

A COMPARATIVE STUDY ON THE EFFECT OF FELODIPINE AND PROPRANOLOL ON SERUM LIPID PROFILE OF RABBITS

TRUPTI REKHA SWAIN*, MANORAMA DAS, S. KANUNGO,
D. MUKHERJI, S. S. MISHRA AND M. C. DAS

*P.G. Department of Pharmacology,
S. C. B. Medical College,
Cuttack - 753 007*

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Abstract : Effect of felodipine on serum lipids of rabbits was studied and was compared with that of propranolol. Lipid parameters were estimated at basal (0 wk), end of 4th and 16th week of diet/drug administration by using standard kits for analysis. There was a significant increase in mean serum cholesterol, TG, VLDL_C, LDL_C and decrease in HDL_C, ($P < 0.05$) in the group of rabbits receiving Atherogenic diet (AD)/Propranolol. This effect was maximally observed in rabbits receiving both AD and propranolol. This change was satisfactorily prevented when felodipine was administered from very beginning ($P < 0.001$). In addition, there was a significant increase in HDL_C (28.89%) of rabbits receiving felodipine from beginning. Thus both AD and propranolol have dyslipidemic effect and early administration of felodipine favorably changes all lipid parameters.

Key words : atherogenic diet (AD)
felodipine

serum lipids
propranolol

INTRODUCTION

Atherosclerosis is now the principal cause of death in western world and would become a major public health problem by the end of this century in almost every developing country (1). Dyslipidemia which is now on an increasing trend is intimately associated with ischemic heart disease (IHD), diabetes and hypertension which are together responsible for morbidity and mortality in human beings to a large extent. Thus prevention and management of dyslipidemia has become important for

both pharmacologists and clinicians. Pharmacotherapy of hypertension, IHD and dyslipidemia which co-exist on many occasions is complicated with various drug related adverse effects including adverse lipid changes. Calcium antagonists (CAs) are considered now-a-days to be a revolutionary group of drugs because of their expanded use like hypertension, IHD, arrhythmias and many non-cardiovascular conditions.

During last 15 years, several studies have shown that CAs are endowed with favourable effects on serum lipids (2-4).

*Corresponding Author

However, most of these studies lack detailed analysis of serum lipids. Contrary to these findings other workers have shown that these drugs reduce atherosclerotic lesions in cholesterol fed rabbits without any significant effect on serum lipids (5-6). Among the CAs, dihydropyridines (DHP) are most commonly used in clinical practice and said to have the most potent antiatherosclerotic property (2). With this interesting background, felodipine, a newer class of DHP group was used in the present study to test if this drug at a low dose known to have antihypertensive effect in human (7) has any effect on serum lipid profile of diet induced dyslipidemic rabbits. This effect was compared with that of propranolol whose dyslipidemic effect is already established (8-11).

METHODS

60 male white New Zealand rabbits from a single vender M/S. F.N. Chakraborty (Calcutta) weighing between 2-3 kg. were randomly selected and placed under controlled condition. Afterward, they were assigned to 6 equal diet/treatment group. Gr-1 and 2 rabbits served as control. Gr-1 rabbit received vehicle (0.2 ml of 95% Ethyl alcohol per day) along with standard diet (S.D), and rest of the groups (2-6) received atherogenic diet (AD) from beginning.

Gr-3 rabbits received felodipine (0.46 mg/kg/day) (7) from beginning (day-0) of AD while Gr-4 received same dose of drug after 4 weeks of AD. Gr-5 rabbits were treated with propranolol (4 mg/kg/day) from beginning while group-6 received combination of propranolol and felodipine, (0.46 mg/kg Felo + 4 mg/kg Prop) from beginning. The total

study period extended for 16 weeks. AD was prepared by adding 2% cholesterol (Sigma Chemicals) and 3% coconut oil to standard diet (7). The average amount of diet per rabbit was 100 gms/day. Water was given *ad lib.* Both drug and vehicle was administered daily orally by tube at about 10 A.M. Blood was collected from central ear artery by a no-21 pediatric needle after an overnight fast at the beginning of study (basal) and at the end of both 4th & 16th week. Blood samples were estimated for total cholesterol (T_c) (12), serum triglyceride (13) (TG), serum HDL_C (14), VLDL_C and LDL_C (15). Lipid parameters were estimated by using kits (GLAXO).

