

Nephroprotective effect of trandolapril and verapamil in normotensive type 1 diabetics — a 12-month follow-up study

Abstract

Background. Clinical studies have demonstrated that the treatment with angiotensin converting enzyme inhibitors and nondihydropyridine calcium antagonist slows down the progression of nephropathy in type 1 diabetic patients. The aim of the present study was to evaluate the effect of a one-year treatment with trandolapril (2 mg) and verapamil SR (180 mg o.d.) on persistent microalbuminuria in normotensive type 1 diabetic patients with incipient nephropathy.

Material and methods. Fifteen normotensive (blood pressure \leq 130/85 mm Hg) type 1 diabetic patients with persistent microalbuminuria (albuminuria 30–300 mg/24 hours, normal glomerular filtration rate) were included in the study: age (mean (\pm SD) 39 ± 5.3 years, known duration of diabetes 21.2 ± 7.9 years, body mass index (BMI) 23.1 ± 1.4 kg/m²).

Results. The mean urinary albumin excretion significantly decreased ($p < 0.001$) from 52.0 ± 30.7 to 21.8 ± 11.2 mg/24 hours ($> 58\%$) within one year. Statistically, systolic

and diastolic blood pressure was significantly ($p < 0.001$; $p < 0.05$) lower, additionally there was a significant mean heart rate decrease ($p < 0.05$). A statistical analysis also showed a significant decrease of average fasting blood glucose ($p < 0.01$) and triglycerides levels ($p < 0.05$). No significant differences in glycosylated hemoglobin, serum urea and creatinine, serum urate, serum potassium, cholesterol, or HDL-cholesterol were noted during the study.

Conclusions. The study indicates that a long-term therapy with ACEI (trandolapril) and nondihydropyridine calcium antagonist (verapamil SR) may delay the progression of incipient diabetic nephropathy. Treatment with ACEI and nondihydropyridine calcium antagonist should be preferred in normotensive type 1 diabetics where an additive reduction in microalbuminuria is needed to intensify the therapy.

key words: diabetes, microalbuminuria, trandolapril, verapamil

Introduction

Our previous studies have confirmed that a long-term therapy with ACEI in normotensive, type 1 diabetic patients with microalbuminuria was beneficial for delaying the progress of diabetic nephropathy. In the present study we assessed the effect of a combined therapy with ACEI (trandolapril) and nondihydropyridine calcium antagonist (verapamil SR) on urinary albumin excretion in normotensive diabetic (type 1) patients with microalbuminuria.

Diabetic nephropathy is the most frequent complication of the advanced renal failure observed in approxi-

mately 2/5 patients with type 1 diabetes. Hypertension, either accompanying diabetes or being the secondary effect of developing kidney disease, is the main cause of the accelerated progress of nephropathy in patients with type 1 diabetes. A diagnosis of nephropathy in diabetes usually predicts microalbuminuria development. In many studies the relationship between microalbuminuria and other markers of organ complications in diabetes have been estimated. Microalbuminuria appears to be a significant risk factor for cardiovascular diseases in patients with type 1 diabetes [1]. The presence of microalbuminuria was determined as a predictor of an early death [2]. It was also confirmed that microalbuminuria predisposes normotensive patients with normal glucose metabolism to the development of cardiovascular complications [3]. Some other studies have indicated that the early normalization of blood pressure (regardless of the class of used drugs) restricts the progress of diabetic nephropathy [4].

Increased intraglomerular pressure is observed in the population of diabetic patients with nephropathy. That is

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the result of significant afferent arterioles dilatation that causes increased blood flow to kidneys and enhanced efferent arterioles sensitivity to vasoconstrictive substances like angiotensin 2, endothelin and vasopressin, and subsequently leads to the additional increase of intraglomerular pressure. Furthermore, in this population of patients one can observe the loss of negative charge in basement membranes and disturbed passage of albumins across the glomerular barrier. It has been documented that ACEIs restore membrane selectivity subsequently decreasing albuminuria. Histological changes that develop in the course of diabetic nephropathy include mesangial hyperplasia with subsequent glomerulosclerosis. The administration of ACEI in the early phase of diabetes significantly lowers intraglomerular pressure and inhibits mesangial cells proliferation and mesangial matrix production. ACEIs decrease albuminuria and delay diabetic nephropathy progress [5]. Nephroprotective effect similar to ACEI action was confirmed for nondihydropyridine calcium antagonists. These drugs decrease diabetic nephropathy and microalbuminuria as well, which is connected with their action on protein biosynthesis within the mesangial matrix [6].

