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Comparison of the Effect of Pentoxifylline and Captopril on Proteinuria in Patients with Type 2 Diabetes mellitus

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Key Words
Captopril · Pentoxifylline · Proteinuria · Diabetes mellitus · Nephropathy

Abstract

Objectives: To compare the relative efficacy of pentoxifylline (PTX) and angiotensin-converting enzyme (ACE) inhibitor, captopril in the treatment of proteinuria of type 2 diabetic patients. ***Design:*** A randomized open, crossover, clinical trial conducted from October 2000 to March 2001. ***Setting and Participants:*** 39 patients with type 2 diabetes age 34–75 years were randomly allocated to the two treatment groups. The first group received PTX (400 mg three times a day) orally for a total of 2 months. The second group received captopril (25 mg three times a day) for 2 months. Response to treatment was assessed at 1, 2, 4, and 8 weeks after start of therapy. ***Results:*** Captopril appeared to be equivalent in efficacy and safety to PTX. A significant decrease in proteinuria occurred in both groups. Of the 20 patients treated with PTX, the mean (SD) of 24 h urinary protein decreased from 1.4 (0.7) to 1.0 (0.7) g/24 h ($p < 0.05$). Correspondingly, in the 19 patients treated with captopril, the mean (SD) of 24 h urinary protein decreased from 1.3 (0.7) to 0.8 (0.7) g/24 h ($p < 0.01$). ***Conclusion:*** This study demonstrates that treatment with PTX and captopril both significantly reduce overt proteinuria in patients with type 2 diabetes. This effect of ACE inhibition has previously been shown to slow progression to renal failure and we postulate that treatment with PTX may have a similar benefit.

Introduction

Diabetes nephropathy due to type 2 diabetes is becoming the single most important reason for end-stage renal disease. Proteinuria is the hallmark of diabetic nephropathy, contributing to the progression of renal disease [1, 2]. Jude et al. [3] showed that the mortality rate of type 2 diabetic patients was directly proportional to the degree of proteinuria.

Pentoxifylline (PTX) is a synthetic methylxanthine derivative, which possesses several properties including hemorheological properties that have favorable effects on microcirculatory blood flow [4]. PTX has been used in the treatment of microcirculatory abnormalities of diabetes mellitus [5]. It has been reported that PTX reduces proteinuria in diabetic patients with normal renal function [6–8], suggesting that the antiproteinuric effect may be

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explained by the rheological and renal hemodynamic actions of this drug [6].

Captopril, an orally active angiotensin-converting enzyme (ACE) inhibitor, has proven efficacy in the prevention and treatment of diabetic nephropathy by decreasing proteinuria in type 1 diabetes mellitus [1]. The long-term renoprotective effect of ACE inhibitor, enalapril, has been demonstrated in type 2 diabetes by preventing the progression of proteinuria [9]. Reducing the level of proteinuria prevents progression of overt nephropathy in patients with type 1 and 2 diabetes [1].

In the present study we compared the effects of PTX and captopril on proteinuria of type 2 diabetic patients to investigate which one would be more efficacious in prevention of progression of overt nephropathy.

Patients and Methods

We used a randomized open crossover design to compare the effect of PTX and captopril on proteinuria of type 2 diabetic patients.

Patients

Patients who sought treatment for diabetes at our Endocrinology and Metabolism Clinic in Amin Hospital affiliated to Isfahan University of Medical Sciences, Iran, between October 2000 and March 2001, were evaluated. The physician using the checklist in the data collection form defined the type of diabetes. Patients were eligible for the study if they had urinary protein excretion >300 mg/24 h and negative urine culture, no previous treatment, no serious concomitant medical problems – such as intracranial hemorrhage, retinal hemorrhage, acute myocardial infarction or hypertension – that were indicated by the medical history, availability for follow-up for 5 months, and gave informed consent to participate in the study. The glycemic control or antihypertensive management was not changed after recruitment of the patients into the study. The study protocol was approved by the Ethical Review Committee of Iranian Ministry of Health, Treatment and Medical Education. The nature of the trial was explained to the patient and his/her written consent obtained.

