The Effects of *N*(4-Methylphenyl)diphenimide on Lipid Metabolism of Sprague Dawley Rats

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N(4-Methylphenyl)diphenimide proved to be an effective hypolipidemic agent in rats at 10 and 20 mg/kg/day. Both serum cholesterol and triglyceride levels were reduced significantly. Decreases in tissue lipids as well as VLDL cholesterol levels were observed. HDL-cholesterol was elevated even at 10 mg/kg/day. The agent was equally effective in hyperlipidemic diet-induced rats, lowering serum lipids and VLDL- and LDL-cholesterol while elevating HDL-cholesterol levels. The drug interfered with the incorporation of ^{3}H-cholesterol and ^{3}H-palmitic acid into chylomicrons, VLDL, and LDL. The two precursors were incorporated at a higher rate into HDL. ^{3}H-Leucine was incorporated into chylomicrons, VLDL, and LDL at a higher rate, but not into HDL. Reduced uptake of the precursor for lipid synthesis was noted in tissues after treatment with the drug.

KEY WORDS: hypolipidemic agents; diphenimide; high-density lipoprotein (HDL)-cholesterol.

INTRODUCTION

A number of cyclic imides have previously been investigated as potential hypolipidemic agents including phthalimide, saccharin, naphthalimide, glutarimide, and succinimide (1–7). One particular compound, *N*-(4-methylphenyl)-diphenimide, was active at 20 mg/kg/day, lowering serum cholesterol 67% and triglyceride levels 66% in rats (5). This compound was one of the few cyclic imides which, after 2 weeks of administration, elevated high-density lipoprotein (HDL)-cholesterol levels significantly (5). The present study focuses on establishing the efficacy of *N*(4-methylphenyl)-diphenimide as a hypolipidemic agent in rats.

MATERIALS AND METHODS

Source of Material

N(4-methylphenyl)diphenimide (Fig. 1) was synthesized and the physical and chemical characteristics were identical to those reported previously (4). Radioisotopes were obtained from New England Nuclear. Biochemical reagents and cofactors were purchased from Sigma Chemical Co. Sprague Dawley male rats were obtained from Charles River Laboratory. Animals were maintained in light cycles of 12 hr at 72°F. Food and water were ad libitum.

Normolipidemic Study

Sprague Dawley male rats (~230 g), maintained on Agway ProLab Animal Diet, as outlined previously were administered orally *N*(4-methylphenyl)diphenimide suspended in 1% CMC at 10 mg/kg/day for 8 weeks. Weekly blood samples were obtained by tail vein bleeding (8).

Hyperlipidemic Rats

Sprague Dawley rats (~300 g) were placed on a commercial diet (U.S. Biochemical Corporation Basal Atherogenic Diet) as reported earlier (9). When the serum cholesterol and triglyceride levels were shown to be elevated, i.e., after 14 days, administration of *N*(4-methyl-phenyl)-diphenimide at 20 mg/kg/day orally was commenced and continued for the next 4 weeks. The rats were maintained on the Basal Atherogenic Diet throughout drug administration.

Animal Weight, Organ Weight, and Food Consumption

Control and treated Sprague Dawley male rat weights were obtained and expressed as a percentage of the initial body weight (week 0). Food consumption (g/day/rat) was noted for weeks 6, 7, and 8 for control and treated rats. After 8 weeks of drug administration, the animals were sacrificed and individual organ weights were obtained for control and treated rats (9).

Enzymatic Studies

In vivo enzymatic studies were performed using 10% homogenates of liver and small intestinal mucosa prepared in 0.25 m*M* sucrose + 0.001 *M* (ethylenedinitrillo)tetraacetic acid, pH 7.2, obtained from Sprague Dawley male rats after oral administration of the agent for 8 weeks at a dose of 10 mg/kg/day. Enzymatic methods used for these studies were reported previously (9,10–19).

