Abstract

Background. Angiotensin (AT)-converting enzyme inhibitors (ACEIs) and AT1-receptor blockers (ARBs) are widely used to reduce urinary albumin excretion (UAE) and slow the progression of diabetic nephropathy. The aim of the present study was to determine whether treatment with trandolapril (an ACEI) and candesartan cilexetil (an ARB) in combination has more effect on UAE and urinary endothelin (ET)-1 excretion than treatment with trandolapril or candesartan cilexetil alone in patients with type 2 diabetes.

Methods. Sixty normotensive type 2 diabetes patients with microalbuminuria were randomly assigned to four treatment groups: (A) treatment with trandolapril at 2 mg/day (n = 15), (B) treatment with candesartan cilexetil at 8 mg/day (n = 15), (C) treatment with trandolapril at 2 mg/day and candesartan cilexetil at 8 mg/day (n = 15), and (D) treatment with placebo (n = 15). The study period was 18 months. UAE, urinary ET-1, and plasma ET-1 levels were measured in the patients before treatment and after 12 and 18 months of treatment.

Results. Before treatment, UAE, urinary ET-1, and plasma ET-1 levels differed little between the four groups. Trandolapril and candesartan cilexetil administered alone reduced UAE and urinary ET-1 excretion to a similar extent (12 months; P < 0.05 and 18 months; P < 0.01). When trandolapril and candesartan cilexetil were coadministered, UAE and urinary ET-1 excretion decreased to a significantly greater extent at 12 and 18 months (P < 0.05) than with trandolapril or candesartan cilexetil alone. However, plasma ET-1 and systemic blood pressure levels were not affected.

Conclusions. The data suggest that combination therapy with trandolapril and candesartan cilexetil has an additive effect on the reduction of microalbuminuria in microalbuminuric normotensive type 2 diabetes patients.

Key words Angiotensin · Candesartan cilexetil · Trandolapril · Endothelin · Microalbuminuria

Introduction

Diabetic nephropathy is a leading cause of endstage renal failure. In addition to the control of glycemia, treatment of risk factors for the progression of diabetic nephropathy should be carried out in diabetes patients with microalbuminuria. Microalbuminuria, which is present in 25% of diabetes patients at the time of diagnosis, is a strong predictor of mortality and of cardiovascular morbidity and mortality. The main goal of any treatment for patients with type 2 diabetic nephropathy should be to prevent the natural progression from microalbuminuria to macroalbuminuria and, finally, to endstage renal failure. Buter et al. stressed the importance of the renin angiotensin system (RAS) rather than structural changes of the glomerular basement membrane in the leakage of urinary protein. That is, urinary protein leakage is best treated by the control of blood pressure and renal hemodynamics in diabetes patients with microalbuminuria. Kuriyama et al. reported that combination therapy with the RAS blockers candesartan cilexetil and cilazapril could be effective in retarding the progression of diabetic nephropathy. Recently, Russo et al. reported that combination therapy with enalapril and losartan had an additive dose-dependent antiproteinuric effect in normotensive proteinuric patients with IgA nephropathy.

In the present study, we examined whether treatment with candesartan cilexetil and trandolapril in combination...
was superior to treatment with candesartan cilexetil or trandolapril alone in reducing urinary albumin excretion (UAE) and endothelin (ET)-1 excretion in normotensive microalbuminuric type 2 diabetes patients.

**Patients and methods**

**Patients**

Sixty patients with type 2 diabetes mellitus (40 men and 20 women; mean age, 56.5 years; mean disease duration, 13.5 years) and 30 healthy control subjects (20 men and 10 women; mean age, 50.0 years) were included in this study. All patients fulfilled the type 2 diabetes criteria of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. The inclusion criteria were diagnosis of type 2 diabetes, normal blood pressure (below 140/90 mmHg), normal renal function (24-h creatinine clearance more than 80 ml/min, serum creatinine less than 1.4 mg/dl), and microalbuminuria, defined as 20–200 µg/min urinary albumin excretion in two of three urine collections. The protocol was approved by the local ethics committee, and informed consent was obtained from all participants. No patient had malignancy or history of heart disease, cerebrovascular disease, liver disease, or collagen disease. Patients treated with any type of antihypertensive drug were not included. Forty of the 60 type 2 diabetes patients were being treated with oral hypoglycemic agents (glibenclamide, n = 20; voglibose, n = 10; both drugs, n = 10) and 20 patients were treated with diet therapy alone.