At the end of study one rabbit from each group was sacrificed to detect atheromatous patch formation after staining with Sudan - IV.

Statistical analysis was done using Student's "t" test for two sample test. P value < 0.05 is considered significant.

RESULTS

Mean serum total cholesterol (T_c), TG, VLDL_C, LDL_C and HDL_C at basal, end of 4th and 16th week of different rabbit groups are shown in Table I. In Gr-1 receiving S.D. and vehicle there was no change in different serum lipid values. All lipid parameters in Gr-2 and 5 increased significantly at the end of both 4th and 16th week except serum HDL_C which decreased ($P < 0.05$). But the changes were distinctly more marked in Gr-5 rabbits than Gr-2. Felodipine when administered from beginning along with AD in Gr-3, there was significant rise of serum HDL_C and rest of the lipid parameters remained significantly less compared to

TABLE I: Effect of diet/drug on serum lipid level (mg%) in different groups of rabbits (n=10).

Groups		Total Cholesterol	Triglyceride	LDL Cholesterol	VLDL Cholesterol	HDL Cholesterol
1. SD+V	0wk	63.39 ± 5.85	76.11 ± 5.4	24.86 ± 5.85	15.22 ± 1.08	23.31 ± 1.05
	4wk	58.08 ± 6.19	81.65 ± 4.3	17.6 ± 7.0	16.33 ± 0.87	24.15 ± 1.41
	16wk	73.0 ± 5.18	82.66 ± 3.07	28.94 ± 6.2	16.98 ± 0.62	27.08 ± 2.25
2. AD	0wk	62.20 ± 2.72	76.24 ± 5.52	18.29 ± 2.3	15.32 ± 1.10	28.59 ± 2.15
	4wk	107.62 ± 4.73 ^{☆☆}	94.35 ± 3.79 [☆]	68.13 ± 7.2 ^{☆☆}	18.87 ± 0.79	20.62 ± 2.33 [☆]
	16wk	202.72 ± 8.94 ^{☆☆}	102.6 ± 6.28 [☆]	163.11 ± 7.0 ^{☆☆}	20.51 ± 1.26 [☆]	19.10 ± 0.62 ^{☆☆}
3. AD+FELO ₀	0wk	66.61 ± 4.53	79.0 ± 4.46	25.75 ± 5.9	15.8 ± 0.89	25.06 ± 1.54
	4wk	74.53 ± 5.92	81.58 ± 3.64	30.84 ± 5.2	16.32 ± 0.79	27.37 ± 1.8
	16wk	72.83 ± 4.08	79.38 ± 4.47	24.65 ± 8.2	15.88 ± 0.89	32.30 ± 2.86 [☆]
4. AD+FELO ₄	0wk	68.39 ± 5.85	72.67 ± 4.97	28.41 ± 4.2	15.13 ± 0.99	24.85 ± 0.91
	4wk	122.9 ± 9.62 ^{☆☆}	87.70 ± 4.56 ^{☆☆}	84.9 ± 9.2 ^{☆☆}	17.54 ± 0.91	20.46 ± 1.49 [☆]
	16wk	119.7 ± 8.53 [☆]	99.76 ± 6.39 ^{☆☆}	75.15 ± 8.1 [☆]	19.95 ± 1.28	24.60 ± 1.83
5. AD+PROP	0wk	62.23 ± 5.12	81.21 ± 4.30	21.29 ± 4.9	16.44 ± 0.86	24.5 ± 1.26
	4wk	109.82 ± 12.95 [☆]	100.98 ± 4.96 ^{☆☆}	68.48 ± 10.2 [☆]	20.20 ± 0.99	21.14 ± 0.71 [☆]
	16wk	214.10 ± 9.95 ^{☆☆}	118.56 ± 3.05 ^{☆☆}	177.69 ± 9.8 ^{☆☆}	23.71 ± 0.61 [☆]	12.7 ± 1.04 ^{☆☆}
6. AD+FELO +PROP	0wk	64.86 ± 4.48	81.0 ± 4.76	23.23 ± 4.6	16.2 ± 0.95	25.43 ± 0.77
	4wk	112.85 ± 16.04 ^{☆☆}	96.34 ± 4.32	71.56 ± 12.6 [☆]	19.27 ± 0.86	22.02 ± 0.96 [☆]
	16wk	123.59 ± 9.24 ^{☆☆}	110.27 ± 3.61 [☆]	81.97 ± 8.9 [☆]	22.05 ± 0.72 [☆]	19.57 ± 1.19 [☆]

S.D = Standard diet
A.D. = Atherogenic diet
FELO₀ = Felodipine from beginning
FELO₄ = Felodipine after 4 week
PROP = Propranolol

[☆]P<0.05, ^{☆☆}P<0.001 when compared to control levels before treatment. Values are mean ± SEM.

