SOME PHARMACOLOGICAL STUDIES OF LACIDIPINE
IN SOME EXPERIMENTAL ANIMALS

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SUMMARY AND CONCLUSION

Lacidipine is a new dihydropyridine calcium channel blocker that has been introduced in recent years. It is characterized by long lasting effect, high vasoselectivity and potent antioxidant properties.

The present work was carried out to screen the pharmacological effects of lacidipine on isolated rabbit aortic strip and isolated rabbit heart. Also the effect of lacidipine on experimentally induced atherosclerosis in rabbits and its role in L-NAME induced hypertension in rats were evaluated.

Moreover the effect of lacidipine on isoprenaline induced heart failure in rats was studied, finally we evaluated the protective effect of lacidipine on cyclosporine induced nephrotoxicity in rats.

Data obtained in the present study pointed out that lacidipine antagonized KCl, norepinephrine and angiotensin II induced contractions in isolated rabbit aortic strip and produced dose dependent reduction of basal myocardial contractility of isolated rabbit heart. The negative inotropic effect of lacidipine was found to be much less than that of nifedipine.

Atherosclerosis was experimentally induced in rabbits by cholesterol feeding in a dose of (100mg/kg) for 10 weeks. Over the same period a group of cholesterol fed - rabbits were treated with lacidipine in a dose of (1mg/kg). At the end of the 10 weeks, blood samples were taken for determination of total cholesterol, LDL, HDL and triglycerides levels. The histological changes in the aorta were determined microscopically by making sections stained with hematoxyline and eosin.
Summary and Conclusion

Cholesterol feeding produced significant (P < 0.05) elevation of total cholesterol, LDL and triglyceride levels while serum HDL level showed insignificant change. Lacidipine administration had no effect on the hyperlipidemia induced by cholesterol feeding.

Histopathological examination of aortic sections at the end of the study period showed no atherosclerotic lesions detected in normal control rabbits. The aortic segments isolated from cholesterol – fed rabbits showed marked degeneration of the aortic intima, foamy histiocytic cell accumulation and fatty streak lesion formation. Lacidipine administration concurrently with cholesterol feeding produced marked reduction in the degree of atherosderotic lesions.

Chronic nitric oxide synthase inhibition was induced in rats by giving them L-NAME in a dose of (400mg/L) in the drinking water for 5 weeks. From the beginning of the 3rd week, lacidipine was given to a group of rats in a dose of 1mg /kg in addition to L-NAME containing drinking water. At the end of the study period blood pressure measurements showed marked elevation of both systolic and mean arterial blood pressure in the non-treated hypertensive rats in comparison to control rats. Lacidipine treatment produced significant (P < 0.05) decrease of systolic and mean arterial blood pressure by the end of the study period.

Microscopic examination of renal sections stained with Masson’s trichrome stain and Van-Giesson stain showed marked increase in the extra cellular matrix deposition indicating renal glomerulosclerosis and arteriosclerosis of non treated hypertensive rats.

Examination of renal sections of lacidipine treated group of rats, showed marked reduction of the extracellular matrix mass. Thus,
lacidipine was found to protect the kidneys from L-NAME induced arteriosclerosis and glomerulosclerosis in rats.

Heart failure was experimentally induced in rats by a single S.C. injection of isoprenaline in a dose of 150mg/kg. After 2 weeks, there was significant decrease (P < 0.05) in the systolic and mean arterial blood pressure, as well as in the aortic blood flow. While in the group of heart failure, renal blood flow showed only insignificant (P > 0.05) decrease compared to control group of rats. Also, there was no significant difference in the heart rate between the two groups.

Lacidipine treatment in a dose of 1mg/kg immediately after isoprenaline injection for the following 2 weeks resulted in significant increase (P < 0.05) in both renal and aortic blood flow, while heart rate, systolic and mean arterial blood pressure showed no significant (P > 0.05) change in comparison to control group.

Histopathological examination of cardiac sections of control group showed no detectable abnormality in cardiac smooth muscle cells. Sections of heart failure group revealed myocyte degeneration & necrosis and interstitial fibrosis. Lacidipine administration effectively decreased these changes.

Cyclosporine induced nephrotoxicity was experimentally induced in rats by daily oral administration of cyclosporine in a dose of 50mg/kg for 2 weeks. The protective effect of lacidipine was evaluated in a group of rats that received lacidipine in a dose of 1mg/kg 3 days before and 2 weeks concurrently with cyclosporine.

At the end of the experiment there was marked elevation of serum urea and creatinine levels in the cyclosporine nephrotoxic group.
Lacidipine treatment significantly (P < 0.05) reduced the elevated serum urea and creatinine. Renal histopathological examination showed no detectable abnormalities in the renal tubules and glomeruli of control rats, sections from cyclosporine nephrotoxic group of rats showed tubular degeneration, hyaline degeneration of glomerular basement membrane and calcification in the renal tubules and renal interstitium.

Lacidipine treatment effectively prevented the cyclosporine induced histopathological changes in the kidney.

In conclusion, lacidipine decreased KCl, norepinephrine and angiotensin II induced contractions in isolated rabbit aortic strip. Also, it inhibited basal myocardial contractility to lesser extent than that of nifedipine. Furthermore lacidipine produced a protective effect on experimentally induced atherosclerosis in rabbits. Also it exerted antihypertensive and nephroprotective effects in the model of L-NAME induced hypertension in rats. Meanwhile, lacidipine has cardioprotective effect on isoprenaline induced heart failure in rats and can effectively antagonize the renal functional and structural changes induced by cyclosporine in rats.