Tissue Lipid Levels

Sprague Dawley male rats (~230 g) which were treated for 8 weeks with *N*-(4-methylphenyl)diphenimide at 10 mg/kg/day were sacrificed and tissue samples of the liver, small intestinal mucosa, and aorta were removed. A 24-hr fecal sample was also obtained. A 10% homogenate in 0.25 *M* sucrose + 0.001 *M* EDTA was prepared for each tissue. An aliquot (2 ml) of the homogenate was extracted by modified methods of Folch *et al.* (20) and Bligh and Dyer (21) as outlined previously.

Serum Lipoprotein Fractions

Sprague Dawley male rats treated for 8 weeks with *N*(4-methylphenyl)diphenimide at 10 mg/kg/day orally were anes-

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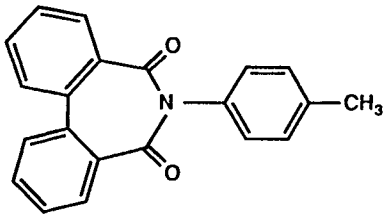

Fig. 1. Structure of *N*(4-methylphenyl)diphenimide.

thetized with ether, and blood (~10 ml) was collected from the abdominal vein. Serum was separated from whole blood by centrifugation at 3500 rpm. Aliquots of the serum were separated into chylomicrons, very low-density lipoproteins (VLDL), HDL, and low-density lipoproteins (LDL) (25), and the apoprotein was separated as reported previously (27).

Rate of Lipoprotein Synthesis

Sprague Dawley rats (~300 g) were administered with *N*(4-methylphenyl)diphenimide at 20 mg/kg/day for 14 days. On day 13, 20 μCi of L-[4,5-^{3}H(N)]leucine (58.5 Ci/mmol), [1,2-^{3}H]cholesterol (40.7 μCi/mmol), [^{14}C]palmitic acid (57 μCi/mmol), or ^{32}P (H_3PO_4) buffer (2 μCi) was injected i.v. into the tail vein in isotonic saline, pH 7.4 (29–31). Sixteen hours later, lipoproteins were collected as previously outlined (28,29).

RESULTS AND DISCUSSION

N(4-Methylphenyl)diphenimide was shown to be an effective hypolipidemic in rats at 10 mg/kg/day, orally. Serum cholesterol levels continued to be lowered by drug treatment through 8 weeks with a 60% reduction; however, the serum triglyceride levels were not reduced more than 50% in the fourth week. Serum triglyceride levels subsequently leveled off at 41% reduction (Table I). Withdrawal of the drug at 8 weeks led to a complete reversal of the reduction of lipids induced by drug treatment at week 10, indicating that the drug caused no irreversible damage to those organs which contributed to the reduction of cholesterol and triglycerides in the serum compartment. There were no observable side effects of the drug based on total body weight or organ weights. Food consumption or caloric intake was not affected by drug treatment.

The lipid content of tissue, e.g., cholesterol, triglycerides, and neutral lipids, was reduced without a comparable protein content reduction after 8 weeks of drug administration (Table II). It should be noted that cholesterol and neutral lipid levels in the aorta were markedly reduced, i.e., 43 and 49%, respectively, which should be helpful in treating atherosclerosis. Lipid excretion into the bile and feces was increased after 2 weeks when the drug was administered at 20 mg/kg/day (3,5). The fecal cholesterol levels were reduced in this study for 8 weeks at 10 mg/kg/day (Table II). This result could be due to the lower dose used in this study or a time difference in the effects of the agent. Nevertheless,

Table I. Effects of *N*(4-Methylphenyl)diphenimide at 10 mg/kg/Day Orally on Serum Lipid Levels in Sprague Dawley Rats (N = 8)

Weeks	Serum cholesterol (mg/dl)	Serum triglycerides (mg/dl)	Weight increase from day 0 (g)	
			Control	Treated
0	75 ± 5	128 ± 7	341	337
2	59 ± 5*	81 ± 6*	382	361
4	38 ± 4*	64 ± 5*	416	384
6	36 ± 4*	92 ± 8	433	408
7	31 ± 8*	76 ± 6*	450	423
8	24 ± 3*	76 ± 3*	457	431
10[a]	93 ± 5	136 ± 8	—	—

