Effects on Urinary Albumin Excretion and Renal Function Changes by Delapril and Manidipine in Normotensive Type 2 Diabetic Patients with Microalbuminuria

CHAICHARN DEEROCHANAWONG, M.D.*, PATTRAPORN KORNTHONG, R.N.*, SUGUNYA PHONGWIRATCHAI, B.Sc.*, SUMONTHA SERIRAT, M.D.*

Abstract

This study was designed to investigate the effect of delapril, an ACE inhibitor, and manidipine, a long action calcium antagonist, on persistent microalbuminuria in normotensive type 2 diabetic patients. Sixty type 2 diabetic patients were randomized to take delapril 30 mg/day or manidipine 10 mg/day for 48 weeks, in an open label design. Twenty eight of thirty subjects in the delapril group and twenty nine of thirty in the manidipine group completed the study. Urine albumin excretion as measured by the urinary albumin creatinine ratio decreased significantly in both groups (112.0±60.9 to 95.3±64.9 mg/g and 108.5±51.0 to 96.4±53.5 mg/g in the delapril and manidipine group respectively, $p < 0.05$, by paired *t*-test). Systolic and diastolic blood pressure were not significantly changed after treatment in the delapril group but significantly decreased in the manidipine group (130.9±7.1/80.2±6.1 to 127.2±7.1/78.0±5.3 mm/Hg, $p < 0.05$, by student's paired *t*-test). After 48 weeks of treatment, two patients in the delapril group and one patient in the manidipine group converted to normoalbuminuria (urinary albumin:creatinine ratio < 30 mg/g) and one patient in each group progressed to overt nephropathy (urinary albumin: creatinine ratio > 300 mg/g). There were no significant changes in fasting plasma glucose, HbA_{1c}, serum fructosamine, creatinine, potassium and lipid profiles after 48 weeks of treatment in both groups. Two cases in the delapril group were withdrawn during the study because of an intolerable cough and one case in the manidipine group because of intolerable dizziness and headache. In conclusion, both delapril and manidipine are effective in the reduction of microalbuminuria in normotensive type 2 diabetic patients with persistent microalbuminuria.

Key word : Type 2 Diabetes, Microalbuminuria, Normotension, Delapril, Manidipine

DEEROCHANAWONG C, KORNTHONG P, PHONGWIRATCHAI S, SERIRAT S
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* Diabetes and Endocrinology Unit, Department of Medicine, Rajavithi Hospital, Department of Medical Services, Ministry of Public Health, Bangkok 10400, Thailand.

Diabetes has become the most common cause of end-stage renal disease[1]. The earliest clinical evidence of nephropathy is the appearance of low but abnormal levels (>30mg/day or 20ug/min) of albumin in the urine, referred to as microalbuminuria, and patients with microalbuminuria are referred to as having incipient nephropathy[2,3]. Without specific interventions, 20-40 per cent of type 2 patients with microalbuminuria progress to overt nephropathy[4]. In addition to its being the earliest manifestation of nephropathy, albuminuria is a marker of greatly increased cardiovascular morbidity and mortality for patients with diabetes[5-7]. Antihypertensive treatment is one of the effective ways to inhibit the progression of diabetic nephropathy[8,9], but the clinical importance of selection of different antihypertensive therapy is still unclear. In normotensive type 1 and type 2 diabetes mellitus patients, ACE inhibitors have postponed the development of overt diabetic nephropathy from persistent microalbuminuria[10-20]. On the other hand, calcium antagonists have recently been controversial, dihydropyridines clearly have a role in the treatment of hypertension, particularly when a significant reduction in blood pressure is required but there is limited data of long acting dihydropyridines in the treatment of normotensive type 2 diabetes patients with microalbuminuria [10,21].

In this study we compared the efficacy of an ACE inhibitor, delapril, with that of a calcium antagonist, manidipine, in inhibiting the progression of diabetic nephropathy when used for the treatment of microalbuminuria in patients with normotensive type 2 diabetes mellitus.

PATIENTS AND METHOD

Sixty patients with type 2 diabetes mellitus were recruited from the outpatient diabetic clinic of Rajavithi Hospital. The inclusion criteria were: patients with type 2 diabetes mellitus aged between 35 and 75 years, normotension (upright blood pressure was less than 140/90 mmHg) and persistent microalbuminuria (early morning urine sample of albumin:creatinine ratio 30-300 mg/g) on two consecutive visits during the six month period without evidence of urinary tract infection. The exclusion criteria were: currently being treated with either calcium antagonist or ACE inhibitor, serum creatinine > 1.5 mg/dl, history of myocardial infarction, stroke, percutaneous transluminal coronary angioplasty or coronary bypass graft within the previous six months and overt proteinuria as determined by a positive result with the standard albustix test on early morning urine specimen.

