Chapter 20. Pharmacologic Regulation of Serum Lipoproteins

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Introduction - Serum lipoproteins interact with the arterial wall to modulate the pathologic process of atherosclerosis. Therefore, regulation of serum lipoproteins is one rational approach toward the treatment and prophylaxis of this disease. This report will review some of the recent advances made in the pharmacologic control of serum lipoproteins in experimental animals and man.

Although the basic relationships between the different classes of serum lipoproteins and atherosclerosis have been known since 1950, the relevance of this information remained largely unappreciated until quite recently. The reexamination by Miller and Miller[1] of the relationship between serum high density lipoproteins (HDL) and coronary artery disease (CAD) sparked a resurgence of interest in the serum lipoproteins and their control. Therefore, most studies concerned with the effect of drugs on lipoproteins have been reported within the past two years.

Of the four basic classes of lipoproteins in human serum, three promote and one retards the development of atherosclerosis. Very low density lipoproteins (VLDL) and low density lipoproteins (LDL) are definitely atherogenic,[2-4] and chylomicrons are probably atherogenic as well.[5] A large body of recent epidemiologic information indicates an inverse relationship between HDL cholesterol and CAD.[6-10] In view of the known relationships between serum lipoproteins and atherosclerosis, a logical framework for combating this disease is to reduce LDL and VLDL and/or increase HDL. But even when the concentrations of serum lipoproteins can presumably be favorably altered by a drug, it should not be assumed that the atherosclerotic process is influenced similarly. It is conceivable, although unlikely, that a drug could reduce serum LDL for example by causing it to deposit in arteries. Any drug that regulates lipoproteins must necessarily be tested for its effect on atherosclerosis.

Effects of Specific Drugs on Lipoproteins

Adamantyloxyphenyl Compounds - One of the first agents reported to markedly decrease LDL and VLDL, while simultaneously increasing HDL in experimental animals, is adamantyloxyphenylpiperidine (AOPP) (1). In cholesterol-cholic acid fed hypercholesterolemic rats, AOPP, at a dose of 200 mg/kg/day, reduced atherogenic lipoproteins (LDL + VLDL) to 153 mg/dl from a control level of 1804 mg/dl, while concomitantly increasing HDL from 87 to 557 mg/dl.[11] AOPP was active after a single dose orally or intravenously and decreased hepatic cholesterol concentration after prolonged administration.[12] In our laboratory all lipoprotein modifying agents are routinely evaluated in SEA Japanese quail for their effect on atherosclerosis.[13-15] AOPP was lethal at an effective lipoprotein modifying dose in this model. However, a closely related analog, adamantyloxyaniline (2),

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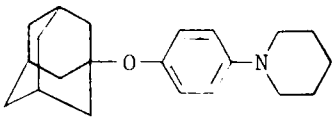
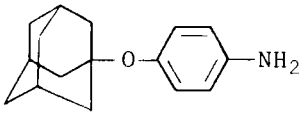


1 Adamantyloxyphenylpiperidine

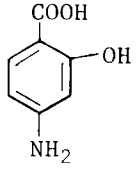


2 Adamantyloxyaniline

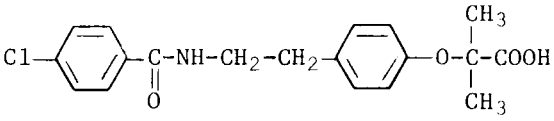
inhibited the development of experimental atheromas in proportion to the reduction of serum atherogenic lipoprotein levels.[16] The adamantyl compounds were discovered as a result of structure activity studies of their bicyclo-octyl analogs for which lipoprotein modifying activity was first reported.[17]

p-Aminosalicylic Acid (3) - This antituberculosis drug has been used on a very limited basis as a lipid lowering agent since it was first reported to lower serum cholesterol in 1954. A detailed study of its effect on serum lipoproteins was first published in 1976 when a reduction in VLDL, LDL, and HDL cholesterol levels of 49, 8, and 14%, respectively, was noted in patients who were mostly type II hyperlipoproteinemics.[18] Expanded studies on 30 patients consisting of both type II and type IV hyperlipoproteinemic individuals substantiated the decrease in VLDL and LDL cholesterol (46 and 6%, respectively) but failed to detect any change in HDL cholesterol.[19] In another study on 63 type II patients treated with this drug a 25% decrease in LDL cholesterol was noted.[20]

