1. ABSTRACT
Hypertension and diabetes-mellitus are common chronic conditions which frequently co-exist and can significantly affect the individual health care needs. Hypertension appears to be critically important in diabetes-mellitus not only because of its increased prevalence, but also because it accelerates both the microvascular and macrovascular complications of diabetes-mellitus. Controlling blood pressure in diabetics is positively more beneficial as far as progression of diabetic complications are concerned. The present work was undertaken to study the effects of various antihypertensives in diabetic as well as non-diabetic hypertensive patients and streptozotocin-diabetic and deoxycorticosterone-hypertensive rats.

The prevalence of hypertension among age and weight matched diabetic populations was found to be 47.85%. The occurrence of cardiac dysfunction was found to be higher in patients with the co-existence of the diabetes and hypertension than those with either essential hypertension or diabetes alone.

Incidences of hyperlipidaemia was found to be comparatively greater in diabetic patients with or without hypertension. This might be one of the factors responsible for the occurrence of cardiac dysfunction in such patients.

Treatment with enalapril, clonidine, nifedipine or atenolol monotherapy for 9 months in diabetic and non-diabetic hypertensive patients produced an effective control of blood pressure in majority of the patients. Enalapril and clonidine was found to favourably alter the lipid profile. Nifedipine, however, did not produce any significant change in lipid profile and atenolol was found to adversely affect the triglyceride and HDL-cholesterol levels. None of these four antihypertensive drugs used produce any significant change in fasting blood glucose levels in non-diabetic hypertensive patients.
In diabetic hypertensive patients, fasting blood glucose levels were found to be significantly decreased in patients receiving antihypertensive treatment along with glibenclamide, as compared to those who did not receive any antihypertensive therapy but only glibenclamide. Further, the dose of glibenclamide required in diabetic patients receiving any of the four antihypertensives was significantly less than those on glibenclamide alone. The dose of glibenclamide required was relatively higher in diabetic hypertensive patients receiving atenolol as compared to those receiving other antihypertensive agents.

Creatinine and urea levels were found to be higher in patients with NIDDM or uncontrolled hypertension. Both the levels were significantly higher in 18% of diabetic hypertensive and 15% of non-diabetic hypertensive patients during 9 months enalapril therapy. Other antihypertensive agents did not affect any of these parameters in both the groups of patients throughout the 9 months of therapy.

Results of the clinical studies suggested that enalapril and clonidine can be considered as the drugs of choice for the treatment of hypertension in a situation where the correction of dyslipidaemia or glycemic-control is warranted. It also appeared that atenolol should not be used, and more studies are required to prove the efficacy of nifedipine in such situation.

Using STZ-diabetic rat model, it was established from our laboratory that while atenolol produces deleterious effects in STZ-diabetic rats (Bangaru et. al. 1991), enalapril was found to produce a number of beneficial effects in STZ-diabetic rats such as prevention of cardiac depression, hyperlipidaemia, hypertension, bradycardia etc. (Bangaru et. al. 1992). Since clinical studies revealed a positive influence of the treatment with nifedipine and clonidine in diabetic patients, it was considered reasonable to undertake a similar study for these agents in STZ-diabetic rat model.
Administration of STZ in rats produced a significant loss of body weight, polydipsia and polyphagia. Treatment with clonidine significantly prevented loss of body weight in diabetic as well as diabetic hypertensive animals. Nifedipine treatment also significantly prevented the loss of body weight and polydipsia in diabetic animals.

Injection of STZ also produced a four fold increase in blood glucose levels which was associated with hypoinsulinaemia and glycosuria. In non-diabetic animals treatment with clonidine produced a rise in blood glucose levels whereas, in diabetic and diabetic hypertensive animals pretreatment with clonidine produced a significant decrease in glucose as well as insulin levels. Treatment with nifedipine produced variable effect on insulin as well as glucose levels, not only in different groups of animals but also at different interval of time of the treatment. In control animals there was an increase in serum insulin observed at the end of 10 days of treatment with nifedipine. Later, nifedipine treatment caused a decrease in insulin levels, serum glucose levels were found to be decreased after 10 days of nifedipine treatment but it was not significant. Similarly there was slight but insignificant increase in serum glucose levels at the end of 20 to 42 days of the treatment. In diabetic rats, nifedipine treatment caused a further decrease in insulin levels. Without any further rise in serum glucose levels after 30th and 42nd days of nifedipine treatment. In diabetic rats, nifedipine treatment caused a further decrease in insulin levels without any further rise in serum glucose levels after 30 and 42 days of treatment.

Administration of STZ or DOCA alone produced a significant elevation of blood pressure in rats. Administration of DOCA in STZ diabetic animals failed to produce an additive rise in blood pressure. Animals treated with either clonidine or nifedipine did not show any
elevation of blood pressure as compared to control. STZ produced significant bradycardia along with hypothyroidism in rats. Treatment with clonidine or nifedipine prevented not only the STZ-induced bradycardia but also STZ-induced hypothyroidism in rats.

LVDP was found to be significantly lower at higher filling pressures in hearts obtained from diabetic animals as compared to those from controls. This was significantly prevented by treatment with clonidine or nifedipine. Cardiac hypertrophy index (Wet heart wt/Body wt) was significantly increased in diabetic animals and this was also prevented by clonidine as well as nifedipine treatment. STZ induced cardiomyopathy as revealed from the histopathological study of myocardium from diabetic hearts was also found to be prevented by treatment with clonidine and nifedipine.

STZ also produced increase in total cholesterol, triglycerides and LDL-cholesterol levels in STZ diabetic rats. Treatment with clonidine or nifedipine significantly prevented the increase in total cholesterol and triglyceride levels. Serum creatinine and BUN levels were also found to be increased in diabetic rats. Clonidine treatment prevented this rise in creatinine levels. SGPT and SGOT levels were found to be increased in diabetic as well as DOCA diabetic rats. Clonidine treatment prevented the rise in SGPT levels in both the groups of animals. Histopathological study of the liver from diabetic animals revealed that there was vacuolisation and disruption in the normal arrangement of hepatic cords and sinusoids as compared to that of control animals. Clonidine treatment partially prevented this changes in liver obtained from diabetic rats.

In conclusion clinical studies revealed that while atenolol adversely affects the lipid profile in diabetic as well as non-diabetic hypertensive patients, nifedipine offers neutral effects on lipid profile in this patients. Enalapril treatment favourably alters the lipid levels in both the groups of patients. Clonidine was also found to
produce favourable effects on lipid levels in both diabetic as well as non-diabetic hypertensive patients. The results of animal studies were found to be consistent with those of clinical observation except for the high mortality observed with clonidine treatment. The preference of antihypertensives in diabetic patients among four groups used may be considered as enalapril > clonidine > nifedipine > atenolol.

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