

ROLE OF LOSARTAN IN DIABETIC NEPHROPATHY

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ABSTRACT:

Based on World Health Organization statistics, the worldwide prevalence of diabetes is expected to increase from an estimated 155 million in the year 2000 to 300 million in 2025. Diabetic nephropathy is an important cause of morbidity and mortality and is now among the most common causes of end stage renal failure (ESRF) in the developed countries. Renin angiotensin system has been implicated in the pathophysiology of diabetic nephropathy and associated complications due to its specific effects on intraglomerular blood flow, resistance and general effects. In this clinical trial we have used antihypertensive agent i.e., Losartan (AT-1 receptor blocker) and found it to be effective both in delaying the development of renal damage secondary to diabetes and avoidance of other major complications associated to diabetic nephropathy.

INTRODUCTION

Diabetes mellitus is a chronic disorder of carbohydrate, fat and protein metabolism. Over 80% of the patients have so called type II diabetes also called non-insulin dependent diabetes mellitus. A defective or deficient insulin secretory response translating into impaired carbohydrate utilization is a characteristic feature of the DM, resulting in hyperglycemia (Crawford and Cotran, 1997). Diabetic nephropathy is an important cause of morbidity and mortality and now among the most common causes of end stage renal failure. Diabetic nephropathy is defined as persistent albuminuria, declining glomerular filtration rate and rising blood pressure. Microalbuminuria is an important and sensitive indicator of the risk of developing nephropathy in diabetes and hypertension (Hasle *et al.*, 1998). Increased urine albumin excretion appears before other measurable changes in renal function and is a marker of small blood vessel disease in kidney. The magnitude of proteinuria is also directly correlated with risk for end stage renal disease

and the rate of progression to renal failure. The greater the magnitude of proteinuria the faster is the loss of renal function (Keane and Eknoyan, 1999).

Losartan is the first (AG II) receptor antagonist. Losartan and its longer active metabolite (E-3174) are specific and selective AT1 receptor antagonists. Losartan interferes with the binding of formed angiotensin II to its endogenous receptor. The active metabolite, E3174 is 10-40 times more potent than Losartan and is primarily responsible for the therapeutic effects of Losartan. The affinity of Losartan and its metabolite is about 1000 fold greater for the AT1 receptor than the AT2 receptor.

Losartan is well absorbed, but undergoes substantial first pass metabolism. The systemic bioavailability is approximately 35%; about 14% of an oral dose is carboxylated in the liver to its active metabolite. Peak serum concentrations occur at 1 hour and 3-4 hours, respectively for the parent drug and metabolite. Losartan and its active metabolite

are highly protein bound, mainly to albumin. Losartan does not readily penetrate the blood brain barrier. Losartan is metabolized to its active and inactive metabolites by cytochrome P450 2c9 and 3A4. The terminal half-life of Losartan is 2 hours and 6 hours for its active metabolite. The maximal effects of Losartan usually occur within the first week of therapy. so provide a highly selective approach for regulating the effects of angiotensin II, by antagonism of the angiotensin type 1 (AT1) receptor and as a result. They block a number of angiotensin II effects that are relevant to the pathophysiology of cardiovascular disease, including vasoconstriction, renal sodium reabsorption, aldosterone and vasopressin secretion, sympathetic activation and vascular and cardiac hypertrophy and hypertrophy.

The kidney may be damaged by diabetes in three main ways by glomerular damage, ischemia resulting from hypertrophy of arterioles and ascending infection (Kumar and Clark, 1998).

Types of Diabetic Nephropathy:
Incipient diabetic nephropathy
Overt diabetic nephropathy

The interval from the clinical onset of diabetes to the development of clinical nephropathy tends to be shorter in NIDDM than in IDDM, probably because the former may be present for some years before diagnosis (Deckert and Grenfell, 1991).

The kidney plays an important role in the blood pressure regulation by at least three mechanisms: 1) Renin angiotensin system 2) sodium homeostasis 3) Renal vasopressor substances (Crawford and Cotran, 1997).

Renin angiotensin system regulates blood pressure, volume and electrolytes balance. Receptors for its principal effector Angiotensin II have been localized throughout the vasculature, heart, kidneys adrenals, nervous system and endocrine system. RAS in recent years have expanded from its purely systemic actions to the local paracrine and autocrine actions of angiotensin II, which

regulate intraorgan functions and have diffuse tropic effects (Siragy, 2000).

While the main actions of angiotensin II are mediated via a specific membrane bound G protein coupled receptor called angiotensin II subtype receptor or AT-1 receptor, actions include.

- 1) Generalized vasoconstriction especially marked in efferent arterioles of the kidney.
- 2) Increased release of nor-adrenaline from sympathetic nerve terminals reinforcing vasoconstriction and increasing the rate and force of contraction of heart.
- 3) Stimulating proximal tubular reabsorption of sodium ions.
- 4) Secretion of aldosterone from adrenal cortex.
- 5) Cell growth in the cardiac left ventricle and in the arterial wall.

These effects are initiated by the G protein, coupled AT-1 receptor, acting via the same intracellular tyrosine phosphorylation pathways as are used by Cytokines (Rang *et al.*, 1999).