Gr-2 rabbits receiving AD alone. Changes in serum lipids in Gr-4 (AD+FELO₄) was like that of Gr-2 upto the end of 4th week. After addition of felodipine at the end of 4th week in Gr-4 the level of T_c and LDL_c was significantly less than Gr-2 at the end of 16th week. In Gr-6 (AD+Prop+FELO) T_c, TG, LDL_c and VLDL_c increased significantly whereas HDL_c decreased (P<0.05) at the end of study, but the corresponding rise and fall

was observably less compared to Gr-5 rabbits receiving propranolol and atherogenic diet.

Intimal surface of ascending thoracic aorta after staining with Sudan - IV showed atheromatous change in Gr-2 and 5 rabbits (Upper arrow mark, photo - 1). No change was observed in the intima of rest of rabbits receiving either early or late felodipine.

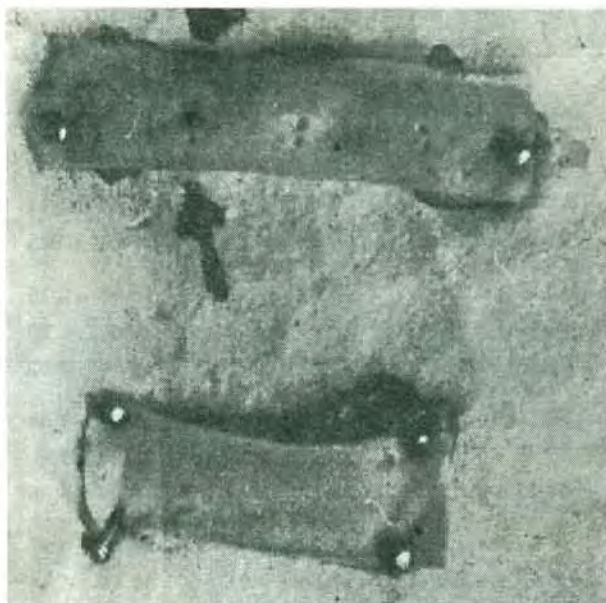
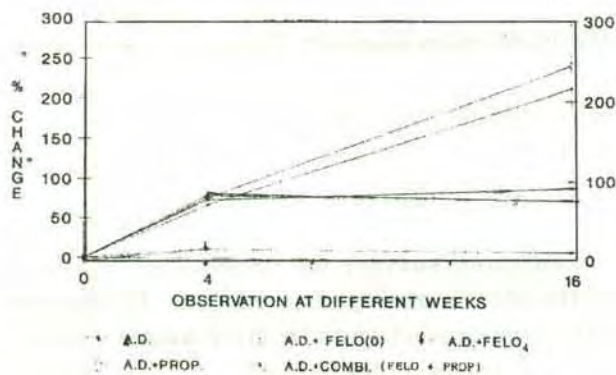


Fig. 1: Intimal surface of thoracic aorta after staining with Sudan-IV.

UPPER - Atheromatous change in rabbits treated with propranolol and AD.

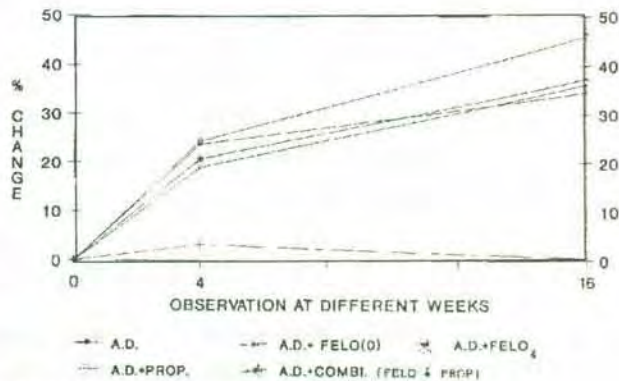
LOWER - No change in intima receiving felodipine along with AD with or without propranolol.