Bezafibrate (4) - This recently developed analog of clofibrate affects serum lipoproteins in much the same way as clofibrate, although at a somewhat lower dose (0.6 vs 1.5 g/day). In one study[21] bezafibrate reduced VLDL cholesterol and triglycerides in both types II and IV hyperlipoproteinemic patients. LDL cholesterol was reduced only in type II patients, and HDL cholesterol was not affected in either type II or IV individuals. Subsequent reports[22,23] by the same authors on a population of mixed hyperlipoproteinemic patients confirmed the reduction in VLDL cholesterol and triglycerides and in addition revealed that bezafibrate increased serum



3 p-Aminosalicylic acid



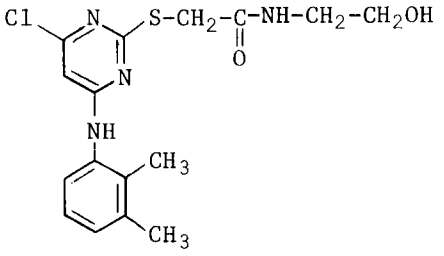
4 Bezafibrate

HDL cholesterol concentrations in the range of 20-30%. Another group of investigators[24,25] confirmed the rather marked effect of bezafibrate in reducing VLDL cholesterol and triglycerides but was not able to demonstrate an effect on HDL cholesterol. It was also noted that LDL cholesterol decreased by 15% in type II patients and increased by 16% in type IV individuals. This is consistent with an earlier finding[21] that the decrement in LDL cholesterol is proportional to the initial LDL level and

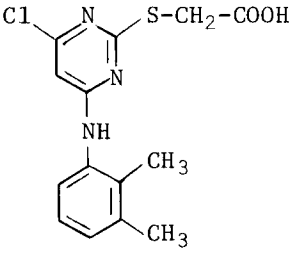
that an increment in LDL may occur when initial levels are low. The question of a bezafibrate induced increment in HDL needs further study to resolve conflicting reports.

Bile Acid Sequestrants - The effect of this class of hypolipidemic drugs on serum lipoproteins and atherosclerosis was reviewed recently.[26] The clinically tested bile acid sequestrants (cholestyramine, colestipol, and polidexide) appear to be approximately equivalent in their biological effects. They reduce LDL, transiently increase VLDL, have no effect on HDL, and probably inhibit and reverse atherosclerosis. Greater LDL reduction can be achieved with sequestrants than with any other drugs presently commercially available in the U.S. Because of a reduction in cardiovascular mortality with long-term administration of colestipol,[27] sequestrants may eventually make a significant impact on controlling atherosclerosis. Two recent studies[28,29] on the effect of cholestyramine on serum lipoproteins confirm conclusions drawn from earlier studies. Reductions in LDL cholesterol of 30 to 40% were reported.

BR-931 (5) - This compound increased HDL cholesterol levels in both ethanol induced and cholesterol-cholic acid induced hyperlipidemic rats.[30,31] In cholesterol fed rabbits BR-931 increased HDL cholesterol by 53% and significantly reduced atherosclerosis in the aortic arch by 39%.[31] Like its parent compound, WY-14,643 (6), BR-931 is a potent inducer of hepatic peroxisomes.

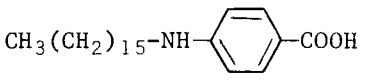


5 BR-931

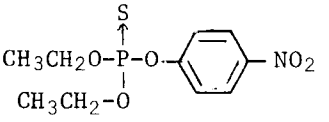


6 WY-14,643

Cetaben (7) - One of the most promising new agents for the control of atherosclerosis is cetaben. In cholesterol fed rabbits sodium cetaben significantly inhibits atherosclerosis and esterification of free cholesterol in the arterial wall.[32] In cholesterol fed cynomolgus monkeys treated with sodium cetaben at 100 mg/kg/day for 6 months, a number of beneficial effects were noted.[33] Atherosclerosis was inhibited by approximately 50% in all arterial beds examined, including coronary,



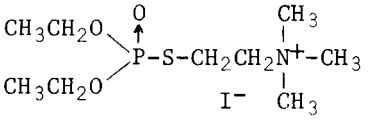
7 Cetaben



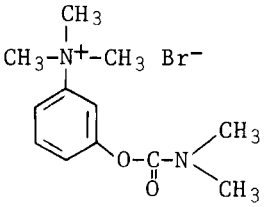
8 Parathion

carotid, and femoral arteries. Arterial cholesterol, collagen, and calcium were reduced likewise. Also, this agent reduced atherogenic LDL and VLDL concentrations in serum and increased HDL levels. Because of these numerous beneficial effects in a nonhuman primate, results of clinical testing are eagerly anticipated.