This study was designed as an open randomized, parallel trial with two treatment groups: delapril 15 mg twice daily (n=30) or manidipine 10 mg once daily (n=30) for 48 weeks. Patients were told not to change their physical activity, dietary regimen and sodium intake during the study period. The patients were followed every 8 weeks. Blood pressure, fasting plasma glucose, adverse events, compliance and concurrent medications were evaluated at every visit. Albumin excretion index (albumin/creatinine ratio of the early morning urine sample),urine analysis, serum creatinine and potassium, fructosamine, HbA_{1c} and lipid profiles (total cholesterol, triglyceride and HDL-cholesterol) were measured at week 0, 24 and 48 weeks. Blood pressure was measured on the same arm by a standard mercury sphygmomanometer with the patient sitting for 5 minutes. The mean of two blood pressure readings taken during each visit was used for the analysis.

Urine albumin was measured by automated immunoturbidimetric assay (Boerhinger Manheim, Germany). Plasma glucose was determined by glucose oxidase method. HbA_{1c} was measured by enzymatic method (DAKO, Germany; normal range 2.6-4.9%). Serum fructosamine was measured by reduction test with nitroblue tetrazolium (Boerhinger Manheim, Germany; normal range 205-285 umol/L). Serum lipid were determined by enzymatic method (Boerhinger Manheim, Germany). Serum biochemical parameters were measured by standard technique at the Clinical Chemistry Laboratory, Rajavithi Hospital.

All data are expressed as the mean $\pm$ S.D. and ranges. Statistical analysis were performed by paired *t*-test and *t*-tests for independent groups depending on the nature of data. P values < 0.05 were considered to be statistically significant.

RESULTS

Sixty normotenisve type 2 diabetes mellitus patients with microalbuminuria were enrolled in this study. Thirty patients were randomized to receive delapril and manidipine in 30 patients.

During the study, 28 patients in the delapril group and 29 patients in the manidipine group completed the study. Two patients in the delapril

Table 1. Clinical and laboratory data at baseline in normotensive type 2 diabetes patients with persistent microalbuminuria.

Variable	Delapril	Manidipine
Number of patients (M:F)	28 (10:18)	29 (8:21)
Age (years)	57.3 ± 7.5 (43-71)	54.9 ± 9.2 (45-73)
Duration of diabetes (years)	6.8 ± 3.2 (2-13)	8.4 ± 4.9 (3-15)
Systolic blood pressure (mmHg)	132.4 ± 6.5	130.9 ± 7.1
Diastolic blood pressure (mmHg)	79.1 ± 5.3	80.2 ± 6.1
Fasting plasma glucose (mg/dl)	144.8 ± 28.5	139.9 ± 31.2
HbA_{1c} (%)	6.7 ± 0.7	6.6 ± 0.9
Serum fructosamine (umol/L)	346.1 ± 32.8	350.7 ± 47.4
Serum creatinine (mg/dl)	0.90 ± 0.22	1.01 ± 0.31
Total cholesterol (mg/dl)	222.4 ± 27.7	218.9 ± 21.4
Triglyceride (mg/dl)	178.6 ± 51.2	183.7 ± 47.1
HDL-cholesterol (mg/dl)	43.0 ± 10.7	43.1 ± 9.8
Albumin excretion index (mg/g creatinine)	112.0 ± 60.9	108.5 ± 51.0

Data are Mean ± SD

Table 2. Albumin excretion index and blood pressure measured at baseline, week 24 and week 48 in normotensive type 2 diabetes patients with microalbuminuria treated with delapril or manidipine.

Variable	Treatment	Week 0	Week 24	Week 48
AEI (mg/g creatinine)	Delapril	112.0 ± 60.9	94.4 ± 52.5*	95.3 ± 64.9**
	Manidipine	108.5 ± 51.0	103.9 ± 67.3	96.4 ± 53.5**
SBP (mm/Hg)	Delapril	132.4 ± 6.5	132.8 ± 8.9	133.2 ± 9.0
	Manidipine	130.9 ± 7.1	126.2 ± 6.4*	127.2 ± 7.1**
DBP (mm/Hg)	Delapril	79.1 ± 5.3	78.9 ± 5.5	78.1 ± 6.2
	Manidipine	80.2 ± 6.1	77.9 ± 4.8*	78.0 ± 5.3**

Data are mean ± SD, (*) Indicates $p < 0.05$ for week 0 and week 24, (**) Indicates $p < 0.05$ for week 0 and week 48

group were withdrawn because of intolerable cough and one patient in the manidipine group was withdrawn because of intolerable dizziness and headache. Table 1 shows the clinical characteristics at the start of treatment for the patients who completed the study. There were no statistically significant differences between the two groups in any baseline characteristics.