Randomization Scheme

All but 1 of the 40 patients completed their treatment without interruption. The 39 participants (24 males, 15 females) were assigned randomly and equally to one of the two treatment groups. The first treatment group received PTX 400 mg three times daily (1,200 mg/day) [6, 9] for a total of 2 months. The second group received captopril (25 mg three times daily) in the first 2-month period of the study. The washout period between two rounds was 1 month. At the end of a 12-week period, the patients were switched to the alternate agent. All patients had a pre-treatment evaluation that consisted of obtaining demographic data, duration of symptoms and previous treatment.

The patients had a mean (SD) duration of diabetes of 11.8 (4.3) years and a mean age of 55.4 (9.8) years (range 34–75 years).

Patient Evaluation

The trial was not blinded and both patient and physician were aware of the type of treatment. Patients were evaluated at 1, 2, 4 and 8 weeks after the start of the first round of therapy to evaluate the development of side effects of the medications and compliance of the patients. All subjects were administered a weight-maintaining diet. At the beginning of the study, patients' blood pressure was determined twice after an interval of 10 min. Fasting plasma glucose, serum creatinine, urinary analysis, urine culture and 24-hour urinary protein, creatinine and volume were measured before and after 2 months of treatment. Before the second round and at its end, the same parameters were measured. Proteinuria was measured by precipitation with 3% sulfasalicylic acid and determination of turbidity by measuring absorbance at a wavelength of 550 nm with a spectrophotometer [6]. Serum creatinine and glucose were measured using conventional laboratory techniques. Creatinine clearance was calculated with the standard formula. In patients on captopril, serum creatinine and potassium were measured before and 1 week after treatment. Clinical evaluation of all patients was made by one physician who knew which patients had received which treatment.

Statistical Analysis

Comparison between groups receiving captopril and PTX was made using Student's t test for independent samples appropriate for the crossover study design [10] and analysis of variance with repeated measures over time; comparisons between basal and post-treatment periods were done by paired Student's t test. Comparisons between proportions were done by χ^2 or Fisher's exact test. No carryover effect was detected for any variables and it was therefore not necessary to analyze any variables as a parallel study. Results are expressed as mean (SD) and $p < 0.05$ was considered statistically significant. All statistical tests were two-sided. The analyses were done on a personal computer using SPSS for Windows [11] and Confidence Interval analysis software [12].

Results

Subject Characteristics

Forty patients who met the entry criteria were enrolled for the study. One patient withdrew from the study after developing a dry cough while on the captopril arm of the study. Patient compliance was good. PTX and captopril treatment was well tolerated. The 39 patients who completed treatment were available for follow-up at 1, 2, 4 and 8 weeks. There were no significance differences in the basal values between the captopril and PTX groups (table 1). The mean (SD) age of the captopril and PTX groups were 54.4 (10.4) and 56.3 (9.3) years, respectively. The mean (SD) of diastolic blood pressure at the start of treatment with captopril and PTX was 88.9 (9.4) and 89.8 (9.8), respectively. The mean (SD) of proteinuria at the start of treatment with captopril and PTX was 1.3 (0.7) and 1.4 (0.7), respectively. There was no statistically significant difference between them.

Table 1. Demographic and biochemical characteristics of type 2 diabetic patients with proteinuria by treatment group at baseline

