ROLE OF ANGIOTENSIN CONVERTING ENZYME INHIBITOR (CAPTOPRIL) IN PROTEINURIA, GLOMERULAR FILTRATION RATE AND LIPID PROFILE IN NIDDM PATIENTS

NASEEMULLAH SIDDIQUI, KAUSAR AAMIR*, AMEENA BEGUM** AND ABDUL LATEEF MAHESAR
Department of Pharmacology, Dow Medical College, Karachi
Department of Pharmacology, BMSI, JPMC, Karachi
*Department of Radiology, Liaquat National Hospital, Karachi

ABSTRACT
Clinical trial has shown the beneficial effects of captopril in delaying the progression of diabetic renal disease. We performed an analysis to determine the efficacy of captopril in slowing the progression of renal disease over a broad range of functional renal and extra renal impairment.

Treatment of individuals with microscopic and macroscopic proteinuria in NIDDM patients with preexisting hypertension and hyperlipidemia by captopril delays, inhibits or even reverses the disease.

INTRODUCTION
Based on WHO statistics the worldwide prevalence of diabetes is expected to increase from an estimated 155 million in year 2000 to 300 million in 2025 (Schrier, 2000). While over 80% of patients have so called type II diabetes also called non-insulin dependent diabetes mellitus (NIDDM). DM is a chronic disorder of carbohydrate, fat and protein metabolism. A defective or deficient insulin secretory response which translates into impaired carbohydrate utilization is a characteristic feature of the DM, resulting hyperglycemia (Crawford & Cotran, 1997).

Diabetic nephropathy is defined by persistent albuminuria, declining glomerular filtration rate and rising blood pressure. Diabetic nephropathy is an important cause of morbidity and mortality and now among the most common causes of end stage renal failure. Microalbuminuria is an important and sensitive indicator of risk of developing nephropathy in diabetes and hypertension (Haslett 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 and heart. 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 & F.Knoyan, 1999).

A decrease in the sensitivity of the body tissues to insulin causes hypertriglyceridemia and abnormal reduction in blood high density lipoprotein (t-IDL) levels, leading to a complex of metabolic abnormalities called pluri metabolic syndrome or insulin resistance syndrome (Rata Y., 1996).

The association between renal disease and hyperlipidemia has been known for more than 40 years. The association between hyperlipidemia and accelerated cardiovascular disease is now well accepted (Appel, 1991). Plasma lipid abnormalities and proteinuria go together even at non-nephrotic ranges and hyperlipidemia may act more as a disease modifier than as an initiator of progression (Mackenzie and Brenner, 1998).

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

Renin angiotensin system regulates blood pressure, volume and electrolytes balance. Receptors for its principal effect or, 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 intra organ 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 A T-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 re-absorption of sodium ion.
4. Secretion of aldosterone from adrenal cortex.

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).

Renin angiotensin system inhibitors include peptide analogues of angiotensin II such as saralasin a partial agonist, angiotensin converting enzyme inhibitors which prevents the conversion of angiotensin I to angiotensin II and more recently the non-peptide inhibitors of angiotensin 11 (AT-1) receptors (Levens & deGasparo, 1998).

**Purpose of Study**

To evaluate the effects of angiotensin converting enzyme (ACE) inhibitor on proteinuria, GFR and lipid profile in NIDDM patients.

**Protocol/Methodology**

The propose 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 for controls.

**Inclusion Criteria:**

1. NIDDM patients of either sex, ages ranging from 30 to 60 years with FBS > 7.8 mmol/L (140 mg/dl) and post prandial level > 11.1 mmol/L (200 mg/dl) according to WHO criteria.
2. NIDDM patients with proteinuria (micro albuminuria +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. IDDM.
4. pregnancy and lactating mothers.
5. Contraindications to the use of ACE1.
6. patients taking drugs that can alter carbohydratesand fat metabolism i.e. betablockers, oral contraceptives.
7. Any other concurrent medical illness affecting renal function.
8. Patients taking antihyperlipidemic drugs.
MATERIALS

**Drugs:**
1. ACE inhibitor Captopril 25 mg.
2. Oral hypoglycemic Glibenclamide 5mg

**Kits:**
1. Sticks for microalbuminuria.
2. Kit for quantitative estimation of proteinuria.
3. Kits for urea, creatinine and lipid profile.
4. Serum potassium performed by autoanalyzer 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 investigations, 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 for control, 15 patients for study selected randomly and divided into groups.

**Group N:**
Fifteen persons that have normal blood pressure and with normal range blood glucose according to WHO criteria selected for controls.

