Effect of Aspirin & Nicotinic Acid Derivative on Hyperlipoproteinemic Rabbits

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SUMMARY

The diagnosis of lipid disorders in terms of lipoprotein abnormalities is now well established and it appears that the efficacy of many hypolipidemic agents is related to the specific lipo-protein disorder being treated. The current emphasis in the field of atherosclerosis involves an evaluation of the relative contribution of individual lipoproteins to atherogenic potential with age and sex difference.

During the course of present work the effect of aspirin is observed on the ratio of HDL, LDL on male white rabbits with usual diet for 120 days. Our result showed that aspirin significantly reduced the hyperlipoproteinemia in treated rabbits as compared to untreated (pathological) groups of rabbits.

INTRODUCTION

Human low-density lipoprotein (LDL) and high-density lipoprotein (HDL) are two of the major carriers of cholesterol in human blood.[1] Plasma level of LDL has been suggested to have a direct correlation with the deposits of cholesterol in plaques on arterial walls and subsequent atherosclerosis.[2,3] There appears to be a positive correlation between LDL and inverse relationship between HDL cholesterol and risk of developing coronary artery disease.[4,5] The cholesterol concentration of HDL represents approximately 25% of total serum cholesterol in normal individuals and less than 20% in those with coronary artery disease.[6,7]

Kritchevsky[8] in 1964 indicated that there is a wide variation among the animal species in the susceptibility of atherosclerosis. Atherosclerosis is characterised by the deposition of cholesterol and other lipids in the connective tissues of the arterial walls.

The increase risk of premature occlusive arterial wall by LDL, in proportion to its plasma concentration in developing arterial lesion.

Increase blood viscosity may well be related to the risk of premature arterial disease in HLP. However, increased blood viscosity may reduce coronary blood flow, and reduction in blood viscosity. by plasma exchange may relieve angina and intermittent claudication in HLP patient.

The lipid rich areas of arterial lesion contain high concentration of bounded lipoprotein[9]. The lipoprotein is released by plasmin, suggesting that it is bound to fibrin.

It was also found that there is an increase in plasminogen in HLP. This is consistent with the increase reported in patient with premature coronary disease, in whom HLP is common.

A wide variety of agents have been reported to be effective in hypercholesterolemic condition such as, Clofibrate, Nicotinic acid and its derivative etc.

Aspirin have been used as anticoagulant as well antilipoproteinemic agent. As cyclo-oxygenase an enzyme which converts arachidonic acid into prostaglandin and thromboxane, can be inhibited by aspirin. The step of inhibition by aspirin has been shown in the schemalic diagram.

Studies in animals and human tissues however, suggested that the enzyme in platelets and

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vascular tissue may be differentially sensitive to acetylation by Aspirin.

MATERIAL AND METHODS

All experiments are carried out on healthy rabbits weighing 1. 5-2.0 kg. Rabbits are classified into the following four groups, each group comprised of 4 rabbits: The details of the groups and their treatment with drugs has already been described elsewhere (Saify etal [10]). In brief for the determination of HDL cholesterol chemical kit (Cat No. 400971 and Cat No. 231347) and for LDL cholesterol chemical kit (Cat No. 124931) of Boehringer Mannheim was used.

RESULT

Results are summarized in Table 1,2,3 and 4. Table 1 shows the level of serum HDL cholesterol (mg/100 ml) in all the 4 groups of rabbit before the treatment with drugs, i.e., for 120 days.

Group 1 (control) shows a slight fluctuation in the level of HDL & LDL cholesterol over the period of 120 days when compared from their own controls (15.98 ± 1.07) and (32.65 ± 3.89). The maximum increase in HDL cholesterol is found at 60th days (17.62 ± 0.70) and maximum increase in LDL at 120 days is found (30.64 ± 2.69).

In Group 2 (pathological control) there is a definite and progressive increase in HDL and LDL cholesterol level with the passage of time. Maximum level in HDL cholesterol is (92.43 ± 5.60 mg/100 ml) and LDL cholesterol is (840.10 ± 140.68 mg/100ml).

Similarly, two other groups (3rd and 4th show a highly significant (< .001) and progressive increase over control values. These two groups are used later on to see the effect of drugs.

Table-3, 4 show the effect of drug on the level of serum HDL and LDL cholesterol (Treated A and Treated B group.) This table also shows the level of serum HDL & LDL cholesterol of the pathological control rabbits without giving any medicine (untreated group).