**Study design**

Patients were randomly assigned to four treatment groups: group A, treatment with trandolapril (Chugai Pharmaceuticals, Tokyo, Japan) at 2 mg/day (n = 15); group B, treatment with candesartan cilexetil (Takeda Chemical Industries, Osaka, Japan) at 8 mg/day (n = 15); group C, treatment with both drugs at the above doses (n = 15); and group D, treatment with placebo (n = 15). Additional informed consent was obtained from all patients treated with placebo. Treatment continued for 18 months. Blood was drawn from the antecubital vein after an overnight fast for the measurement of glucose, hemoglobin (Hb) A1c, serum creatinine, and blood urea nitrogen. Twenty-four-hour creatinine clearance was also measured. Urinary albumin excretion (UAE) was measured by double-antibody radioimmunoassay (Pharmacia, Uppsala, Sweden). Plasma and urinary ET-1 were assayed by radioimmunoassay with polyclonal anti-rabbit antibody (Peninsula Laboratories, Belmont, CA, USA) at a final dilution of 1:24000 for urine and 1:72000 for plasma. Antibody cross-reactivity was 7% with ET-2, 7% with ET-3, and 17% with big ET. Intra- and interassay variabilities were 4% and 10%, respectively, for plasma and 3% and 12%, respectively, for urine. The minimum detectable concentration was 0.1 pg/tube. Results are expressed as picograms per milliliter (pg/ml) for plasma and nanograms per gram (ng/g) urinary creatinine (UC) for urine.

**Statistics**

Data values are shown as means ± SD. Statistical analyses were performed with the Wilcoxon signed rank test for paired data and the Mann-Whitney U-test for unpaired data. Because UAE data were not normally distributed, UAE data were described as medians and ranges and were analyzed non-parametrically with the Mann-Whitney test. In addition, differences between the four groups were analyzed by one-way analysis of variance followed by the Scheffe’s test for multiple comparisons between groups. A P value of less than 0.05 was considered statistically significant.

**Results**

UAE was significantly higher in the 60 type 2 diabetes patients than in the 30 healthy controls (148 µg/min; range, 60–196 µg/min vs 4 µg/min; range, 0–8 µg/min; P < 0.001). Urinary ET-1 levels were significantly higher in the type 2 diabetes patients than in the healthy controls (9.2 ± 2.2 ng/g UC vs 2.6 ± 0.6 ng/g UC; P < 0.01). However, plasma ET-1 levels differed little between the diabetes patients (1.4 ± 0.4 pg/ml) and the healthy controls (1.2 ± 0.4 pg/ml, not significant).

The baseline clinical characteristics of the four treatment groups of diabetes patients are shown in Table 1. Age, sex, disease duration, HbA1c, systolic blood pressure, diastolic blood pressure, serum creatinine, blood urea nitrogen, and 24-h creatinine clearance did not differ significantly between the four patient groups. Changes in UAE are shown in Fig. 1. Trandolapril reduced UAE significantly after 12 months (P < 0.05) and after 18 months (P < 0.01). Candesartan cilexetil also reduced UAE significantly after 12 months (P < 0.05) and after 18 months (P < 0.01). Coadministration of trandolapril and candesartan cilexetil decreased UAE to a greater extent than either trandolapril or candesartan cilexetil alone (12 months; P < 0.05, and 18 months; P < 0.05). UAE showed little change throughout the study period in group D. In group C, 4 of the 15 patients (27%) regressed to normoalbuminuria (less than 20 µg/min).

Changes in urinary ET-1 levels are shown in Fig. 2. Trandolapril reduced urinary ET-1 levels significantly at 12 months (P < 0.05) and at 18 months (P < 0.01). Candesartan cilexetil also reduced urinary ET-1 significantly at 12 months (P < 0.05) and at 18 months (P < 0.01). Coadministration of trandolapril and candesartan cilexetil decreased urinary ET-1 levels to a greater extent than either trandolapril or candesartan cilexetil alone (12 months; P < 0.05 and 18 months; P < 0.05). Urinary ET-1 excretion showed little change throughout the study period in group D.