admission was smaller in the monotherapy group (Table 2). The changes of progression of renal failure are shown in Fig. 2. In patients treated only with an ACE-I (Group A), the decrease in renal function did not change with time before or after the discharge. In contrast, the decline of renal function was significantly reduced by the addition of PGE1 to ACE-I (Group B). Changes in blood pressure and proteinuria were not evident with the use of PGE1 (Table 2).

In addition, we tested the effects of PGE1 on blood pressure and the decline of renal function in patients without ACE-I. The addition of PGE1 to patients with chronic renal failure did not change blood pressure, proteinuria or $\Delta\text{I/Cr}$ (blood pressure: $131\pm5/75\pm3$ to $128\pm5/71\pm2$ mmHg and $143\pm11/71\pm4$ to $135\pm6/69\pm4$ mmHg; proteinuria: 0.6 ± 0.1 to

0.7 ± 0.1 g/day and 1.1 ± 0.5 to 0.8 ± 0.3 g/day; $\Delta\text{I/Cr}$: -0.6 ± 2.5 to $-5.7\pm3.4 \times 10^{-3}$ dl/mg/month and -15.0 ± 6.0 to $-18.7\pm5.4 \times 10^{-3}$ dl/mg/month in patients without PGE1 [$n=21$] and with PGE1 [$n=12$], respectively).

We also analyzed the changes in renal function according to the presence or absence of diabetic mellitus (Fig. 3). Although combination therapy with PGE1 and ACE-I was found to be more effective than monotherapy with ACE-I, as described above, there was no difference in the efficacy between patients with and those without diabetes. PGE1 treatment without ACE-I had no significant effect on blood pressure, urinary protein excretion or progression of renal failure in either diabetic or nondiabetic patients (data not shown). Only three patients complained of vascular pain during the first intravenous drip infusion. This problem was resolved by admission of sodium bicarbonate to the alprostadil alfadex solution from the second infusion in these patients. No other adverse effect of PGE1 administration was noticed throughout the study.

Discussion

The present study clearly demonstrated that PGE1 and ACE-I had additive effects on preventing the progression of renal failure. Although PGE1 and ACE-I both have renoprotective effects, this is the first study to examine their potential use as a combination therapy. The results clearly indicated that the two drugs had a synergistic effect over the long-term.

The renoprotective effect of ACE-I has already been established. Our study was not designed to examine the effect of ACE-I monotherapy on the progression of renal impairment, and ACE-I treatment was continued in all patients before the admission and after the discharge. The rate of progression of renal failure in the ACE-I monotherapy group did not change with time, as predicted. Urinary protein excretion was larger in the combination group than in the ACE-I monotherapy group, which indicated a higher risk of progression of renal failure. In fact these patients had a more rapid progression of renal failure than the patients in the ACE-I monotherapy group (Table 2). These differences of urinary protein excretion and the rate of progression of renal failure before admission may have been due to the larger number of diabetic patients. However, the rate of progression of renal failure in the combination group decreased to a level similar to that in the ACE-I monotherapy group by the PAC therapy. Patients with a higher level of proteinuria might be more sensitive to the PAC therapy. Further studies treating patients with lower urinary protein excretion and lower progression of renal failure by PAC therapy should be conducted to investigate the correlation between the amount of proteinuria and the effect of PAC therapy. Since this study was not randomized, the number of diabetic patients was different between the two groups. There is thus need of an additional randomized trial to remove the influence of the differences in proteinuria and the rate of progression of renal failure. The decreases in blood

Fig. 2. Changes in the decline of renal function by the treatments. *A:* Changes in reciprocals of serum creatinine ($\Delta 1/\text{Cr}$) in each group of patients. $\Delta 1/\text{Cr}$ is shown for each patient in both groups. * $p = 0.0016$. *B:* Average changes in $\Delta 1/\text{Cr}$. Changes in $\Delta 1/\text{Cr}$ are shown in the graph. Group A: ACE-I (+), PGE1 (-). Group B: ACE-I (+), PGE1 (+). The combination therapy with PGE1 and ACE-I significantly ameliorated the decline of renal function, whereas ACE-I monotherapy did not change the decline. Statistical evaluation was performed using nonparametric analysis with Mann-Whitney test. † $p = 0.003$. Cr, serum creatinine; ACE-I, angiotensin-converting enzyme inhibitor; PGE1, prostaglandin E1.

pressure and proteinuria were observed in most cases after admission, probably due to the restriction of sodium and protein intake. The changes in blood pressure were not related with ACE gene polymorphism as reported previously (13) (data not shown). Although renal plasma flow (RPF) was not measured in our study, there is a possibility that the decline of RPF was reduced by PAC therapy. Since the decline of renal function at admission was larger in the combination therapy group than the ACE-I monotherapy group, PAC therapy could have a more beneficial effect in patients with rapid progression of renal failure.