**Group A:**
Fifteen NIDDM patients with same above mentioned inclusion criteria were given diabetic diet with tab glibenclamide (Daonil 5 mg) and tab captopril (Capoten 25 mg) for a period of 90 days. Dosage of glibenclamide is adjusted according to the patients glycemic control.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Parameters</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Urine for microscopic albuminuria (for screening)</td>
<td>On day 0 if positive then day 4</td>
</tr>
<tr>
<td>2.</td>
<td>Fasting blood sugar</td>
<td>On day 0 and then two weekly</td>
</tr>
<tr>
<td>3.</td>
<td>Blood pressure</td>
<td>On day 0 and then two weekly</td>
</tr>
<tr>
<td>4.</td>
<td>24 hours urine for creatinine clearance and proteins</td>
<td>On day 0, 6th week and then 12th week</td>
</tr>
<tr>
<td>5.</td>
<td>Serum urea, creatinine and potassium</td>
<td>On day 0, 6th week and 12th week</td>
</tr>
<tr>
<td>6.</td>
<td>Lipid profile</td>
<td>On day 0, 6th week and then 12 week</td>
</tr>
</tbody>
</table>

**Observations:**

Fifteen diagnosed diabetic hypertensives with albuminuria were studied and 15 normal subjects also selected for control, controls and patients divided into two groups.

**Urinary Proteins:**
Urinary proteins among group N and A were found 24.80 ± 1.67 and 268.30 ± 44.37 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 clay 0 to 90 showed statistically significant value P < 0.001, while the percentage change from baseline to final i.e. day 0 to clay 90 have shown reduction of 50.70%.

**Creatinine Clearance (GFR):**
GFR among group N and A were found 95.53 ± 2.13 and 103.91 ± 7.73 respectively at day0. 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 significant value P<0.02, while the percentage change from baseline to final i.e. 0 day to 90 have shown reduction of 16.41%.
**Serum Cholesterol:**

Serum cholesterol among group N and A were found 177.76 ± 2.35 and 206.87 ± 7.27 respectively at day 0. The difference between control and group A in cholesterol was found statistically significant NvA $P<0.01$. The average difference in treated group from baseline to final i.e. from day 0 to 90 showed statistically significant value of $P<0.02$. While percentage change from day 0 today 90 have shown reduction of 12.40%.

**Serum Triglyceride:**

Serum triglyceride among group N and A were found 106.07 ± 3.63 and 179.87 ± 33.45 respectively at clay O. The difference between control and group A in triglyceride was found statistically significant on day 0 $P < 0.05$. In treated group A from baseline to final i.e. from day 0 to day 90 is statistically non-significant. While the percentage change from baseline to final i.e. from day 0 to day 90 have shown reduction of 17.45%.

**Serum high density lipoproteins (HDL):**

Serum HDL among group N and A were found 40.80 ± 0.91 and 42.07 ± 1.70 respectively at day O. The difference between control and group A in HDL was found statistically non significant. The difference between control and group A in HDL was fund statistically non significant. The average difference in treated group A from baseline to final i.e. from day 0 to day 90 is found statistically significant $P < 0.05$, while the percentage change from baseline to final day 0 today 90 have shown reduction of 5.39%.

**DISCUSSION**

Early diagnosis is the key to better and quicker control of diabetes and most certainly prevention if not total eradiction of the complication of diabetes (Khan, 1985). The ideal anti-hypertensive agent should lower the blood pressure without aggravating atherosclerosis and also improve or delay progresson of nephropathy (DeFronzo et al., 1995).

In our study the mean urinary proteins in 15 normal controls were 24.80 ± 1.62 mg/24 hours which is less than 30 mg/24 hours. More than 30 mg/24 hours is considered significant proteinuria, suggest existence of renal disease observed by Keane and Eknoyan (1999), Bilous (1991), Mogyorosi and Ziyadeh (1996). So our study group a show significant proteinuria. We observed significant reduction of proteinuria in treated group A during a period of 90 days i.e. 60.70% ($P<0.001$) our result of Group A coincides with the result observed by Schrier (2000) in DCCT (Diabetes control and complications trial) that showed reduction of 54% of albuminuria in the microscopic and macroscopic albuminuria in diabetic nephropathic patients. Analogous results were also reported by Mathisen et al. (1991) and Ravid et al. (1997) that showed 48.5% reduction of albuminuria with Captopril. Regarding creatinine clearance reduction of 16.41% in treated group A did not supported by the study of Anderson (2000) that says GFR remained stable during 4 months treatment by losartan and enalapril in diabetic nephropathic patients. Our study regarding GFR did not favour study conducted by Marre et al. (1987), Ruggenenti et al. (1998), Hollenberg (2000), they show compelling evidence that ACEI substantially reduce the rate of GFR decline. In the study of Taniwaki et al. (2000) increased urinary albumin (UAE) excretion was associated with elevation of GFR, possibly suggesting that one mechanism of increased UAE in early diabetic nephropathy may be associated with elevation of GFR. In a study Hoyer et al. (1993) evaluated that ACEI when given in chronic renal failure alter Pharmacokinetics properties like creatinine clearance which was reduced to <30ml/min are completely in favour of Hoyer study.