Characteristics	Treatment group at baseline		Differences (95% CI)
	captopril (n = 19), mean (SD)	pentoxifylline (n = 20), mean (SD)	
Age, years	54.4 (10.4)	56.3 (9.3)	–1.9 (–49.2 to 45.4)
Duration of diabetes, years	10.2 (4.1)	12.4 (4.5)	–2.2 (–5.0 to 0.6)
Systolic blood pressure, mm Hg	136.8 (15.5)	137.0 (15.0)	–0.2 (–10.1 to 9.7)
Diastolic blood pressure, mm Hg	88.9 (9.4)	89.8 (9.8)	–0.9 (–6.8 to 5.0)
Mean arterial pressure, mm Hg	104.4 (10.7)	105.4 (10.0)	–1.0 (–7.7 to 5.7)
Fasting plasma glucose, mg/dl	164.6 (48.3)	175.2 (49.8)	–10.6 (–42.5 to 21.3)
Serum creatinine, mg/dl	1.08 (0.3)	1.1 (0.3)	0.02 (–0.2 to 0.2)
Creatinine clearance, ml/min	66.9 (18.7)	65.9 (16.1)	1.0 (–10.3 to 12.3)
Proteinuria, g/24 h	1.3 (0.7)	1.4 (0.7)	–0.1 (–0.6 to 0.4)
Male, n (%)	12 (63.2)	12 (60.0)	3.2 (–27.4 to 33.7)
Female, n (%)	7 (36.8)	8 (40.0)	–

Table 2. Comparison of blood pressure, fasting plasma glucose, serum creatinine, creatinine clearance and proteinuria in 39 type 2 diabetic patients before and after treatment with captopril and pentoxifylline

Parameters	Captopril (n = 19) mean (SD)		Differences (95% confidence interval)	Pentoxifylline (n = 20) mean (SD)		Differences (95% confidence interval)
	baseline	after therapy		baseline	after therapy	
Systolic blood pressure, mm Hg	136.8 (15.5)	135.3 (10.9)	1.6 (–4.6 to 7.8)	137.0 (15.0)	135.3 (10.4)	1.8 (–3.7 to 7.2)
Diastolic blood pressure, mm Hg	88.9 (9.4)	86.1 (7.0)	2.8 (0.9 to 4.9)**	89.8 (8.8)	86.3 (6.9)	3.5 (1.6 to 5.4)***
Mean arterial pressure, mm Hg	104.4 (10.7)	101.9 (6.9)	2.4 (–0.3 to 5.1)	105.4 (10.0)	102.2 (6.8)	3.2 (0.8 to 5.5)*
Fasting plasma glucose, mg/dl	164.6 (48.3)	143.5 (29.3)	21.1 (5.5 to 36.6)*	175.2 (49.8)	153.2 (35.9)	22.0 (7.3 to 36.7)**
Serum creatinine, mg/dl	1.08 (0.3)	1.05 (0.2)	0.03 (0.05 to –0.08)	1.1 (0.3)	1.0 (0.3)	0.1 (–0.3 to 0.2)
Creatinine clearance, ml/min	66.9 (18.7)	73.8 (16.6)	–6.9 (–14.0 to 0.3)	65.9 (16.1)	78.8 (21.1)	–12.9 (–20.8 to –5.0)**
Proteinuria, g/24 h	1.3 (0.7)	0.8 (0.7)	0.5 (0.2 to 0.8)**	1.4 (0.7)	1.0 (0.7)	0.4 (0.08 to 0.7)*

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Changes of blood pressure, fasting blood glucose, serum creatinine, creatinine clearance and proteinuria, before and after receiving PTX or captopril are shown in table 2. In both groups, diastolic blood pressure, fasting blood glucose and proteinuria significantly decreased. In the PTX group, when basal determination of creatinine clearance and mean arterial pressure were compared to post-treatment values, statistically significant differences were disclosed. In the PTX group, proteinuria significantly decreased from 1.4 to 1.0 g/24 h ($p < 0.05$) and in captopril treatment group from 1.3 (0.7) to 0.8 (0.7) g/24 h, $p < 0.01$.

At 2 months, the creatinine clearance was increased in the PTX treatment group (from 65.9 (16.1) to 78.8 (21.1) ml/min, $p < 0.01$) and in the captopril treatment group (from 66.9 (18.7) to 73.8 (16.6) ml/min, $p > 0.05$).

There were no significance differences in the values at the end of the first and second rounds between the captopril and PTX groups (table 3).