PURPOSE OF STUDY

To evaluate the effects of Losartan on Proteinuria, GFR and Hypertension in diabetic patients (NIDDM).

Protocol/Methodology

The study was spread over 12 weeks and conducted in the department of Pharmacology and Therapeutics, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi. A total of 15 patients were selected from medical ward, nephrology OPD and ward and diabetic clinics of JPMC and other hospitals of Karachi. 15 normal subjects apparently healthy and not taking any medication were included as controls.

Inclusion Criteria:

- 1) NIDDM patients of either sex, age ranging from 30 to 60 years with FBS >

- 7.8 mmol/L (140mg/dl) and post prandial level >11.1 mmol/L (200 mg/dl) according to WHO criteria.
- 2) NIDDM patients with proteinuria (microalbuminuria +ve)
 - 3) Newly diagnosed and untreated hypertensive
 - 4) Fifteen normotensives and non-diabetics for control groups.

Exclusion Criteria:

- 1) Complicated hypertension i.e., IHD, LVF, CCF.
- 2) Diabetics with renal failure
- 3) IIDM
- 4) Pregnancy and lactating mothers
- 5) Contraindications to the use of Losartan
- 6) Patients taking drugs that can alter carbohydrates and fat metabolism i.e., beta-blockers and oral contraceptives
- 7) Any other concurrent medical illness affecting renal function.

MATERIALS

Drugs:

- 1) AT 1 receptor blocker Losartan 50mg.
- 2) Oral hypoglycemic Glibenclamide 5 mg.

Kits:

- 1) Sticks for microalbuminuria.
- 2) Kit for quantitative estimation of proteinuria.
- 3) Kits for urea and creatinine.
- 4) Serum potassium performed by auto analyzer easy lyte, medica.
- 5) Glucometer for serum glucose estimation.

Analyzers:

- 1) Selectra II Vitalab Germany
- 2) Micro lab 200 Merck, Germany

After explaining the limitations, consent was obtained from all study participants before enrolment. The study period consist of 90 days for each patient with follow up visits on every 15 days, the required information such as name, age, sex, occupation, duration of disease, previous medications, laboratory investigation, date of follow up visits, medical

history and physical examination were recorded on a proforma specially designed for this study.

Thirty persons in which 15 normal persons as control and 15 patients for study selected randomly and divided into groups.

Group N:

Fifteen persons that have normal blood pressure and normal range of blood glucose according to WHO criteria were selected as controls.

Group A:

Fifteen NIDDM patients with same above mentioned inclusion criteria were given diabetic diet with tab glibenclamide (Daonil) and tab Losartan (Cozaar) for a period of 90 days. Dosage of glibenclamide was adjusted according to the patients glycemic control.

Observations:

S. N.	Parameters	Time
1.	Urine for microscopic albuminuria (screening)	On day 0 if positive then day 4
2.	Fasting blood sugar	On day 4 and then two weekly
3.	Blood pressure	On day 4 and then two weekly
4.	24 hours urine for creatinine clearance and proteins	On day 0, 6th week and then 12th week
5.	Serum urea, creatinine and potassium	On day 0, 6th week and then 12th week

RESULTS

Urinary Proteins:

Urinary proteins among group N and A were found 24.80mg/24 hours + 1.67mg/24 hours and 247.40mg/24 hours + 38.50mg/24

hours respectively at day 0. The difference between control and group A in urinary proteins was found statistically significant NvA $P<0.001$ on day 0. The average difference in treated group A from baseline to final i.e. from day 0 to day 90 showed statistically significant reductions $P<0.02$, while the percentage change from baseline to final i.e. day 0 to day 90 have shown reduction by 38.42%.

Creatinine Clearance (GFR):

GFR among group N and A were found 95.53 ml/min + 2.13ml/min and 98.27ml/min + 4.89 ml/min respectively at day 0. The difference between control and group A in GFR was found statistically non-significant on day 0. The average difference in treated group A from baseline to final i.e., from day 0 to day 90 showed statistically non-significant value, while the percentage change from baseline to final i.e., day 0 to day 90 shows reduction of 5.16%.

Systolic Blood Pressure:

Systolic blood pressure among group N and A were found 118.00mmHg + 1.39mmHg and 129.60mmHg + 1.89mmHg respectively at

day 0. The difference between control and group A in systolic blood pressure was found statistically significant NvA $P<0.001$ on day 0. The average difference in treated group A from baseline to final i.e. from day 0 to day 90 showed statistically significant value $P<0.001$. While the percentage change from baseline to final i.e. from day 0 to day 90 have shown reduction of 8.95%.

Diastolic Blood Pressure:

Diastolic blood pressure among group N and A were found 75.67mmHg + 1.89mmHg and 90.00mmHg + 1.89mmHg respectively at day 0. The difference between control and group A in diastolic blood pressure was found statistically significant NvA $P<0.001$ on day 0. The average difference in treated group A from baseline to final i.e., from day 0 to day 90 showed statistically significant value $P<0.001$ while the percentage change from baseline of final i.e., from day 0 to day 90 have shown reduction of 5.18%.