	Serum cholesterol (mg/dl)	Serum triglyceride (mg/dl)
Normogenic		
No treatment	75 ± 6	112 ± 7
2 weeks, 20 mg/kg/day	26 ± 3*	30 ± 5*
4 weeks, 20 mg/kg/day	23 ± 4*	30 ± 5*
2 weeks, 10 mg/kg/day	58 ± 5*	81 ± 6*
4 weeks, 10 mg/kg/day	38 ± 4*	64 ± 5*
Hyperlipidemic		
No treatment	344 ± 9	269 ± 7*
1 week, 20 mg/kg/day	62 ± 4*	48 ± 4*
2 weeks, 20 mg/kg/day	34 ± 3*	33 ± 5*
2 weeks, 10 mg/kg/day	285 ± 7*	250 ± 9
4 weeks, 10 mg/kg/day	143 ± 6*	179 ± 6*

[a] Dosing ceased at week 8.
* $p \leq 0.001$, students's "t" test.

Table II. Tissue Lipids After 8 Weeks of Drug Administration of *N*(4-Methylphenyl)diphenimide at 10 mg/kg/Day Orally to Sprague Dawley Male Rats ($N = 8$)

	Percentage of control ($X \pm SD$)					
	mg lipid extracted	Cholesterol	Triglyceride	Neutral lipids[y]	Phospholipids	Protein
Liver						
Control	100 ± 6[a]	100 ± 7[b]	100 ± 6[c]	100 ± 6[d]	100 ± 8[e]	100 ± 6[f]
Treated	71 ± 6	73 ± 5	79 ± 5*	83 ± 4*	113 ± 7	97 ± 8
Small intestine						
Control	100 ± 6[g]	100 ± 7[h]	100 ± 5[i]	100 ± 5[j]	100 ± 7[k]	100 ± 7[l]
Treated	101 ± 5	88 ± 7	115 ± 6	65 ± 5	102 ± 8	108 ± 6
Aorta						
Control	100 ± 5[m]	100 ± 6[n]	100 ± 42[o]	100 ± 6[p]	100 ± 7[q]	100 ± 5[r]
Treated	70 ± 6	57 ± 5*	96 ± 5	51 ± 5	99 ± 6	110 ± 7
Feces						
Control	100 ± 7[s]	100 ± 6[t]	100 ± 6[u]	100 ± 8[v]	100 ± 7[w]	100 ± 6[x]
Treated	108 ± 6	79 ± 5	101 ± 5	90 ± 8	106 ± 6	106 ± 6

[a]50.5 mg/g wet tissue. [b]9.18 mg/g wet tissue. [c]6.37 mg/g wet tissue. [d]15.76 mg/g wet tissue. [e]27.19 mg/g wet tissue. [f]12.02 mg/g wet tissue. [g]68.20 mg/g wet tissue. [h]12.02 mg/g wet tissue. [i]11.20 mg/g wet tissue. [j]16.98 mg/g wet tissue. [k]20.06 mg/g wet tissue. [l]42.0 mg/g wet tissue. [m]11.58 mg/g wet tissue. [n]2.84 mg/g wet tissue. [o]1.86 mg/g wet tissue. [p]3.39 mg/g wet tissue. [q]5.70 mg/g wet tissue. [r]6.99 mg/g wet tissue. [s]67.5 mg/g wet tissue. [t]5.77 mg/g wet tissue. [u]0.95 mg/g wet tissue. [v]15.20 mg/g wet tissue. [w]28.8 mg/g wet tissue. [x]11.71 mg/g wet tissue. [y]Fatty acid and mono- and diglycerols.
*$p \leq 0.001$, students's "t" test.

