

EFFECT OF A NEWLY SYNTHESIZED COMPOUND ON VARIOUS SERUM LIPID PARAMETERS

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SUMMARY: A new compound, 2-methoxy phenacyl nicotinium bromide, was synthesized and its effect on serum total lipid, phospholipid and triglyceride were observed in experimentally induced hyperlipidemic rabbits. It was found that 2-methoxy phenacyl nicotinium bromide exhibit antilipemic activity.

Key Words: Antilipemic, nicotinic acid derivative, experimently induced hyperlipidemia in rabbits.

INTRODUCTION

Analysis of serum lipid and particularly of lipoproteins provide a useful classification of hyperlipidemia as devised by WHO and based particularly on the work of Fredrickson (1). In this classification there are five major types of hyperlipidemia due to either genetic defect in lipid metabolism or environmental factors such as diet, alcohol and drugs including estrogens and corticosteroids.

Hyperlipidemia may be primary or secondary. Primary hyperlipidemia is recognized as either familial or sporadic disease, while secondary hyperlipidemia occurs in association with diabetes mellitus, hypothyroidism, nephrotic syndrome, biliary obstruction and pancreatitis. Nicotinic acid is found to lower triglyceride level at the same time decreasing the concentration of plasma FFA followed by rebound. It was suggested that this effect may partly be the cause of reduction of serum triglyceride and cholesterol level, while nicotinic acid is a well known potent lipid lowering agent exerts its action by decreasing hepatic production of very low density lipoprotein (2-6).

But nicotinic acid itself has side effects such as cutaneous flushing, gastrointestinal disturbances and increased risk for the development of gall stones, therefore its use is limited (7).

To overcome this problem the derivatives of nicotinic acid were prepared and their pharmacological action were observed.

MATERIALS AND METHODS

Animals and their feeding schedule:

White healthy male rabbits supplied by local supplier weighing 1 to 1.5 kg were kept individually in marked cages throughout the experimental period of 150 days.

The animals were grouped as follows:

Group 1: Normal Control (NC) (n = 5), received normal diet throughout the whole experimental period.

Group 2: Pathological Control (PC) (n = 5), rabbits in this group received normal diet plus 200 mg of cholesterol and 2 g of butter per day for 120 days (0 to 120th day) and then cholesterol and butter were withdrawn and the rabbits were kept on normal diet only (121st to 150th day).

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Table 1: Showing the effect of normal diet on the serum triglyceride mg/100 ml in group 1 normal control (NC) rabbits.

DAYS	1A	1B	1C	1D	1E	MEAN	SE	P
00	33.00	24.00	37.00	55.00	46.00	39.00	4.77	
20	38.00	30.00	38.00	51.00	57.00	42.80	4.37	
40	57.00	32.00	49.00	56.00	60.00	50.80	4.50	
60	64.00	35.00	51.00	55.00	56.00	52.20	4.28	
80	92.00	39.00	45.00	56.00	62.00	58.80	8.25	
100	90.00	45.00	50.00	69.00	65.00	63.80	7.09	
120	91.00	62.00	56.00	75.00	70.00	70.80	5.37	
130	99.00	65.00	58.00	67.00	69.00	71.60	6.30	
140	101.00	50.00	61.00	63.00	72.00	69.00	7.72	
150	97.00	66.00	60.00	70.00	73.00	73.20	5.66	

Group 3: Treated (T), this group received normal diet plus 200 mg of cholesterol and 2 g of butter per day (0 to 120th day) and then cholesterol and butter were withdrawn and the rabbits were kept on normal diet plus 30 g of 2-methoxy phenacyl nicotinium bromide for the remaining days (121st to 150th day).

Note: Normal diet; Loosan (Alfa Alfa), Gram seeds (Chick Pea) and bread.

Cholesterol (Merck W. Germany).

Butter (Lurpak Holland).

BIO-CHEMICAL ANALYSIS

5 ml of blood from rabbits (non-fasting) was collected from the marginal ear vein on every 20th day up to 120 days (0, 20, 40, 60, 80, 100, 120) and then on every 10th day (130, 140,

Table 2A: Showing the effect of cholesterol/butter rich diet on the serum triglyceride mg/100 ml in group 2 pathological control (PC) rabbits.

DAYS	2A	2B	2C	2D	2E	MEAN	SE	P
00	32.00	50.00	67.00	43.00	45.00	47.40	5.11	
20	39.00	92.00	90.00	51.00	49.00	64.20	9.95	
40	41.00	110.00	100.00	53.00	55.00	71.80	12.39	
60	47.00	159.00	111.00	121.00	96.00	106.80	16.29	
80	73.00	197.00	120.00	201.00	109.00	140.00	22.64	
100	95.00	260.00	190.00	203.00	171.00	183.80	23.88	
120	145.00	338.00	233.00	292.00	205.00	242.60	30.05	

Table 2B: Showing the effect of normal diet.