Combined medication (for example trandolapril with verapamil) is recommended particularly when ACEI monotherapy is insufficient to reach accurate blood pressure and/or proteinuria control. It has to be noted, however, that in normotensive patients with type 1 diabetes, aggressive pharmacotherapy is not always introduced in the early phase of nephropathy [5].

The aim of the presented study was to assess the efficacy of 12 months of a combined therapy with 2 mg trandolapril and 180 mg verapamil daily on the inhibition of diabetic nephropathy progress.

Materials and methods

Our study included 15 patients (age: 39 ± 5.3 years, BMI: 23.1 ± 1.4 kg/m²) with type 1 diabetes (mean duration: 21.2 ± 7.9 years), normal blood pressure ($\leq 130/85$ mm Hg), persistent albuminuria (30–300 mg/24 h) and normal parameters of renal function. All participants were hospitalized in The Gastroenterology and Metabolic Diseases Clinic, Medical University in Warszawa. The characteristics of the study group are shown in Table 1.

Daily albuminuria, renal function parameters, metabolic control of diabetes and some other biochemical parameters were measured before and during medication, as well as 12 months after the medication. Patients were excluded from the study for the following reasons: ACEI medication within 4 weeks before entering the study, episodes of ketosis or severe hypoglycemia within last 12 months, heart failure, unstable angina pectoris, pre-

Table 1. Characteristics of the study group

Parameter	Value
n	15
Sex (M/F)	6/9
Age (years)	
x \pm SD	39.0 ± 5.3
Median	40.0
(min–max)	(28–45)
Duration of diabetes (years)	
x \pm SD	21.2 ± 7.9
Median	19.0
(min–max)	(10–33)
BMI [kg/m ²]	
x \pm SD	23.1 ± 1.4
Median	23.0
(min–max)	(19.5–25.2)

vious myocardial infarction, previous stroke, gastrointestinal diseases, liver diseases, previous viral hepatitis, renal diseases, urinary tract diseases, neoplasms, HIV-positive and obesity. Furthermore, we did not include patients with contraindications to ACEI: hypotension, both renal (both kidneys) artery stenosis, unilateral artery stenosis in a solitary kidney, pregnancy, breast-feeding, hyper-reactivity on trandolapril or congenital Quincke's edema. All patients enrolled into this study were given 2 mg trandolapril and 180 mg verapamil daily. Patients were on a diabetic diet designed to achieve and maintain a desirable body mass. All the patients gave written consent for their participation in this study. Daily excretion of albumin (radioimmunological assay), urea and creatinine concentrations were periodically determined before and within the 12 months of medication with trandolapril. Furthermore the following parameters were measured: fasting glycaemia, HbA_{1c}, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, uric acid, sodium and potassium. Research material consisted of some (chosen) patients' characteristics and data analyses. To verify the hypothesis of equal mean value of two means a *t*-Student test was applied. The level of significance was set at $P = 0.05$. Correlation coefficient value was verified by the *t*-Student test.

Results

A combined treatment (trandolapril/verapamil SR) resulted in significant reduction of daily albuminuria (from 52.0 ± 30.7 to 21.8 ± 11.2 mg, $P < 0.001$) — 58.1% (Figure 1).

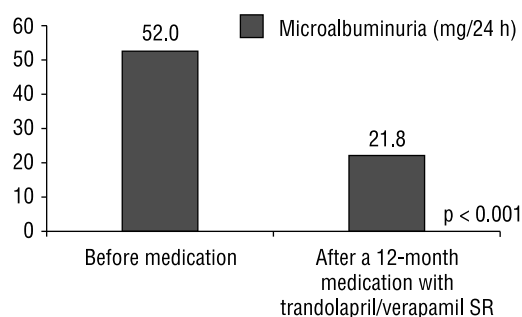


Figure 1. Mean microalbuminuria before and after 12 months of treatment with trandolapril/verapamil SR combination

The mean values of systolic and diastolic blood pressure were significantly lower ($P < 0.001$, $P < 0.05$ respectively) and the heart rate was slower ($P < 0.005$). Applied therapy resulted in the reduction of fasting glycemia values ($P < 0.01$) and triglycerides concentration ($P < 0.05$).