serum lipoprotein fractions showed twofold reductions in VLDL cholesterol levels and twofold elevatations in HDL cholesterol levels after 8 weeks' administration of drug at 10 mg/kg/day (Table III). Compared to the 2 weeks of drug at 20 mg/kg/day, the chylomicron and LDL cholesterol levels were reduced more drastically. The elevation of HDL triglyceride levels in the 2-week study at 20 mg/kg/day was not present in the 8-week study. Phospholipid content was reduced in all four lipoprotein fractions at 8 weeks. Protein content was reduced in the VLDL and LDL fractions, suggesting that the drug may interfere with VLDL apoprotein synthesis in the liver. The apoproteins of LDL consisted only of apo B. However, the HDL fractions demonstrated quantitative differences. Apo AI, apo E, and apo C were all enhanced after 8 weeks of drug treatment at 10 mg/kg/day (Fig. 2).

The enzyme activities that were affected by the drug were at key regulator sites for lipid synthesis, e.g., HMG-CoA reductase, acyl cholesterol acyl transferase, *sn*-glycerol-3-phosphate acyl transferase, and phosphatidylate phosphorylase (Table IV). All of these enzymes were suppressed by the drug *in vivo* in mouse at 10–60 mg/kg/day (5).

Table III. Rat Serum Lipoprotein and Lipid Content After 8 Weeks of Administration of *N*(4-Methylphenyl)diphenimide at 10 mg/kg/Day Orally ($N = 8$)

	Percentage of control ($X \pm SD$)				
	Cholesterol	Triglyceride	Neutral lipids	Phospholipid	Protein
Chylomicrons					
Control	100 ± 7[a]	100 ± 7[b]	100 ± 8[c]	100 ± 7[d]	100 ± 6[e]
Treated	94 ± 6*	92 ± 5	110 ± 8	75 ± 7*	100 ± 5
VLDL					
Control	100 ± 7[g]	100 ± 4[g]	100 ± 6[h]	100 ± 8[i]	100 ± 7[j]
Treated	70 ± 5*	81 ± 6*	101 ± 5	88 ± 9	59 ± 5*
LDL					
Control	100 ± 6[k]	100 ± 7[l]	100 ± 5[m]	100 ± 8[n]	100 ± 6[o]
Treated	92 ± 5	95 ± 6	95 ± 6	87 ± 9	63 ± 7*
HDL					
Control	100 ± 5[p]	100 ± 6[q]	100 ± 5[r]	100 ± 8[s]	100 ± 6[t]
Treated	210 ± 6*	97 ± 5	95 ± 4	89 ± 4	100 ± 8

[a]337 μg/ml. [b]67 μg/ml. [c]420 μg/ml. [d]149 μg/ml. [e]184 μg/ml. [f]190 μg/ml. [g]98 μg/ml. [h]221 μg/ml. [i]26 μg/ml. [j]50 μg/ml. [k]210 μg/ml. [l]10 μg/ml. [m]45 μg/ml. [n]41 μg/ml. [o]122 μg/ml. [p]540 μg/ml. [q]27 μg/ml. [r]620 μg/ml. [s]153 μg/ml. [t]657 μg/ml.
*$p \leq 0.001$, students's "t" test.

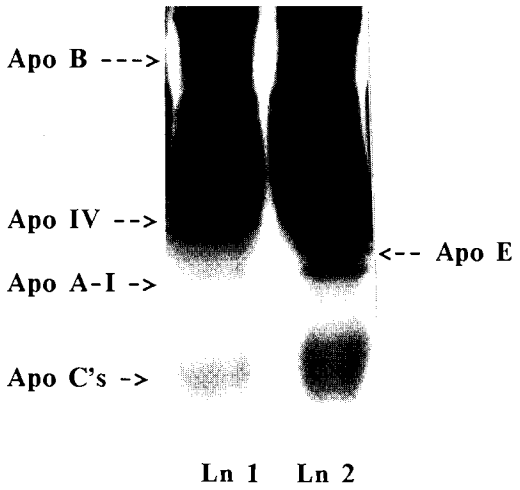

Fig. 2. Sodium dodecyl sulfate (SDS)–PAGE HDL-apoprotein separation. Lane 1, control; Lane 2, *N*(4-methylphenyl)diphenimide treated (10 mg/kg/day for 8 weeks).

