



Original Research Article

Biochemical Effects of Telmisartan versus Ramipril in Experimental Diabetic Nephropathy

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ABSTRACT

Objective: The present study was undertaken to evaluate and compare the effects of ramipril which is an angiotensin converting enzyme inhibitor (ACEI) and telmisartan, an angiotensin receptor blocker (ARB) in streptozotocin (STZ) induced diabetic nephropathy in rats.

Materials and Methods: The diabetic rats were divided into four groups of six each. They were administered test drugs such as telmisartan (10mg/kg), ramipril (5mg/kg) or vehicle for 16 weeks. Blood samples were collected for the estimation of blood glucose, blood urea nitrogen, serum creatinine. Urine was collected for the measurement of protein and determination of creatinine clearance.

Results: STZ diabetic rats exhibited marked hyperglycemia, proteinuria, uremia and reduction in creatinine clearance. Telmisartan pretreatment reduced blood glucose level after 8 weeks which was not observed with ramipril. Both telmisartan and ramipril significantly altered the remaining parameters towards normal.

Conclusion: Although telmisartan is superior to ramipril with respect to blood glucose lowering effect, the renoprotective action of telmisartan appears to be similar to ramipril. Therefore telmisartan may be used as an alternative to ramipril in the treatment of hypertensive diabetic patients with nephropathy.

Key words: STZ, telmisartan, ramipril, diabetic nephropathy.

INTRODUCTION

Diabetic nephropathy accounts for approximately 40% of new cases of end stage renal disease. [1] As the earliest sign of developing nephropathy, microalbuminuria is an important marker for renal disease as well as indication of damage to the vasculature as a whole. [2] While renal disease causes an increase in blood pressure, high blood pressure accelerates loss of function of the diseased kidney. Thus, the treatment of hypertension has become an

important component in the treatment of most chronic kidney disease (CKD) patients not only to prevent cardiovascular complications but also to protect the kidney. [2]

The Renin-angiotensinogen-system (RAS) plays an important role in the pathogenesis of kidney disease. [3] Indeed, the RAS is particularly important in development and progression of diabetic nephropathy because angiotensin II formation is stimulated by hyperglycemia

and glycation end products. [3] Angiotensin II acting via angiotensin II type 1 (AT1) receptors causes renal dysfunction via two inter-related mechanisms: glomerular hypertension and endothelial dysfunction. [4] It is a potent vasoconstrictor of efferent arterioles, resulting in increased intraglomerular pressure. Decreased renal perfusion leads to interstitial hypoxia; this in turn causes loss of peritubular capillaries and tubulointerstitial scarring, which contribute to chronic hypoxia, thereby establishing a vicious circle of kidney damage. [5] In addition, angiotensin II exerts direct profibrotic and proinflammatory effects that contribute to kidney damage. [4]

In view of the central role played by angiotensin II in the pathogenesis of renal dysfunction, the potential benefits of inhibitors of the RAS have been extensively investigated. [6] There is now clear evidence that both angiotensin-converting enzyme (ACE) inhibitors [7] and AT1-receptor blockers (ARBs) [8] can delay the onset of diabetic renal disease and attenuate or potentially even stop, the progression of established disease. As a result, these agents are now recognized as first-line therapy for diabetic patients with hypertension, both in current hypertension management guidelines [9] and the US National Kidney Foundation guidelines for the treatment of hypertension in all patients with CKD. [10]

Since the 1980s, numerous studies have shown that the use of ACE inhibitors have beneficial effects when treating hypertension and diabetic renal disease. [7] However results of recently published trials such as RENAAL [11] (Reduction of end points in NIDDM with Angiotensin II antagonist Losartan), IDNT [12] (Irbesartan Diabetic Nephropathy Trial), IRMA II [13] (Irbesartan in patients with type II Diabetes and Microalbuminuria Study II) - question whether angiotensin receptor type I blockers can replace ACE inhibitors as the agent of

choice in treating diabetic nephropathy. Several head-to-head studies have been published, but these have usually been of relatively short duration (upto a year or so), had relatively small number of patients, and used the intermediate end point of reduction in albuminuria. [8] Direct comparative studies between ACEIs and ARBs in diabetic nephropathy are lacking.

Telmisartan has a unique profile among ARBs, with a high affinity for the angiotensin II type 1 receptor, a long duration of receptor binding, high lipophilicity and a long plasma half life. Also telmisartan has been reported to have a partial agonistic effect on PPAR in addition to the effect of angiotensin II blockade. [14] So telmisartan is expected to have more potent effects in diabetic nephropathy than ramipril. In the present study, we tested the hypothesis that telmisartan might produce a greater beneficial effect on diabetic nephropathy than ramipril. Hence, the objective of the present study is to evaluate and compare the effects of telmisartan (ACEI) and ramipril (ARB) in diabetic nephropathy in streptozotocin induced diabetic rats.