PGs has been demonstrated to mitigate the renal dysfunction by anti-platelet effects (14), dilatation of the afferent

arteries (15), anti-proliferative effects on smooth muscle (16), suppression of inflammatory cytokines (17), protection of endothelial cells (18) and suppression of the renin-angiotensin-aldosterone system (RAS) (19). Although PGs has a marked potential to dilate the afferent arteries in the glomerulus, it remains a matter of controversy whether PGs should be administered to patients with renal disease. This is because prostanoids have been reported to increase plasma renin activity (20), which further stimulates activation of RAS in the kidney. Inadequate activation of RAS could lead to development of renal hypertension in cases of chronic renal failure. Activation of RAS causes intraglomerular hyperfiltration. On the other hand, ACE-I has the potential to dilate the efferent

Fig. 3. Changes in the decline of renal function in patients with or without diabetes mellitus in the two groups. Patients were divided according to the presence or absence of diabetes. There was no difference in the $\Delta 1/Cr$ between diabetic and non-diabetic patients. Cr, serum creatinine; DM, diabetes mellitus.

arterioles in the kidney, which could reduce the intraglomerular hyperfiltration. Both medicines also have been shown to decrease the contraction of mesangial cells (21). Taken together, these results indicate that simultaneous administration of PGs and ACE-I improves intraglomerular circulation without increasing intraglomerular pressure. Our results support this hypothesis.

In our study, PGE1 monotherapy did not slow the progression of renal failure. The renoprotective effect that PGE1 exert by improving the renal hemodynamics may not last long. It is also possible that PGE1 caused an increase of intraglomerular pressure *via* an increase of renin activity over the long-term. Subanalysis of the patients according to the absence or presence of diabetes demonstrated that PGE1 monotherapy did not improve the decline of renal function in diabetic patients. The improvement of renal hemodynamics by PGE1 may be larger in diabetic patients than non-diabetic ones, since microvascular damage is greater in diabetic patients. However, the renoprotective effect of the combination therapy was not different between diabetic and non-diabetic patients. In the current study, improvement of the progression of chronic renal failure was exerted by PGE1 administration on a long-term basis only in combination with an ACE-I. This result supports our hypothesis that PAC therapy would have a long-term renoprotective effect both in diabetic and non-diabetic patients. However, although this study showed that PGE1 and ACE-I had additive beneficial effects when used together, an important study limitation should be mentioned. Since the current study was not double-blind and randomized, as discussed above, it remains uncertain whether

this combination therapy could be effective in all kinds of renal disease. Further randomized, double-blind and prospective studies will be required to confirm our results.

Angiotensin II increases PGs synthesis (15), and PGs can increase plasma renin activity (19), which in turn could eventually lead to an inadequate increase in PGs synthesis in the kidney. On the other hand, ACE-I reduces the production of angiotensin II, which means that synthesis of PGs could be reduced in the kidney. PGE1 might potentiate the renoprotective effect of ACE-I by maintaining an ideal level of PGs synthesis, which could improve the intraglomerular circulation. Previous reports have suggested that both dilatations of the afferent arterioles and those of the efferent arterioles can have a renoprotective effect, which could explain the similarity in results between these studies and the present one (22, 23). Our findings are also supported by a recent study (24) in which PGs was shown to counteract the renal actions of endogenous angiotensin II.

In summary, in this study it was demonstrated that PAC therapy has beneficial and long-term efficacy and is expected to be useful as a new tool for preventing the progression of chronic renal failure. PGE1 could reinforce the renoprotective effects of ACE-I in patients with chronic renal failure. Recently, an angiotensin II receptor antagonist was also shown to exert a renoprotective effect (25). Trials employing other PG derivatives and/or the addition of angiotensin II receptor antagonists should be conducted to investigate whether other combination therapies could also prevent the progression of chronic renal failure in patients with renal disease.

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