Group A is given Aspirin and it shows a progressive decrease in HDL and LDL cholesterol levels at each time point which is statistically

TABLE 1: THE CONCENTRATION OF SERUM α-LIPOPROTEIN (HDL) IN CONTROL AND EXPERIMENTAL RABBITS (mg/100 ml)

	CONTROL						PATHOLOGICAL CONTROL						
DAYS	1A	1B	1C	1D	MEAN	±SEM	2A	2B	2C	2D	MEAN	±SEM	P
00	13.39	18.62	16.18	15.73	15.98	1.07	16.77	20.53	17.22	14.57	17.27	1.23	
20	15.21	18.97	17.23	15.84	16.81	0.83	30.26	41.36	20.56	18.66	27.71	5.21	N.S.
40	13.82	17.54	15.91	16.23	15.87	0.77	48.07	57.22	33.06	27.30	41.41	6.85	> .01
60	15.97	19.21	18.22	17.11	17.62	0.70	54.31	77.20	42.57	40.50	53.64	8.41	< .01
80	12.63	17.90	17.50	16.58	16.15	1.20	61.24	86.09	67.59	55.00	67.48	6.71	<.001
100	14.21	20.10	17.97	14.33	16.65	1.44	78.63	93.15	82.10	71.36	81.31	4.53	<.001
120	13.55	19.62	16.54	16.01	16.43	1.24	87.63	106.53	95.27	80.31	92.43	5.60	<.001

	GROUP 'A'							GROUP 'B'						
DAYS	3A	3B	3C	3D	MEAN	±SEM	P	4A	4B	4C	4D	MEAN	±SEM	P
00	13.96	15.24	10.31	17.53	14.26	1.50		11.72	16.51	12.15	18.64	14.75	1.68	
20	18.98	26.06	15.64	28.31	22.24	2.96	N.S.	27.98	39.55	29.36	30.00	31.72	2.64	< .01
40	30.15	42.32	27.30	44.64	36.10	4.32	< .01	36.44	51.21	38.20	42.09	41.98	3.29	>.001
60	51.23	63.54	36.96	60.20	52.98	5.93	>.001	50.10	79.00	47.39	63.23	59.93	7.23	<.001
80	63.34	76.14	45.01	78.60	65.77	7.68	<.001	66.38	93.65	64.15	84.19	77.09	7.11	<.001
100	70.11	87.32	51.56	91.03	75.00	9.04	<.001	75.86	109.07	81.33	96.06	90.58	7.49	<.001
120	86.03	100.41	64.73	116.69	91.96	11.02	<.001	88.70	105.62	89.91	118.47	100.67	7.07	<.001

TABLE 2 : THE CONCENTRATION OF SERUM β-LIPOPROTEIN (LDL) IN CONTROL AND EXPERIMENTAL RABBITS (mg/100 ml)

DAYS	CONTROL 1A	1B	1C	1D	MEAN	± SEM	PATHOLOGICAL CONTROL 2A	2B	2C	2D	MEAN	± SEM	P
00	38.42	21.39	37.28	33.51	32.65	3.89	23.63	18.92	31.96	27.60	25.52	2.78	
20	31.40	23.13	31.27	30.20	29.00	1.97	80.10	91.37	98.21	84.15	88.45	3.99	< .001
40	37.77	25.58	25.13	28.51	29.24	2.93	184.36	175.65	181.63	169.53	177.79	3.30	< .001
60	30.10	19.18	29.88	32.33	27.87	2.94	299.63	216.03	384.11	298.01	299.44	34.31	< .001
80	28.14	17.13	32.31	35.16	28.18	3.94	407.67	329.15	656.24	401.20	448.56	71.47	< .01
100	38.55	21.11	28.88	31.20	29.93	3.59	558.19	456.55	901.26	684.22	650.05	95.80	< .001
120	33.16	23.18	35.63	30.59	30.64	2.69	635.11	576.21	1163.79	985.31	840.10	140.68	< .01

DAYS	GROUP 'A' 3A	3B	3C	3D	MEAN	± SEM	P	GROUP 'B' 4A	4B	4C	4D	MEAN	± SEM	P
00	20.33	36.59	18.64	27.78	25.83	4.09		31.96	21.31	26.54	28.11	26.98	2.20	
20	93.24	116.54	66.39	86.25	90.60	10.34	< .01	57.28	33.38	49.97	57.64	49.56	5.67	<.02
40	169.15	239.41	130.15	194.27	183.24	22.90	<.001	189.64	82.99	121.23	164.31	139.54	23.55	<.01
60	256.30	401.64	227.26	306.33	297.88	38.24	<.001	392.29	173.11	312.15	356.00	308.38	47.97	<.01
80	345.10	775.27	286.34	655.14	515.46	118.50	<.001	666.15	251.07	409.73	544.39	467.83	89.23	<.01
100	469.09	982.34	319.51	786.19	639.28	150.13	< .01	882.31	382.55	541.12	727.17	633.28	108.85	<.01
120	562.32	1296.15	379.54	916.22	788.55	202.57	< .01	1018.73	463.98	684.98	958.87	781.94	128.04	<.01

TABLE 3 : CHANGES PRODUCED BY ASPIRIN (A) AND NICOTINIC ACID DERIVATIVE (B) IN HDL LEVEL OF RABBIT SERUM (mg/100ml)