MATERIALS AND METHODS

Chemicals

Telmisartan and ramipril were purchased from Glenmark Pharmaceuticals Ltd. Mumbai and STZ was purchased from Sigma Chemical Co St Louis, USA.

Animals

Adult albino rats, of either sex, weighing between 250-300g were maintained under standard conditions with food and water *ad libitum*. The study was approved by the Institutional Animal Ethical Committee.

Grouping & treatment

Animals were divided into four groups of 6 animals each and treated for 8 wks as follows:

- Group - I: Normal control
- Group - II: Diabetic rats treated with distilled water
- Group - III: Diabetic rats treated with telmisartan (10 mg/kg)
- Group - IV: Diabetic rats treated with ramipril (5 mg/kg)

Induction of diabetes in experimental animals

Diabetes was induced in rats by single intraperitoneal injection of streptozotocin (STZ) at a dose of 60 mg/kg body weight dissolved in 0.01 M (ph 4.5) citrate buffer. STZ induces diabetes within 3 days by destroying the beta cells. [15] Three days after STZ injection, rats with blood glucose levels of more than 250 mg/dl were included in the study. Human antihypertensive doses of telmisartan (80 mg) and ramipril (20 mg) were converted into animal doses as per the guidelines set by USFDA. In STZ-diabetic rats, nephropathy develops after approximately 8 weeks. Treatment with test drugs (telmisartan and ramipril) were started 5 days prior to STZ injection and continued for a period of 16 weeks.

Collection of urine:

The rats were individually housed in metabolic cages (1 per one metabolic cage) provided with a wire mesh bottom and funnel with stainless steel sieves to retain feces and allow the urine to pass and 24 hr urine sample was collected. Urine samples were collected at 0 weeks, 4 weeks, 8 weeks, 12 weeks and 16 weeks.

Biochemical Parameters:

1. **Measurement of blood glucose concentration:** To measure blood glucose level, the blood samples were collected from the retro orbital sinus. The blood glucose level was estimated 72 hrs after STZ administration and thereafter every 4 weeks for 16 weeks by Automatic

Autoanalyzer based on the principle of Glucose Oxidase Method. [16]

2. **Blood urea nitrogen (BUN):** The blood urea nitrogen levels were evaluated with the diagnostic kit by Automatic Autoanalyzer based on the principle of glutamate dehydrogenase-urease method. [17]
3. **Plasma creatinine:** The plasma creatinine levels were evaluated by diagnostic kit based on principle of Jaffe's Method. [18]
4. **Urine creatinine:** Renal function was estimated by determining urine creatinine concentration in all experimental animals by automatic analyzer using diagnostic kit [17]
5. **Total urinary protein:** was measured by precipitation with trichloroacetic acid and the precipitate was dissolved in 1N NaOH and quantitated by Biuret method. [19]
6. **Determination of glomerular filtration rate :**

Glomerular filtration rate was calculated using the following formula [20]

$$\text{GFR (ml/min)} = \frac{\text{Urinary Creatinine (mg/dl)} \times \text{Urine volume (ml)} \times 1000\text{g}}{\text{Plasma creatinine (mg/dl)} \times \text{Body weight (g)} \times 1440 \text{ (min)}}$$

Statistical Analysis

All data are shown as mean \pm SEM. Results were analyzed by analysis of variance. Significance between the groups was estimated using student t test. A p value of < 0.05 is considered as statistically significant.

RESULTS

Blood glucose concentration:

The mean blood glucose values in the normal control group (Group I) was 86.7 ± 2.4 mg/dl. STZ induced diabetic rats (Group II) showed a marked increase in

blood glucose levels within 72 hrs and the levels gradually increased to 315.3 ± 5.9 mg/dl. The increase was statistically significant ($P < 0.001$) as compared with normal control group. Telmisartan significantly decreased ($P < 0.05$) blood

glucose levels in diabetic rats at 8 wks, 12 wks and 16 wks. However, there was no significant lowering of blood glucose levels in ramipril treated diabetic rats groups. (Table 1)

Table 1: Effect of telmisartan and ramipril on blood glucose level in rats with STZ induced diabetic nephropathy.