EFFECT OF DRUGS ON SERUM CHOLESTEROL OF RABBITS



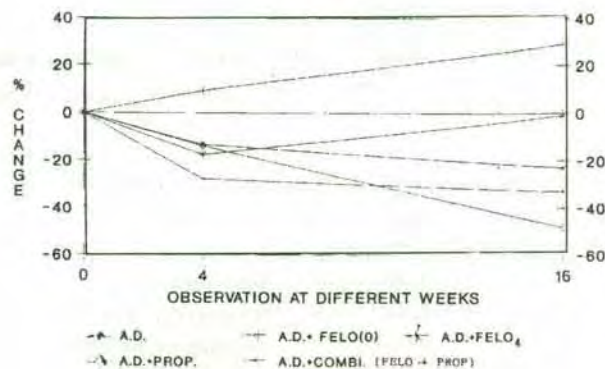
GRAPH NO. 1

EFFECT OF DRUGS ON SERUM TRIGLYCERIDE OF RABBITS



GRAPH NO. 2

EFFECT OF DRUGS ON SERUM HDL_c LEVEL OF RABBITS



GRAPH NO. 3

DISCUSSION

Atherogenic diet (AD) and propranolol in Gr-2 and 5 increased adversely T_c, TG, LDL_c and VLDL_c whereas HDL_c decreased significantly. The higher rate of rise (T_c, TG, LDL_c, VLDL_c) and fall (HDL_c) in Gr-5 compared to Gr-2 in this study is due to additive effect of propranolol and AD. The dyslipidemic feature of propranolol was

significantly more marked on serum TG, VLDL_c and HDL_c than other parameters. This dyslipidemic feature of both AD and propranolol has been proved by many workers (9,10,16,17). Administration of felodipine from beginning along with AD in Gr-3, has successfully prevented the rise in T_c, TG, LDL_c, and VLDL_c both at the end of 4th week and 16th week compared to Gr-2 receiving AD alone. Interestingly HDL_c increased by 28.89% at the end of study in Gr-3. Late administration (after 4 weeks of AD) of felodipine in Gr-4, though is able to prevent further aggravation, the dyslipidemia that already existed could not return to normal. Significant lower values of T_c and LDL_c at the end of 16th-week in Gr-4, than Gr-2 could be explained due to protective effect of felodipine. The rate of rise of T_c, TG, VLDL_c, LDL_c and fall of HDL_c in Gr-6 rabbits (AD + FELO + PROP) is significantly less when compared to corresponding values of Gr-5 (AD + PROP). All these findings strongly suggest a favorable effect of felodipine on different serum lipid parameters. Similar effect of other calcium antagonists have been reported by Will et al (3), Overturf et al (18), Swain et al (19) and Ohata et al (2).

In contrast, some workers (7) could not observe any beneficial effect of CAs, when administered after 10 weeks of starting of AD. So also in our study when felodipine was added to AD at the end of 4 weeks (Gr-4), it was unable to show similar beneficial effect as compared to early administration in Group-3. This can be explained by the

fact that, delayed administration of these drugs are supposed to have negligible influence once a state of persistent dyslipidemia leads to excess vascular smooth muscle lipid content. For appreciation of favorable effect of felodipine, its early administration is a key factor as observed by us in our previous study (19).

Atheromatous changes in ascending aorta of rabbits treated with propranolol and AD and its absence in rabbits receiving felodipine in other groups satisfactorily correlates different serum lipid levels in different groups of rabbits as well as reconfirms the beneficial effect of felodipine.

The favorable effect of felodipine on serum lipids has not been explained conclusively. Increased uptake and degradation of LDL by skin fibroblasts, aortic endothelial cells, smooth muscle cells by augmenting LDL receptor proliferation (20), induction of *denovo* apoprotein synthesis are thought to be the possible mechanisms.

From this study, we can conclude that propranolol has adverse effects on all lipid parameters which is more marked on TG, VLDL_c and HDL_c. Felodipine when administered early alters all the lipid fractions favourably and can successfully prevent the dyslipidemic effects of propranolol. Further studies confirming these findings may consider the use of felodipine in dyslipidemic situations.

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