Our result, which show statistically significant change in cholesterol reduction i.e. $P<0.02$ (12.40%) in contrast to Neilson (1997) which showed minor reduction. Pollare (1989) have evaluated in his study that 48 hypertensive NIDDM were kept on
captopril show a decrease in the serum cholesterol from 230.43 mg/dl to 158.37 mg/dl, HDL-Cholesterol showed little change. Our study is in agreement with the study of Pollare as serum cholesterol level decreased from 206.87 mg/dl to 181.21 mg/dl, serum Triglyceride decreased from 179.87 mg/dl to 148.47 mg/dl. This is being related to improved glucose disposal, probably improvement in insulin sensitivity and significant correction of proteinuria caused by captopril, similar results regarding lipid profile in hypertensive NIDDM patients have been indicated in the studies conducted by Gagne (1993) and Ratheiser et al. (1992). Our study completely correlates with them. Keilani et al. (1993). Concluded that ACEI (Fosinopril) can result in a sustained reduction in serum total Cholesterol, LDL cholesterol and plasma lipoprotein (a) proteins levels in conjunction with a partial reduction in proteinuria. This conclusion completely supports our results in which lipids decreased in association with reduction in proteinuria. ACEI shown to reduce microalbuminuria in patients with diabetic and nondiabetic renal disease of the lipid abnormalities associated with overt proteinuria concluded by Ruilope (1998) also supports our results showing reduction of lipids with reduction of proteinuria.

**CONCLUSION**

In this study we concentrate on the primary and secondary aims of the trail which was to obtain data on the effects of ACE inhibitor. The efficacy variables were the changes in proteinuria, lipid profile and creatinine clearance.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Groups</th>
<th>Day 0</th>
<th>Day 90</th>
<th>P Value (D0-D9)</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary proteins</td>
<td>N</td>
<td>24.80 ± 1.67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>268.30 ± 44.36</td>
<td>132.26 ± 28.78</td>
<td>P&lt;0.001</td>
<td>50.70↓</td>
</tr>
<tr>
<td>GFR</td>
<td>N</td>
<td>95.53 ± 2.13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>103.91 ± 7.33</td>
<td>86.85 ± 4.13</td>
<td>P&lt;0.02</td>
<td>16.41↓</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>N</td>
<td>177.67 ± 2.35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>206.87 ± 7.22</td>
<td>181.20 ± 9.44</td>
<td>P&lt;0.02</td>
<td>14.40↓</td>
</tr>
<tr>
<td>Serum triglyceride</td>
<td>N</td>
<td>106.07 ± 3.63</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>179.87 ± 33.45</td>
<td>148.48 ± 23.28</td>
<td>Nonsignificant</td>
<td>17.45↓</td>
</tr>
<tr>
<td>Serum HDL</td>
<td>N</td>
<td>40.80 ± 0.91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>42.07 ± 1.70</td>
<td>39.80 ± 1.45</td>
<td>P&lt;0.05</td>
<td>5.39↓</td>
</tr>
</tbody>
</table>

Mean values at day 0 and day 90 of control group (N) and treated group A of urinary protein, GFR, serum cholesterol serum triglyceride and serum high density lipoproteins.
Group N = Control group
Group A = Diabetic diet + Tab. Glibenclamide + Tab. Captopril
Each group represents mean error of total observations
± indicates standard error of mean
Because RAS has been implicated in the pathophysiology of diabetic nephropathy due to its effects on intraglomerular blood flow and resistance. It has therefore been suggested that anti hypertensive agents that inhibit the activation of RAS may be helpful both in delaying the development of renal damage secondary to diabetes and avoidance of other major complications associated to diabetic nephropathy.

REFERENCES


Marie M., Lebnac M. and Suarez L. (1987). ACEI and kidney function in normo-