Thus, it appears that a dose of 10 mg/kg/day orally is sufficient to inhibit effectively the regulatory enzymes for de novo lipid synthesis with tissue lipids and serum lipoprotein lipid content retaining the decreased levels for treatment of hyperlipidemic states. The fact that the drug elevates neutral cholesterol ester hydrolase activity suggests that more peripheral tissue cholesterol esters are broken down to free cholesterol for HDL uptake so that less is stored in tissues, e.g., aorta, with more cholesterol being conducted to the liver for excretion. Drug treatment had no effect on lysosomal free enzyme activities of the liver and small intestinal mucosa after 8 weeks.

When the incorporation of radiolabeled precursors into serum lipoprotein fractions was examined, drug therapy reduced ^{3}H-cholesterol and ^{14}C-palmitic acid incorporation into chylomicron, VLDL, and LDL fractions after 2 weeks (Table V). Both precursors were incorporated at a faster rate into the HDL fraction after 14 days. ^{32}P was incorporated into LDL at a faster rate than the control but was reduced in HDL. ^{3}H-Leucine incorporation was increased in chylomicrons, VLDL, and LDL, suggesting that protein or apoprotein content is altered by drug therapy through a metabolic process probably at the site of synthesis. Polyacrylamide gel electrophoresis (PAGE) indicated that HDL apoproteins, e.g., apo AI and E levels, are increased, with some indication of the apo C's being elevated in the treated animals. The uptake of HDL cholesterol by the liver is mediated by AI and E apoproteins of HDL because these are the recognition proteins for the liver high-affinity membrane receptors for the reverse cholesterol pathway (30). This process, if accelerated by drug treatment, should clear cholesterol from the serum compartment and peripheral tissues as demonstrated in the *in vivo* studies. The lipid chemical analysis of the same lipoprotein fractions used for the incorporation studies showed that cholesterol, palmitic acid, and phospholipids of each lipoprotein fraction followed the same trend in reduction by drug therapy as the incorporation study with the exception of leucine incorporation into proteins (Table V). The lipid appears to be removed from the lipoprotein fractions after treatment with the drug causing reduction in protein content. Apoprotein synthesis appears to be elevated with drug treatment; however, at this time the protein con-

Table IV. The Effects of *N*(4-Methylphenyl)diphenimide on Enzyme Activities of Liver and Small Intestinal Mucosa After 8 Weeks at 10 mg/kg/Day Orally (N = 6)

	Percentage of control ($X \pm$ SD)			
	Liver		Small intestine mucosa	
Enzyme, 8th week	Control	Treated	Control	Treated
ATP-dependent citrate lyase	100 ± 7[a]	98 ± 6	100 ± 6[k]	97 ± 5
Acetyl CoA synthetase	100 ± 8[b]	94 ± 5	100 ± 5[l]	96 ± 6
HMG CoA reductase	100 ± 8[c]	78 ± 4*	100 ± 8[m]	111 ± 9
Cholesterol ester hydrolase	100 ± 7[d]	172 ± 6*	100 ± 7[n]	197 ± 8
Acyl cholesterol acyl transferase	100 ± 7[e]	71 ± 6*	100 ± 6[o]	63 ± 3*
Cholesterol 7-α-hydroxylase	100 ± 8[f]	118 ± 7*	100 ± 7[p]	70 ± 4
Acetyl CoA carboxylase	100 ± 6[g]	140 ± 6	100 ± 7[q]	98 ± 5*
sn-Glycerol-3-phosphate acyl transferase	100 ± 6[h]	74 ± 5*	100 ± 7[r]	116 ± 7*
Phosphatidylate phosphohydrolase	100 ± 6[i]	67 ± 4*	100 ± 6[s]	78 ± 8
Proteolytic activity	100 ± 5[j]	112 ± 7	100 ± 5[t]	89 ± 6*