Discussion

In the current study, both PTX and captopril decreased proteinuria. Earlier studies showed that PTX decreased arterial blood pressure, and decreasing blood pressure was assumed to be the mechanism of its effect on proteinuria [13]. However, some other studies pointed

Table 3. Comparison of blood pressure, fasting plasma glucose, serum creatinine, creatinine clearance and proteinuria in 39 type 2 diabetic: patients during each treatment regimen (2 months after first and second round of crossover)

Parameters	First round mean (SD)		Differences (95% confidence interval)	Second round mean (SD)		Differences (95% confidence interval)
	captopril	pentoxifylline		captopril	pentoxifylline	
Systolic blood pressure, mm Hg	135.3 (10.8)	135.3 (10.4)	0.0 (–6.9 to 6.9)	130.8 (9.5)	129.8 (8.0)	1.0 (–4.6 to 6.7)
Diastolic blood pressure, mm Hg	86.1 (7.0)	86.3 (6.9)	–0.2 (–4.7 to 4.3)	80.8 (3.8)	79.3 (4.7)	1.5 (–1.2 to 4.3)
Mean arterial pressure, mm Hg	101.9 (6.9)	102.2 (6.8)	–0.3 (–4.7 to 4.2)	96.9 (4.3)	95.8 (4.3)	1.1 (1.6 to 4.0)
Fasting plasma glucose, mg/dl	143.5 (29.3)	153.2 (35.9)	–9.6 (–30.9 to 11.7)	134.3 (26.8)	140.1 (28.7)	–5.8 (–23.8 to 12.3)
Serum creatinine, mg/dl	1.05 (0.2)	1.01 (0.3)	0.04 (–0.1 to 0.2)	1.1 (0.2)	1.1 (0.2)	0.0 (–0.11 to 0.12)
Creatinine clearance, ml/min	73.8 (16.6)	78.9 (21.1)	–5.0 (–17.4 to 7.3)	77.7 (16.9)	77.9 (15.5)	–0.2 (–10.6 to 10.4)
Proteinuria, g/24 h	0.8 (0.7)	1.0 (0.7)	0.2 (–0.6 to 0.3)	1.2 (0.8)	1.3 (0.8)	0.1 (–0.6 to 0.4)

out that PTX has no effect on blood pressure [6, 7]. Our results indicated that PTX and captopril decreased diastolic and mean arterial blood pressure, although captopril and PTX did not change systolic blood pressure. So, the decrease in proteinuria in patients may be the result of decreasing diastolic blood pressure. Although the patients were on a weight-maintaining diet and the doses of their insulin or oral hypoglycemic agents were not changed, captopril and PTX decreased fasting plasma glucose. Similar to the present research, the studies of Raptis et al. [14] demonstrated that PTX administered concurrently to any antidiabetic type of treatment led to a better blood glucose control, but not all studies supported their findings [6, 15]. However, improved glycemic control with captopril or PTX might have reduced the protein excretion rate [16].

As the creatinine clearance did not significantly change in captopril-treated patients but was increased in PTX-treated patients, it seems that at least an increase in creatinine clearance might play a more prominent role in the beneficial effects of PTX on proteinuria. The present results are consistent with data obtained in the study of Tripathi et al. [8] who demonstrated improvement in creatinine clearance after 3 months of PTX administration. PTX has several protective mechanisms against molecular injury [17, 18]. These multiple effects can explain its more prominent effects in decreasing proteinuria.

The effect of PTX on decreasing proteinuria has been reported in several studies [6, 8]. Enalapril, an ACE inhibitor, has similar effects in type 2 diabetic patients [6]. A recent study showed that captopril can also decrease proteinuria of type 2 diabetic patients. Therefore, both captopril and PTX can prevent the progression of renal disease and decrease their mortality rate by reducing the amount of proteinuria of type 2 diabetic patients [2, 3]. The encouraging results obtained in this trial warrant further studies and a larger-scale, probably blinded trial is needed.

In conclusion, PTX is a suitable medication in the treatment of macroproteinuria in diabetic nephropathy. It is logical to administer PTX instead of ACE inhibitor in normotensive diabetic patients or in those who do not respond or cannot tolerate it because of its side effects. The evaluation of the effects of PTX on microalbuminuria of diabetic patients remains to be proven.

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