130	129.00	286.00	200.00	247.00	133.00	199.00	27.66	
140	120.00	277.00	191.00	228.00	95.00	182.20	30.08	
150	108.00	196.00	162.00	201.00	73.00	148.00	24.14	

Table 3A: Showing the effect of cholesterol/butter rich diet on the serum triglyceride mg/100 ml in group 3 treated (TI) rabbits.

DAYS	3A	3B	3C	3D	3E	MEAN	SE	P
00	63.00	36.00	79.00	24.00	37.00	47.80	9.00	
20	80.00	65.00	83.00	101.00	91.00	84.00	6.37	
40	127.00	88.00	110.00	214.00	179.00	143.60	17.41	
60	169.00	97.00	173.00	287.00	268.00	198.80	29.12	
80	185.00	146.00	225.00	396.00	380.00	266.40	43.25	
100	222.00	155.00	287.00	521.00	405.00	318.00	45.22	
120	262.00	187.00	319.00	628.00	437.00	366.60	45.17	
Table 3B: Effect of 2-methoxy phenacyl nicotinium bromide 30 mg/day.								
130	193.00	126.00	283.00	326.00	342.00	254.00	38.50	N.S.
140	152.00	101.00	205.00	298.00	215.00	194.20	22.15	N.S.
150	89.00	71.00	158.00	102.00	151.00	114.20	17.91	N.S.

150). The blood samples were centrifuged and serum was separated. In these serum samples total lipid, phospholipid and triglyceride levels were determined according to the instruction sheets provided with the reagent kits.

All the values are expressed as the mean and standard error, T Test is performed and P values are observed according

to Bailey (8).

The reagent kits and Control Sera were supplied by Boehringer Mannheim (W. Germany). For the determination of serum total lipid, phospholipid and triglyceride reagent kits having Cat. No. 124303, 124974 and 701912 respectively were used.

Table 4: Showing the effect of normal diet on the serum phospholipid mg/100 ml in group 1 normal control (N.C.) rabbits.

DAYS	4A	4B	4C	4D	4E	MEAN	SE	P
00	181.00	115.00	176.00	127.00	163.00	152.40	11.90	
20	190.00	126.00	180.00	150.00	180.00	165.20	10.60	
40	185.00	140.00	152.00	160.00	185.00	164.40	8.00	
60	176.00	147.00	155.00	152.00	182.00	162.40	6.90	
80	154.00	130.00	160.00	147.00	180.00	154.20	7.30	
100	160.00	135.00	163.00	154.00	168.00	156.00	5.10	
120	163.00	125.00	162.00	158.00	170.00	155.60	7.10	
130	168.00	111.00	139.00	171.00	189.00	155.60	12.30	
140	175.00	125.00	121.00	168.00	195.00	156.80	12.90	
150	138.00	138.00	127.00	168.00	196.00	153.40	10.80	

Table 5A: Showing the effect of cholesterol/butter rich diet on the serum phospholipid mg/100 ml in group 2 pathological control (P.C.) rabbits.

DAYS	5A	5B	5C	5D	5E	MEAN	SE	P
00	161.00	147.00	196.00	167.00	153.00	164.80	7.60	
20	277.00	213.00	145.00	118.00	232.00	197.00	25.90	
40	318.00	229.00	181.00	127.00	191.00	209.20	28.40	
60	375.00	216.00	238.00	154.00	327.00	262.00	35.40	
80	494.00	257.00	302.00	195.00	403.00	330.20	47.60	
100	535.00	512.00	496.00	283.00	458.00	456.80	40.50	
120	847.00	784.00	618.00	519.00	776.00	708.80	54.20	
Table 5B: Showing the effect of normal diet.								
130	653.00	519.00	437.00	485.00	688.00	556.40	43.50	
140	476.00	374.00	275.00	309.00	427.00	372.20	39.20	
150	292.00	257.00	180.00	260.00	347.00	267.20	24.28	

Table 6A: Showing the effect of cholesterol/butter rich diet on the serum phospholipid mg/100 ml in group 3 treated (T1) rabbits.

DAYS	6A	6B	6C	6D	6E	MEAN	SE	P
00	159.00	183.00	122.00	137.00	198.00	159.80	12.60	
20	178.00	216.00	195.00	286.00	286.00	232.20	20.40	
40	427.00	264.00	278.00	372.00	263.00	320.80	29.90	
60	463.00	280.00	321.00	505.00	221.00	358.00	48.50	
80	571.00	296.00	334.00	964.00	318.00	496.60	113.60	
100	665.00	613.00	619.00	1317.00	367.00	716.20	155.80	
120	874.00	779.00	667.00	1521.00	414.00	851.00	117.40	
Table 6B: Effect of 2-methoxy phenacyl nicotinium bromide 30 mg/day.								
130	695.00	387.00	214.00	1493.00	335.00	624.80	206.70	N.S.
140	418.00	152.00	98.00	1027.00	169.00	372.80	154.40	N.S.
150	186.00	97.00	79.00	608.00	71.00	208.20	91.30	N.S.