Results of the albumin excretion index and blood pressure at baseline, week 24 and week 48 are shown in Table 2. In the delapril group, systolic and diastolic blood pressure were not statistically significantly changed from baseline after treatment at both weeks 24 and 48. In the manidipine group, systolic blood pressure was statistically significantly decreased from 130.9±7.1 mmHg at baseline to 126.2±6.4 and 127.2±7.1 mmHg at weeks 24 and 48, respectively. Diastolic blood pressure in the manidipine group also decreased significantly from 80.2±6.1 mmHg at baseline to 77.9±4.8 and 78.0±5.3 mmHg at weeks 24 and 48, respectively. For the albumin excretion index, delapril significantly decreased microalbuminuria (albumin:creatinine ratio) from 112.0±60.9 mg/g at baseline to 94.4± 52.5 and 95.3±64.9 mg/g at weeks 24 and 48, respectively. Manidipine did not significantly decrease microalbuminuria (albumin:creatinine ratio) at week 24 of treatment but was significantly decreased at week 48 (108.5±51.0 to 96.4±53.5 mg/g). At the end of treatment (week 48) two patients in the delapril group and one patient in the manidipine group converted to normoalbuminuria (urinary albumin:creatinine ratio < 30 mg/g) and

Table 3. Fasting plasma glucose, HbA_{1c}, serum fructosamine, creatinine, potassium and lipid profile at baseline and during follow-up in normotensive type 2 diabetes patients with microalbuminuria treated with delapril or manidipine.

Variables	Treatment	Week 0	Week 24	Week 48
FPG (mg/dl)	Delapril	144.8 ± 28.5	152.1 ± 34.5	149.0 ± 28.8
	Manidipine	139.8 ± 32.8	145.3 ± 36.4	147.6 ± 34.9
HbA_{1c} (%)	Delapril	6.7 ± 0.7	6.6 ± 1.0	6.8 ± 0.8
	Manidipine	6.6 ± 0.9	6.6 ± 1.2	6.9 ± 1.1
Fructosamine (ug/L)	Delapril	346.1 ± 32.8	358.7 ± 45.3	360.7 ± 45.4
	Manidipine	350.7 ± 47.4	364.9 ± 51.2	374.1 ± 54.3
Serum creatinine (mg/dl)	Delapril	0.90 ± 0.22	0.88 ± 0.20	0.90 ± 0.22
	Manidipine	1.01 ± 0.31	0.99 ± 0.29	0.98 ± 0.36
Serum potassium (mEq/L)	Delapril	4.0 ± 0.3	4.1 ± 0.3	4.2 ± 0.4
	Manidipine	4.1 ± 0.4	4.0 ± 0.3	4.0 ± 0.3
Total cholesterol (mg/dl)	Delapril	222.4 ± 27.7	217.8 ± 27.5	219.6 ± 30.1
	Manidipine	218.9 ± 21.4	214.6 ± 23.5	221.3 ± 26.9
Triglyceride	Delapril	178.6 ± 51.2	165.6 ± 50.8	181.9 ± 42.3
	Manidipine	183.7 ± 47.1	178.9 ± 46.3	188.1 ± 56.9
HDL-Cholesterol	Delapril	43.0 ± 10.7	42.8 ± 11.0	42.0 ± 8.0
	Manidipine	44.2 ± 12.6	43.1 ± 11.6	43.0 ± 10.9

Data are mean ± SD

one patient in each group of the treatment progressed to overt nephropathy (urinary albumin: creatinine ratio > 300 mg/g). All three patients who converted to normoalbuminuria had a baseline albumin:creatinine ratio less than 80 mg/g while the other two patients who progressed to overt nephropathy had a baseline albumin:creatinine ratio more than 150 mg/g.

The results of clinical laboratory tests are shown in Table 3. The change in renal function, represented by the values of the serum creatinine were not statistically significantly changed from baseline in both the delapril and manidipine group. Serum potassium, fasting plasma glucose, serum fructosamine, HbA_{1c} and lipid profiles did not change significantly in either treatment group during the study.

DISCUSSION

In this study we measured early morning urine albumin:creatinine ratio (30-300 mg/g) as an index for microalbuminuria according to American Diabetes Association guidelines and United States National Kidney Foundation expert panel recommendation (22-23). This method can easily be carried out in an office setting and generally provides accurate information.