DAYS	CONTROL 1A	1B	1C	1D	MEAN	± SEM	PATHOLOGICAL CONTROL 2A	2B	2C	2D	MEAN	± SEM	P
00	13.55	19.62	16.54	16.01	16.43	1.24	87.63	106.53	95.27	80.31	92.43	5.60	
05	15.07	18.33	17.03	17.29	16.93	0.68	73.20	96.24	87.32	77.01	83.44	5.20	
10	16.53	19.62	15.75	17.99	17.47	0.85	66.54	92.33	76.56	63.59	74.75	6.48	
15	13.96	17.11	18.32	16.23	16.40	0.92	57.38	89.26	61.36	54.17	65.54	8.04	
20	12.99	16.60	17.01	15.98	15.64	0.90	43.65	86.42	48.38	38.27	54.18	10.94	

DAYS	TREATED 'A' 3A	3B	3C	3D	MEAN	± SEM	P	TREATED 'B' 4A	4B	4C	4D	MEAN	± SEM	P
00	86.03	100.41	64.73	116.69	91.96	11.02		88.70	105.62	89.91	118.47	100.67	7.07	
05	67.51	75.36	51.24	95.39	72.37	9.16	N.S.	57.28	86.16	75.66	99.51	79.65	12.60	N.S.
10	36.29	46.28	44.36	57.00	45.98	4.26	< .01	36.57	51.08	46.19	75.32	52.29	8.91	> .05
15	27.82	28.19	27.99	21.56	26.39	1.61	< .01	21.42	28.71	22.64	38.20	27.74	3.83	< .01
20	18.76	16.22	15.07	13.95	16.00	1.03	< .02	8.75	13.60	10.71	15.13	12.04	1.43	< .01

TABLE 4: CHANGES PRODUCED BY ASPIRIN (A) AND NICOTINIC ACID DERIVATIVE (B) IN LDL LEVEL OF RABBIT SERUM (mg/100 ml)

DAYS	CONTROL 1A	1B	1C	1D	MEAN	± SEM	PATHOLOGICAL CONTROL 2A	2B	2C	2D	MEAN	±SEM
00	33.16	23.18	35.63	30.59	30.64	2.69	635.11	576.21	1163.79	985.31	840.10	140.68
05	31.23	24.56	34.91	28.64	29.83	2.17	580.29	464.09	886.27	810.23	685.22	98.30
10	34.82	23.98	36.55	32.52	31.96	2.78	301.20	327.59	716.33	633.28	494.60	105.55
15	30.41	21.64	32.11	33.17	29.33	2.62	298.17	209.11	523.01	412.26	360.63	68.24
20	36.29	22.15	36.99	34.59	32.50	3.48	184.51	176.46	467.33	281.04	277.33	67.64

DAYS	TREATED 'A' 3A	3B	3C	3D	MEAN	±SEM	P	TRERATED 'B' 4A	4B	4C	4D	MEAN	±SEM	P
00	562.32	1296.15	379.54	916.22	788.55	202.57		1018.73	465.98	684.20	958.87	781.94	128.04	
05	318.95	781.25	215.53	627.00	485.68	131.69	N.S.	752.19	318.17	329.54	726.50	531.60	120.07	N.S.
10	137.50	412.09	164.79	319.90	258.57	65.05	N.S.	321.26	233.06	262.97	336.83	288.53	24.38	N.S.
15	85.26	182.66	79.33	169.20	129.11	27.19	<.02	196.88	132.91	128.65	196.24	163.67	19.00	<.05
20	18.51	37.82	15.99	22.65	23.74	4.88	<.01	34.27	18.07	20.54	27.98	25.21	3.68	<.01

significant ($\leq$ .01) and the level reached to near normal on 20th day.

Nicotinic acid derivative treated group (Group-B) also shows a progressive decrease in serum HDL and LDL cholesterol level starting from the 5th day through 20th day though statistically not significant except on 15 and 20th days (<.01).

DISCUSSION

The goal of serum lipid lowering in HLP is prevention of atherosclerosis complications. This effect is believed to operate through an influence on the serum lipoprotein levels of the development of atheroma. The complications of the atherosclerosis may result, in acute myocardial infarction, angina pectoris, and sudden death. A more direct way of measuring the effect of the lipid lowering treatment would determine the concentration of lipoprotein, i.e., LDL & HDL before and after treatment[11].

Plasma lipoproteins concentration is studied in rabbits with HLP and in matched controls. It is suggested that the premature arterial disease associated with HLP may be related to increase blood viscosity, which reduces arterial blood flow, and gradually the symptoms of HLP decreases.

In these studies it is suggested that low dose of aspirin (100 mg/day) may be of value in thrombotic condition and may act as antilipoproteinemic agent where the infrequent use of 300mg aspirin may be of no value.

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