During our study some parameters did not change, i.e., HbA_{1c}, total cholesterol, urea, creatinine, uric acid and sodium concentration in blood. Slight increase of HDL-cholesterol and potassium concentrations was noticed. Those results are shown in Table 2.

During a one-year observation period 10 out of 25 enrolled patients were withdrawn from the study because of the excessive blood pressure reduction.

Discussion

It has been frequently demonstrated that the early treatment with ACEI in normotensive, diabetic (type 1) patients with microalbuminuria reveals the nephroprotective effect.

The results of our study have proved that a combined therapy with trandolapril/verapamil SR in these patients provides a substantial delay of diabetic nephropathy progress. Thus in patients with type 1 diabetes, normal blood pressure and proteinuria it might be reasonable to consider a combined treatment with angiotensin converting inhibitor, trandolapril and nondihydropyridine calcium antagonist (verapamil SR), especially if ACEI monotherapy seems to be insufficient. The beneficial effect of hypotensive therapy on renal function in patients with type 1 diabetes, complicated by albuminuria or nephropathy was previously reported in many studies. The efficacy of ACEI and nondihydropyridine calcium antagonists in reduction of albuminuria and renal structural damage were well documented in patients with hypertension, diabetes and microalbuminuria [7, 8]. Decreased albuminuria correlates with glomerular filtration reduction [9] regardless of the achieved blood pressure level [10], however hypotensive mechanism involvement in this phenomena may not be excluded. The usefulness of ACEI administration in diabetic patients with imminent and apparent nephropathy was confirmed in many clinical trials, including EUCLID (EURO-DIAB-controlled trial of Lisinopril in insulin dependent diabetes), ATLANTIS (ACEI Inhibitor Trial to Lower Albuminuria in Normotensive Insulin Dependent Subjects), IMSG (Italian Microalbuminuria Study Group) and MDNSG (Melbourne Diabetic Nephropathy Study Group). In all those trials a decrease in albuminuria was observed without a substantial reduction of systemic blood pressure [11–15]. Many observations indicate a long-term limitation of nephropathy progress by ACEI. The reduction of albuminuria in normotensive patients with type 1 diabetes after 1 and 2 years of ACEI therapy was over 45% and about 70%, respectively [16].

Table 2. Effects of treatment with trandolapril/verapamil SR combination on blood pressure, heart rate and some metabolic parameters

Parameter	Baseline	End point	Statistical significance
Systolic pressure [mm Hg]	134.6 ± 4.8	125.0 ± 9.1	$P < 0.001$
Diastolic pressure [mm Hg]	83.7 ± 5.5	79.3 ± 5.6	$P < 0.05$
Heart rate/min	87.3 ± 8.4	82.3 ± 7.8	$P < 0.05$
Fasting glycemia [mmol/l]	10.9 ± 1.9	9.2 ± 1.4	$P < 0.01$
HbA _{1c} (%)	9.0 ± 1.4	8.7 ± 1.4	NS
Urea [mmol/l]	12.4 ± 2.7	13.5 ± 1.7	NS
Creatinine [μ mol/l]	88.4 ± 17.7	84.0 ± 14.1	NS
Uric acid [mmol/l]	0.25 ± 0.04	0.25 ± 0.04	NS
Potassium [mmol/l]	4.35 ± 0.27	4.44 ± 0.20	NS
Cholesterol [mmol/l]	4.94 ± 0.56	4.53 ± 0.50	NS
HDL-cholesterol [mmol/l]	1.11 ± 0.16	1.06 ± 0.25	NS
Triglycerides [mmol/l]	1.42 ± 0.49	1.08 ± 0.40	$P < 0.05$

Barkis et al. found a 62% reduction of proteinuria after 12 months of a combined treatment with trandolapril/verapamil SR in patients with type 2 diabetes and hypertension [17]. In the BENEDICT study (Bergamo Nephrologic Diabetes Complications Trial) carried out for 3 years a 61% reduction of relative risk of albuminuria was found after a combined therapy trandolapril/verapamil in type 2 diabetic patients with hypertension [18]. In some other studies a 33% reduction of microalbuminuria was observed after 12 weeks of trandolapril/verapamil SR administration [19]. Clinical trials presented above confirmed the efficient long-term action of combined therapy with ACEI in hypertensive patients and normotensive diabetic patients with microalbuminuria on the inhibition of diabetic nephropathy. In the population of patients with diabetes and microalbuminuria it is recommended to introduce the pharmacotherapy in the normotensive phase. Such a treatment inhibits glomerular damage and significantly slows down the progression of diabetic nephropathy. Furthermore, in normotensive patients with type 1 diabetes treated with ACEI and/or nondihydropyridine calcium antagonist, the nephropathy develops less frequently than in the untreated individuals.