Cholinesterase Inhibitors - What may prove to be one of the most important clinical observations in the field of lipoprotein research was made by Kutty et al.[34] in 1975 on a 10 year old boy who was hospitalized after ingestion of the insecticide parathion (8). LDL levels were determined in the boy's serum drawn at 2 hour intervals for the first 12 hours after hospitalization. LDL levels dropped dramatically after only 6 hours from an initial value of 240 mg/dl to 30 mg/dl. The authors attributed the fall in LDL to the inhibition of serum cholinesterase by the parathion poisoning since this enzyme is intimately associated with LDL.[35] The same investigators have demonstrated that phospholine iodide (9) in guinea pigs[34] and



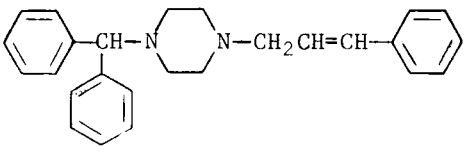
9 Phospholine iodide



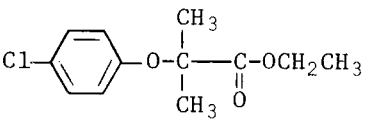
10 Neostigmine

neostigmine (10) in rats[36] cause a significant reduction in serum LDL levels that parallels the simultaneous reduction in serum cholinesterase activity. Assuming the validity of the rapid and dramatic reduction of LDL in the clinical case of parathion poisoning, much further work needs to be performed on the mechanism of this effect and the development of nontoxic drugs to mimic this activity.

Cinnarizine (11) - This antihistaminic and vasoactive agent has been used in Europe for several years to treat peripheral vascular disorders[37] and recently was tested for its effect on serum lipoproteins in a group of type II and IV hyperlipoproteinemic patients.[38] A progressive decrease in both LDL and VLDL was noted monthly through six months of treatment, at which time these lipoproteins were reduced by 35 and 78%, respectively. Even though it is vasoactive and hypolipoproteinemic, further studies will be necessary to evaluate the effect of cinnarizine on atherosclerotic disease in experimental animals or man.



11 Cinnarizine

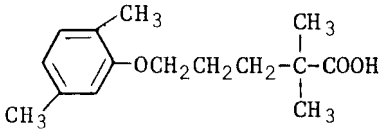


12 Clofibrate

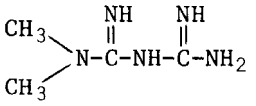
Clofibrate (12) - Even though clofibrate is the most widely used and one of the first developed hypolipidemic agents in the world, surprisingly few studies have appeared on the effect of this drug on serum lipoproteins either in experimental animals or in man. Muller[39] reported that clofibrate in rats at 200 mg/kg/day reduced VLDL, LDL, and HDL cholesterol by 20, 22, and 41%, respectively. In another study[40] in normal rats at a dose of 120 mg/kg clofibrate reduced all lipoproteins, but with the greatest absolute reduction occurring in HDL. In normal baboons LDL cholesterol is increased by about 50% at 50 mg/kg and HDL cholesterol is decreased approximately 30% at 200 mg/kg.[41] Clinically, it has been known for several years that clofibrate exerts its greatest effect on VLDL.[42] More recently the clofibrate induced elevation in LDL was emphasized.[43] It now appears that the clofibrate induced LDL alterations from the treatment of hypertriglyceridemia are dependent on initial LDL values, with elevations occurring at initially low values and reductions effected at initially high LDL concentrations.[44] Clofibrate may induce a slight elevation in HDL cholesterol concentrations,[44-47] but at best the effect seems marginal.

Gemfibrozil (13) - Although this agent was disclosed for the first time only recently,[48,49] numerous studies have appeared concerning its effect on serum lipoproteins in man.[47,50-58] Howard[59] has recently summarized these studies, and in all clinical trials conducted with this drug there was a reduction in lipoprotein cholesterol of 58, 47, and 6% for chylomicrons, VLDL, and LDL, respectively. HDL cholesterol was increased 15%. Triglycerides were decreased in all lipoprotein fractions with reductions of 79, 43, 26, and 23% occurring in chylomicrons, VLDL, LDL, and HDL, respectively.