The present study confirmed the results of the recent trials demonstrating that ACE inhibitors lead to a significant reduction of microalbuminuria in normotensive type 2 diabetes patients[10,11,14-18]. This was also the first study of delapril showing this effect. Short acting dihydropyridines calcium antagonists, nifedipine, were shown to increase microalbuminuria in normotensive type 2 diabetes patients in one study[10] but there was limited data of long acting dihydropyridines in the treatment of normotensive type 2 diabetes patients with microalbuminuria. Crepaldi et al, showed that both lisinopril and long acting nifedipine were effective in decreasing microalbuminuria and delaying the occurrence of macroalbuminuria in normotensive type 1 diabetes patients with microalbuminuria [20]. Okabe et al, reported the reduction of microalbuminuria after 4 months' treatment with manidipine, the long acting dihydropyridines calcium antagonists, without altering systemic blood pressure in normotensive type 2 diabetes patients[21]. Our study confirmed the efficacy of manidipine in the reduction of the microalbuminuria but the systolic and diastolic blood pressure in our study was significantly decreased after treatment (3.7 mmHg for SBP and 2.2 mmHg

for DBP difference at week 0 and week 48). The urine microalbumin in the delapril and manidipine group at the 48th week of the study were not significantly different.

The rate of progression of microalbuminuria in type 2 diabetes has been shown to be related with blood pressure, degree of microalbuminuria at baseline, glycemic control and dyslipidemia[24]. Confounding variables which may have affected urinary albumin excretion were similar within and between our two groups before and after treatment except for blood pressure. In the delapril group the systolic and diastolic blood pressure were not significantly changed from baseline but in the manidipine group both systolic and diastolic blood pressure were slightly but significantly decreased from the baseline at the end of the study. This result may underscore the effect of manidipine in decreasing microalbuminuria irrespective of hypo-tensive effect.

Long-term studies have examined the effects of ACE inhibitors and calcium channel blockers on kidney function in hypertensive type 2 diabetes patients with incipient nephropathy[25-28]. These reports showed that calcium channel blockers prevented the GFR fall in a fashion similar to that of ACE inhibitors, although the decrease of AER was significantly greater with ACE inhibitors.

The mechanisms by which ACE inhibitors and calcium channel blockers modulate renal and vascular function are different[29]. Studies in animals have suggested that ACE inhibitors decrease intraglomerular pressure. Most dihydropyridines calcium channel blockers do not decrease intraglomerular pressure because they dilate afferent arterioles more than efferent arterioles[30,31]. Non-dihydropyridines calcium channel blocker and some dihydropyridines such as manidipine and ephonidipine can decrease intraglomerular pressure because they dilate both afferent and efferent arterioles[32-34]. ACE inhibitors blunt or suppress the vasoconstrictor, hypertrophic effects of angiotensin II on mesangial and vascular smooth muscle cells. Studies in humans have shown no consistent differences in the degree of such inhibition caused by different ACE inhibitors[29,30]. The favorable effect of calcium channel blockers may be related to the modulation of intracellular free calcium concentrations, which are altered in patients with essential hypertension and with diabetes[35-37]. Furthermore, calcium channel blockers inhibit the effects of angiotensin II, but also of other mitogens, on renal function[30].

In conclusion, our data show that both delapril and manidipine treatment for 48 weeks are effective in decreasing microalbuminuria without altering renal function in normotensive type 2 diabetes patients. Because microalbuminuria strongly predicts overt proteinuria, end-stage renal disease and cardiovascular mortality, both treatments may appear capable of delaying the occurrence of such complications in normotensive type 2 diabetes patients with incipient nephropathy. This favorable outcome was not accompanied by untoward side effects, such as postural hypotension and hyperkalemia.

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ผลของยาเดลาพริลและยาแมลนิดิพีนต่อระดับอัลบูมินในปัสสาวะและการทำงานของไตในผู้ป่วยเบาหวานชนิดที่ 2 ที่มีภาวะไมโครอัลบูมินยูเรียและความดันโลหิตปกติ

ชัยชาญ ดีโรจนวงศ์, พ.บ., ภัทราพร ก้อนทอง, พย.บ.*, สุกัญญา พงศ์วิรัตน์ไชย, วท.ม.*, สุมณฑา เสรีรัตน์, พ.บ.**