Trandolapril/verapamil SR therapy efficiently reduces microalbuminuria, decreases blood pressure and slows down the heart rate. In normotensive patients with type 1 diabetes the trandolapril/verapamil SR treatment usually provides a small and transient reduction of blood pressure. This enables to continue the treatment. Adverse effects related with hypertensive symptoms were noted in 2/5 cases [19].

Combined pharmacotherapy with trandolapril/verapamil SR seems to be a very beneficial method of diabetic nephropathy treatment in the normotensive phase. ACEIs are the first choice drugs in diabetic nephropathy. Strict blood pressure control (< 130/80 mm Hg and in patients with proteinuria <125/75 mg Hg) is recommended during the medication. When albuminuria occurs in a normotensive phase, the ACEI therapy should be started as soon as possible in increasing doses, step by step [20]. In the ESPRIT trial (European Study for Prevention of Renal disease in Type 1 diabetes) the administration of full ACEI doses has been postulated. Using large doses of ACEI (trandolapril 4 mg vs. 0.5 mg) in normotensive patients with type 2 diabetes substantially improved glomerular filtration rate (GRF) and other parameters of renal function [20, 21]. The ACEI and calcium antagonist combined therapy in diabetic patients with hypertension and microalbuminuria provides a more efficient reduction of blood pressure and microalbuminuria than the ACEI monotherapy [22, 23].

The crucial factor in diabetic nephropathy treatment is a very good metabolic control of diabetes [21, 23, 24]. Our study has documented that the trandolapril/verapamil SR medication resulted in a statistically significant reduction in

fasting glycemia and triglycerides concentration, without substantial changes in other lipids levels. While a combined therapy with other classes of drugs, for example beta-adrenolytics and/or diuretics, may cause negative changes in those parameters. Previously published data revealed that the trandolapril/verapamil SR combination improved the insulin sensitivity coefficient by about 20% although calcium antagonists alone had no influence on the peripheral glucose utilization [25, 26]. The results of other studies have shown that trandolapril significantly decreases triglycerides concentration [23, 27, 28].

Data collected from our study proved that the combined trandolapril/verapamil SR treatment had no substantial effect either on renal and liver function parameters or on electrolytes concentration. The trandolapril/verapamil combination appeared safe in diabetics with hypertension and did not impair renal function parameters in patients with moderate renal failure [27].

Diabetic patients are at high risk of cardiovascular complications. A combined therapy with trandolapril and verapamil is useful for the prevention and treatment of cardiovascular events due to their cardioprotective action. They are recommended in diabetic patients with hypertension, heart failure, myocardial infarction (with and without left ventricular dysfunction), and in secondary prevention after the myocardial infarction [23, 29, 30].

The trandolapril/verapamil therapy in diabetic patients with hypertension provides the reduction of left ventricular hypertrophy, increases ejection fraction and improves myocardial contractibility in persons with myocardial ischemia and heart failure [1, 22–24, 29, 30].

An early introduction of pharmacotherapy with ACEI and/or nondihydropyridine calcium antagonist may significantly delay the development of advanced diabetic nephropathy, regardless of blood pressure reduction. The medication with ACEI and/or nondihydropyridine calcium antagonist in patients with type 1 diabetes and microalbuminuria makes it possible to prevent renal complications. It seems that the combined trandolapril/verapamil SR therapy should be recommended particularly when the ACEI monotherapy is not sufficient to the adequate reduction of proteinuria [23, 29, 30].

Conclusions

The study indicates that a long-term therapy with ACEI (trandolapril) and nondihydropyridine calcium antagonist (verapamil SR) may delay the progression of incipient diabetic nephropathy. Treatment with ACEI and nondihydropyridine calcium antagonist should be preferred in normotensive type 1 diabetics where an additive reduction in microalbuminuria is needed to intensify the therapy.

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