Like clofibrate, gemfibrozil does not appear to act via a single mechanism. It inhibits peripheral lipolysis, hepatic uptake of plasma free fatty acids, and synthesis of VLDL apoprotein.[59]



13 Gemfibrozil



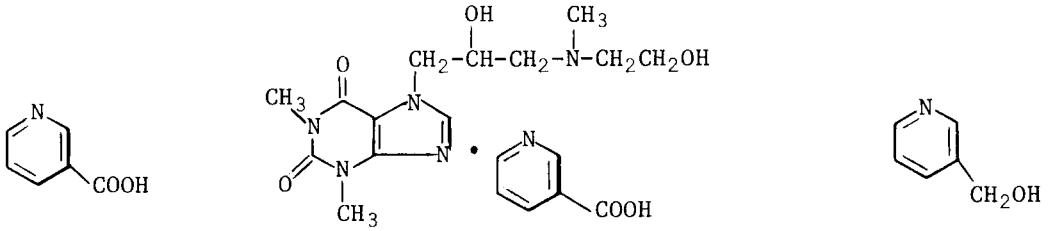
14 Metformin

Metformin (14) - Theoretically it is possible for a drug to alter the atherogenicity of a serum lipoprotein without altering its absolute concentration. The best documented example of such drug induced structural alteration in lipoproteins is metformin which inhibits the development of experimental atherosclerosis in cholesterol fed rabbits,[60] whereas other hypoglycemic agents do not.[61,62] Serum lipoproteins of cholesterol fed rabbits consist largely of cholesterol ester rich particles that float in

the VLDL density range.[63,64] In a series of papers published within the past two years, Sirtori and his research group have demonstrated that metformin (a) increased the fractional catabolic rate of VLDL in hypercholesterolemic rabbits,[65] (b) altered the phospholipid composition of VLDL,[65,66] (c) reduced the interaction of VLDL with the arterial wall,[65] and (d) changed the apoprotein composition of serum lipoproteins.[66-69] Apolipoprotein E was decreased and albumin was increased in VLDL and HDL_2 by metformin in cholesterol fed rabbits. Apolipoprotein A-I levels were increased in chylomicrons, VLDL, and LDL. In man the concentrations of VLDL and intermediate density lipoprotein (IDL) were reduced in addition to the changes in apoprotein composition.[68-70]

In contrast to metformin, there is some controversy about the effect of other oral hypoglycemic agents on serum lipoproteins.[71,72] Controversy also exists about the effect of insulin on HDL in man.[72,73]

Nicotinic Acid (15) and Derivatives - In normal rats nicotinic acid decreased LDL and VLDL but had no effect on HDL cholesterol.[39] Clinically nicotinic acid has been reported to behave much like clofibrate causing a decrease in VLDL and either an increase or decrease in LDL depending on pretreatment values.[44] Xantinol nicotinate (16) has been reported to (a) decrease LDL[74] and not affect VLDL in type IIA hyperlipoproteinemia,[75] (b) decrease LDL and VLDL in type IIB,[75] (c) decrease chylomicrons and VLDL, increase LDL, and not affect HDL in type V hyperlipoproteinemia,[76] (d) decrease VLDL but not affect LDL and HDL in type IV,[77] and (e) have no effect on any lipoproteins in type IIA.[78] β-Pyridyl carbinol (17) decreased LDL approximately 30% in type IIA patients but had no effect on VLDL or HDL.[78]

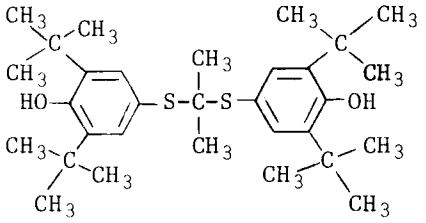


15 Nicotinic acid 16 Xantinol nicotinate 17 β-Pyridyl carbinol

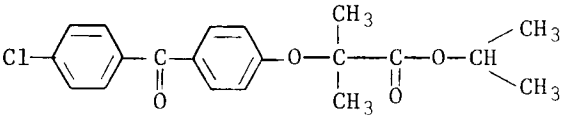
Probucol (18) - Very little is known about the effect of probucol on serum lipoproteins. In a group of 30 type II patients probucol reduced both LDL and HDL cholesterol levels to a small extent but had no effect on VLDL.[79]

Procetofene (19) - This new lipoprotein modifying agent produces a more favorable effect on serum lipoproteins in man than any agent reported to date. Rossner and Oro[80,81] compared procetofene with clofibrate, bezafibrate, and gemfibrozil in type II and type IV patients and found it caused a 57% decrease in VLDL triglyceride in type IV, a 37% decrease in