DISCUSSION

Early diagnosis of DM is the key to its better and quicker control, and also to the

Table

Parameters	Groups	Day 0	Day 90	P value (D0-D90)	% Change
Urinary proteins	N	24.80 ± 1.67			
	A	247.40 ± 38.50	152.33 ± 19.11	$P<0.02$	38.42 ↓
GFR	N	95.53 ± 2.13			
	A	98.27 ± 4.89	93.20 ± 5.60	NS	5.16 ↓
Systolic Blood Pressure	N	118.00 ± 1.39			
	A	129.60 ± 1.89	118.00 ± 1.03	$P<0.001$	8.95 ↓
Diastolic Blood Pressure	N	75.67 ± 1.89			
	A	90.00 ± 1.05	76.33 ± 1.10	$P<0.001$	15.18 ↓

Mean values at day 0 and day 90 of control group N and treated group A of urinary protein GFR and Blood pressure.

Group N= Control group.

Group A – Diabetic diet + Tab Glibenclamide + Tab Losartan

Each group represents mean error of total observations, + indicates standard error of mean.

prevention if not the total eradication of its complications (Khan, 1985). The ideal anti hypertensive agent should lower the blood pressure without aggravating atherosclerosis and improve or delay the progression of nephropathy (DeFrozo *et al.*, 1995).

In our study the mean urinary proteins in 15 normal controls were 24.80mg/24hours + 1.62 mg/24 hours which is less than the normal 30 mg/24 hours. More than 30mg/24 hours is considered significant proteinuria and suggest existence of renal disease observed by Keane and EKnoyan (1999), Bilous (1991), Mogyrosi and Ziyadeh (1996). Our study group A shows significant proteinuria and we observed significant reduction in it during study a period of 90 days i.e., by 38.42% ($P<0.02$). Our result of Group A coincide with the result observed by Schrier (2002) in DCCT (Diabetes control and complications trial) was showed 54% reduction of microscopic and macroscopic albuminuria in diabetic nephropathic patients. The study of Russo *et al* (1999) showing reduction of 30% in proteinuria by Losartan as monotherapy coincide with our results showing 38.42% reduction in proteinuria. Our results is also supported by the study of BOS *et al* (2000) that shows the individual antiproteinuric response to ACEI positively correlated to the response to angiotensin type I (AT-1) receptor blockade in diabetic ($P<0.01$) as well as non diabetic patients ($P<0.01$). Anderson (2000) concluded that angiotensin II (AT-1) receptor antagonist Losartan reduces albuminuria and MABP (Mean arterial Blood pressure) similar to ACEI i.e., 33%-44% of albuminuria on Losartan and 45%-59% reduction of albuminuria on captopril, also favors our results showing 38.42% reduction of albuminuria in AT-1 receptor blocker. Lacourcieve (2000) shows urinary albumin excretion decreased significantly ($P<0.001$) in patients treated with Losartan from 64.1mg/d to 41.5mg/d. This also supports our results.

Our result of group A showing significant reduction of proteinuria $P<0.02$ (38.42) is also being supported by the study of Liou *et al*

(1995) and Hannedouche (1994) that shows 23% reduction in 24 hours protein excretion that accompanied Losartan therapy and is consistent with observation that blockade of the RAS reduces protein excretion in patients with proteinuria. Our results are also in agreement with previous reports that Losartan significantly decrease protein excretion among patients with large range proteinuria where GFR was maintained (Gansvoort *et al.*, 1994).

Our result is also by the study of Toto *et al* (1998) that shows antiproteinuric effects of Losartan in study population. This significant improvement in our parameters may be due to direct vasodilator action of the drug attributable to the modification of intrarenal haemodynamics or to a change in the glomerular permeability which improves the renal functions significantly. As mentioned by Remmuzzi *et al* (1997), who suggested RAS inhibition despite control of systemic blood pressure, effectively prevent proteinuria and glomerular injury while comparable blood pressure control by other antihypertensive was not associated with renal protection.

These results suggest that RAS inhibition could protect glomerular microcirculation by a mechanism that is not directly related to their antihypertensive action.

Our observation of group A regarding creatinine clearance was not statistically changed with the control is not supported by the study of Anderson (2000) that says GFR remained stable during 4 months treatment by Losartan in diabetic nephropathic patients simultaneously statistically non-significant (5.169%) change of creatinine clearance in group A is being supported by the same study of Anderson (2000).

Regarding changes in blood pressure of patients, we have found very significant changes in both systolic and diastolic blood pressure with a $P<0.001$ in treated group of patients. This reduction is due to the fact that our diabetic hypertensive nephropathic patients were previously untreated for hypertension.

CONCLUSION

Diabetes mellitus is a highly prevalent metabolic and vascular disease commonly associated with complications specifically nephropathy, hypertension, obesity, dyslipidaemia. As RAS has also been implicated in the pathophysiology of above mentioned complications, due to its effect on intraglomerular blood flow and resistance. So it is suggested that antihypertensive agents that inhibit the activation of RAS may be used, because early diagnosis and treatment is the key to better and quicker control of diabetic complications and most certainly prevention if not total eradication.

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