Table 7: Showing the effect of normal diet on the serum total lipid mg/100 ml in group 1 normal control (N.C.) rabbits.

DAYS	7A	7B	7C	7D	7E	MEAN	SE	P
00	273.00	205.00	291.00	240.00	269.00	255.60	13.47	
20	274.00	209.00	252.00	262.00	268.00	253.00	10.36	
40	285.00	228.00	260.00	251.00	280.00	260.80	9.22	
60	293.00	226.00	265.00	261.00	292.00	267.40	10.99	
80	305.00	238.00	279.00	274.00	299.00	279.00	10.54	
100	325.00	242.00	283.00	292.00	307.00	289.80	12.44	
120	317.00	256.00	295.00	304.00	327.00	299.80	10.94	
130	334.00	255.00	298.00	307.00	335.00	305.80	13.10	
140	341.00	262.00	290.00	325.00	392.00	322.00	19.80	
150	352.00	291.00	305.00	365.00	372.00	337.00	14.60	

Table 8A: Showing the effect of cholesterol/butter rich diet on the serum total lipid mg/100 ml in group 2 pathological control (P.C.) rabbits.

DAYS	8A	8B	8C	8D	8E	MEAN	SE	P
00	243.00	252.00	308.00	255.00	270.00	265.60	10.29	
20	392.00	421.00	378.00	302.00	399.00	378.40	18.17	
40	505.00	596.00	483.00	397.00	541.00	504.40	29.40	
60	615.00	821.00	633.00	594.00	779.00	688.40	41.50	
80	825.00	982.00	821.00	865.00	922.00	883.00	27.46	
100	1142.00	1491.00	1220.00	1111.00	1032.00	1199.20	70.50	
120	1591.00	1972.00	1563.00	1678.00	1631.00	1687.00	66.00	
Table 8B: Showing the effect of normal diet.								
130	1200.00	1562.00	1139.00	1348.00	1251.00	1300.00	66.10	
140	917.00	1136.00	824.00	1074.00	956.00	981.00	47.17	
150	656.00	823.00	734.00	785.00	632.00	726.00	33.96	

Table 9A: Showing the effect of cholesterol/butter rich diet on the serum total lipid mg/100 ml in group 3 treated (T.I.) rabbits.

DAYS	9A	9B	9C	9D	9E	MEAN	SE	P
00	245.00	279.00	269.00	213.00	289.00	259.00	12.18	
20	301.00	394.00	401.00	519.00	490.00	421.00	34.50	
40	689.00	561.00	621.00	830.00	622.00	664.60	41.18	
60	925.00	722.00	892.00	1170.00	923.00	926.40	63.90	
80	11.23.00	921.00	1120.00	1791.00	1218.00	1234.60	131.70	
100	1429.00	1269.00	1591.00	2329.00	1522.00	1628.00	164.00	
120	1794.00	1551.00	1746.00	2739.00	1845.00	1935.00	185.20	
Table 9B: Effect of 2-methoxy phenacyl nicotinium bromide 30 mg/day								
130	1302.00	856.00	1075.00	2295.00	1369.00	1379.40	220.09	N.S.
140	768.00	475.00	557.00	1684.00	797.00	856.20	193.01	N.S.
150	387.00	226.00	360.00	858.00	495.00	465.20	95.82	N.S.

RESULTS AND DISCUSSION

In our laboratory other nicotinic acid derivatives were already prepared and their effects were observed on rabbits serum and their results were compared with Aspirin (9). This paper deals only with the effects of 2-methoxy phenacyl nicotinium bromide i.e. triglycerides, phospholipid and total lipids.

Detail of the effect of 2-methoxy phenacyl nicotinium bromide on serum triglyceride, phospholipid and total lipid are given in Tables 1-9 but the important features are as follows:

This compound showed lowering effect on serum triglyceride from 366 mg/100ml to 114mg/100ml, in case of phospholipid it was from 851 mg/100ml to 208 mg/100ml and for total lipid it was from 1935 mg/100 ml to 465 mg/100ml.

One of most interesting aspect of this research is that the synthesis of this compound, 2-methoxy phenacyl nicotinium bromide is very simple and its yield is also 61%.

During present course of research, the structure elucidation was done with the help of spectroscopic techniques (UV, IR, NMR and Mass).

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