LDL cholesterol in type II, and a 14% increase in HDL cholesterol in type IV. These effects of procetofene were better overall than those of any of the other drugs with which it was compared. Other investigators have also reported very favorable results with procetofene. These include a



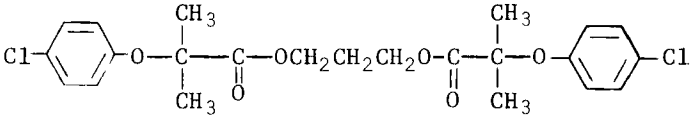
18 Probucol



19 Procetofene

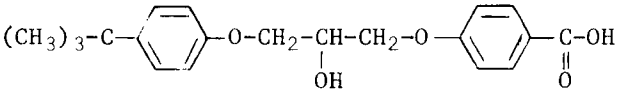
23% increase in apolipoprotein A from HDL in type II,[82] a 50 and 30% fall in VLDL and LDL cholesterol in type IIB,[83] and a 35% decrease in LDL cholesterol in type IIA.[83] In experimental animals such as hypercholesterolemic rats, procetofene markedly reduces VLDL and concomitantly increases HDL to a similar degree.[84] Based on its pronounced lipoprotein effects, this drug may retard the development of clinical atherosclerosis.

Simfibrate (20) - One would expect a priori that this closely related analog of clofibrate would have an identical effect on serum lipoproteins. As expected, VLDL was substantially reduced with simfibrate. Surprisingly, LDL was also reduced to a similar extent.[85,86]



20 Simfibrate

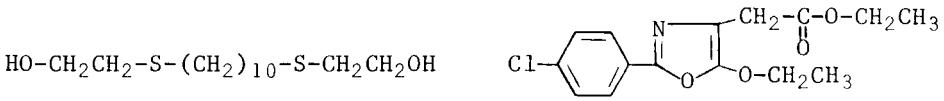
Terbufibrol (21) - Based on preclinical data in rats[40,87] and baboons,[41] terbufibrol exerts a rather dramatic effect in the reduction of serum lipoproteins, especially LDL and VLDL. In the normal rat at a dose of 120 mg/kg/day terbufibrol caused a 32, 83, and 40% reduction in LDL, VLDL, and HDL, respectively.[40] Terbufibrol reduced also serum lipoproteins in fructose induced hypertriglyceridemic rats and in rats with hypercholesterolemia induced by thiouracil, Triton, or cholesterol feeding, apparently by inhibition of lipoprotein synthesis or release in these models.[88,89]



21 Terbufibrol

In the normal baboon at a dose of 200 mg/kg/day this drug reduced serum LDL and HDL by approximately 70 and 50%, respectively.[41] The effect was even greater in baboons on a high fat, high protein diet where an LDL reduction of 80% was observed at a dose of 60 mg/kg/day.

Tiadenol (22) - In type IIA hyperlipoproteinemia tiadenol reduced LDL and HDL cholesterol 23 and 36%, respectively, from basal levels after 4 months of drug therapy but had no effect on VLDL triglyceride levels.[90]



22 Tiadenol

23 Y-9738

Y-9738 (23) - This newly disclosed compound effectively reduced LDL in hypercholesterolemic rats, and the 50% reduction in serum cholesterol seen in monkeys with Y-9738 treatment can be accounted for almost entirely by a reduction in LDL.[91]

Summary

A reduction of total serum cholesterol and triglycerides elicited by a drug represents only the net effect on all classes of serum lipoproteins. Since different lipoproteins may have distinctly opposite effects on atherogenesis, it is now of paramount importance to obtain information about the effect of drugs on individual lipoproteins so that some reasonable assessment can be made regarding the probability for a beneficial effect of the drug on clinical atherosclerosis. Given the present state of the art in atherosclerosis research, simple measurement of total serum cholesterol and/or triglycerides only is no longer rationally acceptable. Even when a drug appears to favorably alter lipoproteins, its effect on atherosclerosis must be verified experimentally, since an effect on lipoproteins does not necessarily assure an effect on atherosclerosis. Pharmacologic regulation of serum lipoproteins is an exciting and rapidly advancing area of research, and, as a result of intensive efforts underway in many pharmaceutical laboratories, new and better agents for controlling serum lipoproteins and atherosclerosis can be expected to be forthcoming.

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