Groups	0 wks	4 wks	8 wks	12 wks	16 wks
I (Normal control)	86.7 ± 2.4	88.8 ± 6.12	88.3 ± 2.8	87.8 ± 2.16	87.1 ± 2.74
II (Diabetic control)	274.2 ± 5.27^a	280.4 ± 3.12^a	286.3 ± 5.16^a	292.6 ± 5.58^a	315.3 ± 5.9^a
III (Diabetic + telmisartan)	275.1 ± 4.38	277.3 ± 4.95	266.5 ± 5.89^b	272.6 ± 3.65^b	299.3 ± 5.53^b
IV (Diabetic + ramipril)	274.6 ± 4.05	279.1 ± 5.12	285.6 ± 5.76	290.6 ± 4.5	311.8 ± 6.83

Values are mean \pm SEM for 6 animals in each group; $P^a < 0.001$ when compared with normal control; $P^b < 0.01$ when compared with diabetic control

Urinary protein:

There was no excretion of protein in urine in the control group (Group I). However, there was a significant ($p < 0.001$) and sustained increase in urinary protein excretion after 4 weeks of STZ. Telmisartan

and ramipril pretreatment significantly ($p < 0.01$) retarded the increase in proteinuria compared with untreated diabetic group. However there was no significant difference between the effects of telmisartan and ramipril treated diabetic group. (Table 2)

Table 2: Effect of telmisartan and ramipril on urinary protein in rats with STZ induced diabetic nephropathy.

Groups	0 wks	4 wks	8 wks	12 wks	16 wks
I (Normal control)	0	0	0	0	0
II (Diabetic control)	0	1.0 ± 0.07^a	1.6 ± 0.06^a	1.96 ± 0.08^a	2.0 ± 0.14^a
III (Diabetic + telmisartan)	0	0.26 ± 0.05^b	0.4 ± 0.05^b	0.48 ± 0.05^b	0.51 ± 0.05^b
IV (Diabetic + ramipril)	0	0.28 ± 0.05^b	0.48 ± 0.04^b	0.5 ± 0.08^b	0.56 ± 0.08^b

Values are mean \pm SEM for 6 animals in each group; $P^a < 0.001$ when compared with normal control; $P^b < 0.01$ when compared with diabetic control

Blood urea nitrogen:

There was a significant ($p < 0.001$) increase in blood urea nitrogen in STZ induced diabetic animals as compared to control group. Telmisartan and ramipril pretreatment significantly ($p < 0.01$)

significantly reduced the elevated levels of blood urea in diabetic rats (Table 3). However, when compared with ramipril pretreated group, reduction in blood urea level was significantly higher in telmisartan group after 8 weeks.

Table 3: Effect of ACE inhibitors and ARBs on BUN levels in rats with STZ induced diabetic nephropathy.

Groups	0 wks	4 wks	8 wks	12 wks	16 wks
I (Normal control)	18.0 ± 0.83	18.16 ± 0.55	19.33 ± 0.66	19.0 ± 0.53	20.16 ± 0.73
II (Diabetic control)	20.1 ± 0.54	58.66 ± 1.02^a	60.33 ± 1.16^a	61.16 ± 1.68^a	63.33 ± 1.72^a
III (Diabetic + telmisartan)	16.8 ± 0.79	27.66 ± 1.06^b	29.8 ± 1.25^{bc}	30.6 ± 1.75^{bc}	33.83 ± 1.38^{bc}
IV (Diabetic + ramipril)	16.8 ± 1.16	28.66 ± 0.82^b	33.33 ± 1.19^b	35.6 ± 1.55^b	37.33 ± 1.49^b

Values are mean \pm SEM for 6 animals in each group; $P^a < 0.001$ when compared with normal control; $P^b < 0.01$ when compared with diabetic control; $P^c < 0.05$ when compared with ramipril treated diabetic group

Creatinine clearance:

Creatinine clearance was taken as a parameter to assess GFR. The diabetic control (Group II) when compared with normal control exhibited a significant

($P < 0.01$) increase in creatinine clearance which was 2.2 ± 0.14 at 4 wks, returned to normal levels at 8 wks and significantly decreased ($P < 0.01$) at 12 wks and 16 wks. Groups III & IV significantly reduced

($P < 0.05$) the rise in creatinine clearance at 4 wks to and also significantly reduced ($P < 0.05$) the fall in creatinine clearance at

12 & 16 wks. There was no significant difference in creatinine clearance produced by the test drugs.

Table 4: Effect of telmisartan and ramipril on creatinine clearance (ml/min) in rats with STZ induced diabetic nephropathy.

Groups	0 wks	4 wks	8 wks	12 wks	16 wks
I(Normal control)	1.1 ± 0.12	1.1 ± 0.11	1.4 ± 0.19	1.3 ± 0.12	1.1 ± 0.08
II(Diabetic control)	1.2 ± 0.10	2.2 ± 0.13 ^a	1.0 ± 0.05	0.5 ± 0.05 ^a	0.3 ± 0.07 ^a
III(Diabetic + telmisartan)	1.1 ± 0.09	1.4 ± 0.16 ^b	1.2 ± 0.08	0.9 ± 0.07 ^b	1.0 ± 0.05 ^b
IV(Diabetic + ramipril)	1.1 ± 0.10	1.6 ± 0.15 ^b	1.0 ± 0.07	0.8 ± 0.07 ^b	0.9 ± 0.07 ^b

Values are mean ± SEM for 6 animals in each group; $P^a < 0.01$ when compared with normal control; $P^b < 0.05$ when compared with diabetic control.

