Eearly effects of the AT_2 receptor antagonist eprosartane mesylate (EM) in diabetic patients with and without chronic renal failure

N. Nenchev, B. Deliyska, M. Bankova, P. Radulova, G. Kimenov and E. Marinova

Medical University, Sofia, Bulgaria

Abstract

ATII receptor antagonists are effective in the control of the arterial hypertension (AH) in patients with CRF. Different factors take part in the pathogenesis of the AH in the diabetic mellitus (DM) patients: volume overload, sodium retention, renin-angiotensin system (RAAS), activity of the sympatic system (SNS) and endothelin system.
The aim of the study is assessment of the effectiveness of the EM on the blood pressure (BP) and pulse pressure (PP) which are incriminated factors for the cardiovascular morbidity and mortality.
22 patients (14 male and 8 female) with DM and AH, mean age 52±8 years, divided in 2 groups were followed for 3-month period. On 0, 1st, 4th, 12th week the following parameters were followed: systolic BP, diastolic BP, mean arterial pressure (MAP), PP, heart rate, weight, height, basic laboratory tests. All the patients received 600 mg EM (Teveten®) once a day in the morning (10 of them as a mono therapy and the rest in a combination with other antihypertensive therapy, which was not changed during the study).
There were significant changes in the mean blood pressure and PP in both groups at 4 and 12 week. There were not significant changes in HF between the groups. At the end of the study mean BP decreased in group A for 20,4% and in group B for 26,9%. PP decreased in group A for 35,7% and in group B for 38,9%. Serum creatinine did not changed significantly neither in group A nor in group B (group A from 98+/-11,1 to 95,9+/-8,4 μmol/l; group B from 321+/-76 to 349+/-21,3 μmol/l). We did not observed also a significant changes in creatinine clearance in the two groups (group A from 111+/-15,1 to102+/-11 mmol/min; group B from 18+/-2, 2 to 20,6+/-4,8 mmol/min).
ATII receptor blocker EM leads to significant control over BP and PP after 4th week in DM patients with and without CRF. This effect is probably due to a dual mechanism of action over AH – control over RAAS and SNS. The drug is well tolerated with no side effects.

Key words: AT_2 receptor antagonist, diabetes mellitus, renal failure

Introduction

There is a relationship between cardiovascular and kidney diseases. Treatment of an early nephropathy has also cardioprotective effect in the hypertensive patients. Renoprotective drugs improve the renal and endothelial dysfunction that is connected with overactivation of the renin-angiotensin-aldosterone system (RAAS). RAAS-directed antihypertensive agents are both angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) that have renoprotective effects. They decrease both high blood pressure and proteinuria (8). Metabolic syndrome is a cluster of common cardiovascular risk factors that includes hypertension and insulin resistance. Hypertension and diabetes mellitus are frequent comorbidities and like metabolic syndrome, increase the risk of cardiovascular events. Eprosartane, an antihypertensive agent with evidence of partial peroxisome proliferator-activated receptor activity-gamma (PPARgamma) activity, may improve insulin sensitivity and lipid profile in patients with metabolic syndrome (1).
The aim of the study was to evaluate early efficacy of eprosartane mesilate (EM) (Teveten®-Solvei) on the blood pressure (BP) and pulse pressure (PP) in diabetic patients with and without chronic renal failure (CRF).

Patients and methods

The study was conducted in 22 patients with diabetic nephropathy. Fourteen from them were males with a mean age of 52±8 years. The patients were divided into 2 groups. Group A, 8 patients without CRF and group B, 14 CRF patients. The follow-up period was 12 weeks. At 0, 4 and 12 week the followed parameters were: mean blood pressure (BP), PP, hearth frequency (HF), body weight, high, serum creatinine and creatinine clearance. All patients were treated with EM, 600 mg once daily. Ten patients were with monotheray by EM, all others received before EM another antihypertensive treatment and EM were additional included.

Results

The results of PB, PP, HF of the patients from two groups are shown in Table 1.