[a]9.2 mg citrate hydrolyzed/g wet tissue. [b]10.0 mg acetyl CoA formed/g wet tissue. [c]103,020 dpm/g wet tissue. [d]22443 dpm/g wet tissue. [e]86,640 dpm/g wet tissue. [f]289,450 dpm/g wet tissue. [g]43,000 dpm/g wet tissue. [h]87,620 dpm/g wet tissue. [i]11 μg P_i released/g wet tissue. [j]30.6% free. [k]9.17 mg citrate hydrolyzed/g wet tissue. [l]5.27 mg acetyl CoA formed/g wet tissue. [m]113322 dpm/g wet tissue. [n]259,099 dpm/g wet tissue. [o]64,819 dpm/g wet tissue. [p]23,099 dpm/g wet tissue. [q]54,892 dpm/g wet tissue. [r]73,219 dpm/g wet tissue. [s]111 μg P_i released/g wet tissue. [t]35.2% free.
*$p \leq 0.001$, students's "t" test.

Table V. Incorporation of Radiolabeled Precursors into Serum Lipoproteins of Sprague Dawley Rats After 2 Weeks' Administration of 4(*N*-Methylphenyl)diphenimide ($N = 6$)

	Percentage of control ($X \pm SD$)							
	Cholesterol		^{14}C-Palmitic acid		^{32}P (H_3PO_4)		^{3}H-Leucine	
	^{3}H-dpm	μg/ml	dpm	μg/ml	dpm	μg/ml	dpm	μg/ml
Chylomicron								
Control	100 ± 5[a]	100 ± 5[b]	100 ± 6[c]	100 ± 6[d]	100 ± 7[e]	100 ± 6[f]	100 ± 5[g]	100 ± 5[h]
Treated	33 ± 6*	46 ± 4	46 ± 7*	89 ± 5	83 ± 6*	94 ± 5	173 ± 5*	86 ± 4
VLDL								
Control	100 ± 6[i]	100 ± 4[j]	100 ± 5[k]	100 ± 5[l]	100 ± 8[m]	100 ± 8[n]	100 ± 5[o]	100 ± 6[p]
Treated	73 ± 5*	85 ± 3	66 ± 3*	89 ± 6	109 ± 7*	48 ± 5*	168 ± 1*	82 ± 7
LDL								
Control	100 ± 5[q]	100 ± 6[r]	100 ± 9[s]	100 ± 6[t]	100 ± 8[u]	100 ± 7[v]	100 ± 7[w]	100 ± 7[x]
Treated	37 ± 3*	55 ± 4	83 ± 4*	70 ± 5	129 ± 9	215 ± 9*	145 ± 6*	97 ± 7
HDL								
Control	100 ± 5[y]	100 ± 6[z]	100 ± 7[aa]	100 ± 7[bb]	100 ± 6[cc]	100 ± 6[dd]	100 ± 5[ee]	100 ± 8[ff]
Treated	117 ± 5*	201 ± 8	183 ± 6*	127 ± 6	78 ± 5*	162 ± 7*	76 ± 7*	96 ± 6

[a]2091 dpm/ml. [b]337 μg/ml. [c]764 dpm/ml. [d]67 μg/ml. [e]211 dpm/ml. [f]149 μg/ml. [g]11,492 dpm/ml. [h]184 μg/ml. [i]403 dpm/ml. [j]190 μg/ml. [k]386 dpm/ml. [l]98 μg/ml. [m]424 dpm/ml. [n]26 μg/ml. [o]4722 dpm/ml. [p]50 μg/ml. [q]403 dpm/ml. [r]210 μg/ml. [s]110 dpm/ml. [t]10 μg/ml. [u]140 dpm/ml. [v]45 μg/ml. [w]2909 dpm/ml. [x]41 μg/ml. [y]424 dpm/ml. [z]122 μg/ml. [aa]379 dpm/ml. [bb]540 μg/ml. [cc]379 dpm/ml. [dd]153 μg/ml. [ee]3866 dpm/ml. [ff]657 μg/ml.
*$p \leq 0.001$, students's "t" test.