DISCUSSION

This study was designed to evaluate and compare the effects of telmisartan (ARB) and ramipril (ACEI) in STZ induced diabetic nephropathy in rats. Results of the present study confirm that STZ, which is commonly used to induce diabetes in experimental animals, causes hyperglycemia and diabetic nephropathy slowly progressing to end stage renal disease. The untreated diabetic rats demonstrated hyperglycemia, macroproteinuria, increase in blood urea nitrogen & plasma creatinine as well as decrease in glomerular filtration rate (GFR). Hyperglycemia is an important causal factor in mediating the development and progression of diabetic kidney disease. [21] Our results showed that there was a significant reduction in blood glucose level at the end of 8 weeks in telmisartan treated diabetic rats. This finding is in consistent with the results of the previous study in which telmisartan is shown to have a glucose lowering property. [22] Telmisartan has been reported to have a structural similarity with the molecule of pioglitazone, a ligand of peroxisome proliferator activated receptor γ , which stimulates insulin sensitivity, thereby decreasing the blood glucose level independent of the action of renin angiotensin system. [14] Likewise, the development of microalbuminuria or macroalbuminuria tended to be decreased with telmisartan or ramipril treatment. Thus, in this direct comparative study, telmisartan

and ramipril reduced albuminuria to comparable extent which is in accordance with the ONTARGET study. [23] This indicates that telmisartan is as effective as ramipril in delaying the progression of proteinuria. The delay in the progression of proteinuria was due to blockade of action of angiotensin II which plays an important role in mediating proteinuria by various mechanisms including hyperfiltration, opening of nonselective pores in the ultrafiltration barrier, modifying the composition of glomerular basement membrane and reducing nephrin expression on podocytes. [24] It is apparent from our results that both telmisartan and ramipril significantly reduced BUN levels after 8 weeks but the effect of telmisartan was significantly greater than ramipril in treated diabetic rats. The protective effect of telmisartan and ramipril on kidney function may be attributed to the blockade of angiotensin II action which is known to produce deleterious effects on kidney by affecting blood pressure and renal haemodynamics, production of growth promoting and profibrotic factors, renal tubular and glomerular hypertrophy and oxidative stress in kidney. [25] Further, PPAR- γ receptors have been localized in urinary system including glomerulus, collecting ducts, proximal tubules and renal vasculature. There have been reports suggesting that activation of PPAR- γ triggers protection in different models of

renal failure like chronic allograft renal damage [26] and renal ischaemia- reperfusion injury. [28] The studies have suggested that activation of PPAR- γ receptors directly attenuate glomerular diseases possibly by inhibiting mesangial growth, which occurs early in the process of nephropathy. Telmisartan can function as both an ARB and as a PPAR activator. This could be a possible explanation for greater BUN lowering effect of telmisartan compared to ramipril in diabetic rats. However, in the absence of clear evidence of differences in larger trials the clinical implications of these differences remain uncertain. The creatinine clearance test has been used to estimate GFR. Our results showed that in STZ induced diabetic rats, the creatinine clearance increases at 4 weeks, normalize at 8 weeks and then gradually decline after 12 weeks. It is speculated that intrarenal generation of angiotensin II constricts renal efferent arteriole and causes an increase in glomerular hydrostatic pressure. However if this change is sustained, it will result in glomerular injury and an accelerated loss of kidney function over time [27] Telmisartan and ramipril were found to be equally effective in slowing the loss of GFR in diabetic rats. This was in accordance with the findings of DETAIL study which showed comparable effects of telmisartan and enalapril on GFR decline. [28] With respect to the side effects, the increased levels of bradykinin and substance P that occur with ACE inhibition are responsible for adverse effects such as cough and angioedema. [29] There is also possibility of increased fibrosis in vascular smooth muscle cells of kidney via modulating TGF- β , MAPK pathways due to elevated blood levels of bradykinin produced by ACE inhibitors. [30] This may be one of the important factors responsible for decreased effectiveness of ACE inhibitor on long term.

CONCLUSION

Although telmisartan has a unique structure and pharmacological profile, there were no significant differences in urinary albumin excretion and creatinine clearance between telmisartan and ramipril treated diabetic groups. Our study revealed that telmisartan has a greater blood glucose lowering effect but the protective action on kidney was similar to ramipril. Therefore, telmisartan may be used as a safe alternative to ramipril, for controlling blood pressure in hypertensive patients with type 2 diabetes, providing at the same time renoprotection or in the treatment of diabetic nephropathy.

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