Group A

Parameter	Baseline	1st week	4th week	12th week
MAP (mm Hg)	113 ± 6	110 ± 5	96 ± 7 *	90 ± 5 **
PP (mm Hg)	70 ± 8	62 ± 6	51 ± 5 *	45 ± 4 **
Heart rate	75 ± 9	75 ± 4	70 ± 4	72 ± 6

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Correspodence to: N. Nenchev, Medical University, Sofia, Bulgaria

the study mean BP decreased in group A for 20,4% and in group B for 26,9%. PP decreased in group A for 35,7% and in group B for 38,9%. Serum creatinine did not changed significantly neither in group A nor in group B (group A from 98+/-11,1 to 95,9+/-8,4 μmol/l; group B from 321+/-76 to 349+/-21,3 μmol/l). We did not observe also a significant changes in creatinine clearance in the two groups (group A from 111+/-15,1 to102+/-11 mmol/min; group B from 18+/-2, 2 to 20,6+/-4,8 mmol/min).

Group B

Parameter	Baseline	1st week	4th week	12th week
MAP (mm Hg)	130 ± 9	127 ± 4	105 ± 7 *	95 ± 8
PP (mm Hg)	90 ± 8	100 ± 2	80 ± 5 *	55 ± 9 **
Heart rate	88 ± 9	86 ± 3	82 ± 4	75 ± 4

* p < 0,01 ; ** p< 0,001

Discussion

Eprosartane is a well tolerated ARB drug. There were evidences for its reno- and cardioprotection especially in diabetic patients. Therapy with ARB is suitable also for patients with primary and secondary glomerulonephritis. The effectiveness of a combined therapy with ARB and ACE inhibitors may have been at least partly due to the greater inhibition of the action of angiotensin II in patients with IgA nephropathy. This strategy apparently reduced mild-to-moderate proteinuria in patients with normotensive IgA nephropathy (9). The angiotensin II changes glomerular permeselective function via the opening of large pores after elevations in transmembrane pressure and by acting on the glomerular pressure, too. There is evidence that angiotensin-converting enzyme inhibitors (ACEI) alone or with the ARB's may improve the glomerular size-selective function and the hemodynamic intrarenal accounted output of plasma proteins that result in decreasing of proteinuria. It was not only by the drug related reduction in systemic blood pressure (4). The combination of ARB and ACEI seems to be beneficial and may offer an additional renoprotective effect (10). Hemodialysis patients have uremic dyslipidemia, represented by elevated serum intermediate-density lipoprotein cholesterol (IDL-C) levels, and an increased cardiovascular mortality rate. The effect may be in connection with changes on pulse wave velocity (PWV), which predicts cardiovascular morbidity and mortality. Long-term blockade of the RAAS may have a beneficial effect on the acceleration of atherosclerosis and uremic dyslipidemia in hemodialysis patients (5). Several recent morbidity and mortality trials with ARB's provide an evidence-based rationale for the use of the drugs in patients with hypertension. Studies with comparison to conventional antihypertensive agents showed improved morbidity and mortality outcomes in patients with hypertension and left ventricular hypertrophy (Losartan®) and diabetes mellitus (Losartan® and Irbesartan®) (13). Systemic and renal hemodynamic responses to acute AT1R blockade are, at least in part, genetically determined (12). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure emphasizes the urgent need to lower blood pressure to a goal of <140/90 mmHg in patients with uncomplicated hypertension and to <130/80 mm Hg in high-risk patients, such as those with diabetes mellitus or chronic kidney disease, to prevent cardiovascular disease morbidity and mortality. ARBs are highly effective antihypertensive agents with excellent tolerability profiles. Many studies found that monotherapy with an ARB can generally result in the attainment of the diastolic BP goal of <90 mm Hg in approximately 50% of hypertensive patients (10). A few studies (LIFE, RENAAL etc.) recommended therapy with ARB's in diabetic patients not only for lowering the BP but also to reduce cardiovascular and renal events (3). Another benefitial effect of ARB's is that RAAS inhibition consistently and significantly reduces the incidence of diabetes mellitus type 2 in individuals with arterial hypertension (6). There are evidences that the new generation of ARB's is associated with a more favorable modification of hemostatic/fibrinolytic status (2,11). There is a growing evidences that using such drug can improve renal hemodynamic and exert a protective renal effect beyond BP control in patients with hypertension (7,8).

Conclusions

According to the data of our study Teveten improved significantly mean BP, PP without changes in HF in diabetic patients with and without CRF. The effect on those parameters was significant on 4 weeks after beginning of the therapy. We did not observed significant changes in creatinine and creatinine clearance. It was well tolerate from the patients without any adverse effects.

In conclusion we suppose that eprosartane has early and beneficial effect in hypertensive diabetic patients with or without renal failure.

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