การศึกษานี้มีวัตถุประสงค์เพื่อดูผลของการรักษาด้วยยาเดลาพริล (ยาในกลุ่มยับยั้งเอนไซม์ในการเปลี่ยนแองจิโอเทนซิน) และยาแมลนิดิพีน (ยาในกลุ่มต้านฤทธิ์แคลเซียมที่ออกฤทธิ์ยาว) ในผู้ป่วยเบาหวานชนิดที่ 2 ที่มีภาวะไมโครอัลบูมินยูเรียและความดันโลหิตปกติ ผู้ป่วยเบาหวานจำนวน 60 รายได้ถูกสุ่มแบ่งเป็น 2 กลุ่ม กลุ่มที่หนึ่งจำนวน 30 ราย ได้รับการรักษาด้วยยาเดลาพริลขนาด 30 มก.ต่อวัน และอีกกลุ่มหนึ่งจำนวน 30 ราย ได้รับการรักษาด้วยยาแมลนิดิพีนขนาด 10 มก.ต่อวันเป็นระยะเวลา 48 สัปดาห์ ผู้ป่วย 28 รายในกลุ่มที่ได้รับยาเดลาพริล และ 29 รายในกลุ่มที่ได้รับยาแมลนิดิพีนได้รับการรักษาและติดตามผลจนสิ้นสุดการศึกษา ระดับอัลบูมินในปัสสาวะลดลงอย่างมีนัยสำคัญทางสถิติหลังการรักษา 48 สัปดาห์ในทั้ง 2 กลุ่ม (กลุ่มที่ได้รับยาเดลาพริลระดับอัลบูมินลดลงจาก 112.0 ± 60.9 เป็น 95.3 ± 64.9 มก.ต่อกรัม และกลุ่มที่ได้รับยาแมลนิดิพีนระดับอัลบูมินลดลงจาก 108.5 ± 51.0 เป็น 96.4 ± 35.5 มก.ต่อกรัม) ผู้ป่วย 2 รายในกลุ่มที่ได้รับยาเดลาพริลและ 1 รายในกลุ่มที่ได้รับยาแมลนิดิพีนมีระดับอัลบูมินในปัสสาวะลดลงจากภาวะไมโครอัลบูมินยูเรียมาอยู่ในเกณฑ์ปกติ (อัลบูมินต่อครีตะนีนในปัสสาวะน้อยกว่า 30 มก.ต่อกรัม) และผู้ป่วย 1 รายในแต่ละกลุ่มมีระดับอัลบูมินในปัสสาวะเพิ่มขึ้นเป็นภาวะแมคโครอัลบูมินยูเรีย (อัลบูมินต่อครีตะนีนในปัสสาวะมากกว่า 300 มก.ต่อกรัม) ความดันโลหิตทั้งซิสโตลิกและไดแอสโตลิกไม่พบว่ามีการเปลี่ยนแปลงอย่างมีนัยสำคัญทางสถิติหลังการรักษาในกลุ่มที่ได้รับยาเดลาพริล ในขณะที่ความดันโลหิตซิสโตลิกและไดแอสโตลิกลดลงเล็กน้อยอย่างมีนัยสำคัญทางสถิติหลังการรักษาในกลุ่มที่ได้รับยาแมลนิดิพีน (ความดันโลหิตลดลงจาก 130.9 ± 7/80.2 ± 6.1 เป็น 127.2 ± 7.1/78.0 ± 5.3 มม.ปรอท) การศึกษานี้ไม่พบว่ามีการเปลี่ยนแปลงอย่างมีนัยสำคัญทางสถิติของระดับพลาสมากลูโคส, ฮีโมโกลบินเอวันซี, ซีรั่มฟรุคโตซามีน, ระดับครีตะนีน, โปแตสเซียมและไขมันในเลือด เมื่อเปรียบเทียบระหว่างก่อนและหลังการรักษาในทั้ง 2 กลุ่ม ผู้ป่วย 2 รายในกลุ่มที่ได้รับยาเดลาพริลถูกถอนจากการศึกษาเนื่องจากมีอาการไอมาก และผู้ป่วย 1 รายในกลุ่มที่ได้รับยาแมลนิดิพีนถูกถอนจากการศึกษาเนื่องจากมีอาการเวียนศีรษะและปวดศีรษะ โดยสรุปยาเดลาพริลและยาแมลนิดิพีนมีประสิทธิภาพในการลดระดับอัลบูมินในปัสสาวะในผู้ป่วยเบาหวานชนิดที่ 2 ที่มีภาวะไมโครอัลบูมินยูเรียและความดันโลหิตปกติ

คำสำคัญ : เบาหวานชนิดที่ 2, ไมโครอัลบูมินยูเรีย, ความดันโลหิตปกติ, ยาเดลาพริล, ยาแมลนิดิพีน

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* งานต่อมไร้ท่อ, กลุ่มงานอายุรกรรม, โรงพยาบาลราชวิถี, กรุงเทพฯ 10400