tents in the lipoproteins have not returned to their normal levels. The increase in synthesis, at least with HDL, appears to be selective for specific apoproteins apo AI, E, and C's. Incorporation of ^{3}H-cholesterol into major organs, e.g., brain, lung, heart, spleen, kidney, and reproductive organs, was reduced significantly (25–81%) by drug treatment. ^{14}C-Palmitic acid incorporation into major organs was decreased 30–96% by drug treatment. ^{3}H-Cholesterol uptake was increased in the small (105%) and large intestine (20%), the chyme (113%), and the feces (13%). ^{32}P incorporation was increased in the lung (63%), liver (21%), thymus (65%), reproductive organs (64%), chyme (265%), and feces (96%). In hyperlipidemic rats, the drug at 20 mg/kg/day was effective after 2 weeks in reducing both serum cholesterol and triglyceride levels at 10 mg/kg/day (Table I). The levels had not achieved the normal serum lipid levels (mg/dL), but they were significantly reduced from the hyperlipidemic state (mg/dl). Probably continued dosing at 10 mg/kg/day would further reduce the serum lipid levels with time. When the serum lipoproteins of hyperlipidemic rats were examined, cholesterol levels were reduced in the VLDL and LDL but elevated in the HDL fractions (Table VI). It should be noted that the hyperlipidemic states displayed an increased lipid content compared to that of lipoproteins from normogenic rats (see footnotes to Table I). In general, the lipid changes were similar to those in the normogenic rats at 2 and 8

Table VI. Effects of 4(*N*-Methylphenyl)diphenimide at 10 mg/kg/Day Orally in Hyperlipidemic Sprague Dawley Rats on Serum Lipoprotein After 4 Weeks of Diet and 4 Weeks of Drug Administration ($N = 6$)

	Percentage of control ($X \pm SD$)				
	Cholesterol	Triglyceride	Neutral lipids	Phospholipids	Proteins
Chylomicron					
Control	100 ± 7[a]	100 ± 6[b]	100 ± 9[c]	100 ± 5[d]	100 ± 5[e]
Treated	87 ± 5	105 ± 7	86 ± 7	102 ± 7	94 ± 4
VLDL					
Control	100 ± 6[f]	100 ± 5[g]	100 ± 6[h]	100 ± 8[i]	100 ± 6[j]
Treated	24 ± 5*	102 ± 6	66 ± 7*	69 ± 5*	46 ± 4*
LDL					
Control	100 ± 5[k]	100 ± 4[l]	100 ± 6[m]	100 ± 11[n]	100 ± 7[o]
Treated	61 ± 4*	42 ± 3*	81 ± 4*	268 ± 10*	109 ± 67
HDL					
Control	100 ± 5[p]	100 ± 5[q]	100 ± 5[r]	100 ± 6[s]	100 ± 5[t]
Treated	149 ± 6*	62 ± 4*	72 ± 7*	147 ± 8*	113 ± 6*

[a]371 μg/ml. [b]79 μg/ml. [c]554 μg/ml. [d]231 μg/ml. [e]96 μg/ml. [f]773 μg/ml. [g]142 μg/ml. [h]294 μg/ml. [i]78 μg/ml. [j]15 μg/ml. [k]836 μg/ml. [l]62 μg/ml. [m]54 μg/ml. [n]231 μg/ml. [o]73 μg/ml. [p]4689 μg/ml. [q]16 μg/ml. [r]397 μg/ml. [s]184 μg/ml. [t]315 μg/ml.
*$p \leq 0.001$, students's "t" test.

weeks. These data suggest that the drug would be effective in hyperlipidemic states clinically and in modulating favorably the lipid content of the lipoproteins.

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