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Lipid-Lowering Drugs
An Overview of Indications and Optimum Therapeutic Use

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Summary

Drug treatment of patients with hyperlipoproteinaemia is indicated to reduce the risk of atherosclerosis in patients with increased concentrations of atherogenic lipoproteins, and to lower the plasma concentrations of triglyceride-rich lipoproteins in patients with severe hypertriglyceridaemia who are at risk of abdominal pain and pancreatitis. Such therapy should be initiated only after satisfactory exclusion of secondary causes of hyperlipoproteinaemia, and should be regarded as an adjunct to rather than a substitute for appropriate dietary therapy. Drug therapy should be strongly considered in those patients with concentrations of atherogenic lipoproteins which exceed the 90th to 95th percentile for age.

In patients with increased plasma concentrations of low density lipoproteins (LDL), agents which enhance the rate of LDL catabolism (cholestyramine and colestipol) or reduce the rate of LDL synthesis [e.g. nicotinic acid (niacin)] are the 'drugs of choice'. For those patients with concurrent hypertriglyceridaemia, nicotinic acid is the preferred initial drug, and in both patient groups combined drug therapy is often necessary to attain optimal reductions in LDL cholesterol concentrations. Clofibrate remains the 'drug of choice' for the rare patient with type III hyperlipoproteinaemia, whereas the newer agent gemfibrozil should be used in patients with plasma triglyceride concentrations above 1000 mg/dl who are at increased risk of abdominal pain and pancreatitis.

Although currently limited to investigational use, mevinolin and related compounds, which are specific inhibitors of the rate-limiting enzyme in cholesterol biosynthesis (HMG Co-A reductase), offer considerable promise in the therapy of patients with primary hypercholesterolaemia due to elevated levels of LDL cholesterol.

The term hyperlipoproteinaemia refers to conditions in which the concentrations of cholesterol- and/or triglyceride-rich lipoproteins in plasma are elevated above normal levels. There are 4 important clinical reasons for concern about the correct diagnosis and treatment of hyperlipoproteinaemia. The first is the strong causal relationship between elevated concentrations of cholesterol-rich lipoproteins and accelerated rates of atherosclerosis of both the coronary and peripheral circulation. The second reason is the correlation of certain hyperlipoproteinaemias with the occurrence of xanthomas in the skin and tendons, which may present cosmetic problems, and in the case of tendon xanthomas, are frequently associated with recurrent episodes of tendinitis. The third reason for concern lies in the causal relationship between severe hypertriglyceridaemia and symptoms of abdominal pain and acute pancreatitis. The fourth and final reason for clinical concern is that the occurrence of hypercholesterolaemia or hypertriglyceridaemia may point to another disease to which the lipoprotein abnormality is secondary (e.g. hypothyroidism). Thus, the assessment of a patient with hyperlipoproteinaemia should include a detailed history (including family history), physical examination, and blood tests to exclude secondary causes of hyperlipoproteinaemia.

Determination of the plasma concentrations of cholesterol and triglyceride constitutes the basic lipid profile which is obtained in most patients. In discussing hyperlipoproteinaemic states as they pertain to a given patient, this review uses the basic cholesterol and triglyceride determinations as a starting point and divides the discussion of treatment into 3 categories: (a) patients with hypercholesterolaemia in whom triglyceride concentrations are normal (type IIA phenotype) [section 3];

(b) patients with combined elevations of cholesterol and triglyceride wherein the triglyceride levels are up to twice the cholesterol values (phenotype IIB and III) [sections 4 and 5]; and (c) conditions associated with a primary elevation in the concentrations of triglyceride-rich lipoproteins and in which cholesterol levels are nearly normal (type IV phenotype) or increased to a much smaller extent than are the triglycerides (phenotypes I and V) [section 6]. Individual drugs are discussed in detail in the sections that correspond to their primary areas of use.

1. Physiology of Lipid and Lipoprotein Transport

Cholesterol and triglycerides, which are the 2 indices normally measured in assessing hyperlipoproteinaemias, are transported in plasma as components of large globular particles termed lipoproteins. These particles contain other lipids (e.g. phospholipids) and specific apoproteins. There are 4 broad categories of lipoproteins (chylomicrons, very-low density lipoproteins, low density lipoproteins and high density lipoproteins), which differ from each other in size and density as well as in the relative proportions of triglyceride, cholesterol, and protein and in the specific apoproteins which they contain (Schonfeld 1983).

Chylomicrons, which are the largest of the lipoprotein particles, are formed in intestinal mucosal cells and constitute the form in which dietary (exogenous) lipids are transported from the intestine to lymphatics and plasma. Chylomicrons are responsible for the lipaemia seen in postprandial plasma samples and are not normally present in plasma samples obtained 10 to 12 hours after a meal. Chylomicrons are triglyceride-rich lipoproteins, and upon entry into the systemic circulation much of the triglyceride is removed in peripheral tissues by the action of the enzyme lipoprotein lipase. Apoprotein E on the remnant chylomicron particle is recognised by specific hepatic receptors (Mahley & Angelin 1984) which facilitates hepatic uptake of the chylomicron remnant (fig. 1).

Very-low density lipoproteins (VLDL) are produced by the liver and serve as the major transport form for endogenously synthesised triglycerides from the liver. Increased plasma concentrations of VLDL cause a slight turbidity in plasma, and like chylomicrons these particles also contain triglyceride as the major lipid component. Hydrolysis of the triglyceride component of VLDL is dependent on the enzyme lipoprotein lipase. Intravascular catabolism of VLDL particles leads to the formation of progressively smaller lipoproteins (termed intermediate density lipoproteins, IDL) and ultimately to low density lipoproteins (LDL). Conversion of VLDL to LDL also appears to require interaction of the VLDL remnant particles with hepatic receptors which recognise one specific apoprotein (apoprotein E) present on the VLDL remnant particle. The extent to which VLDL particles are converted to LDL differs in different hyperlipoproteinaemic states, but most LDL is derived from the intravascular catabolism of VLDL (fig. 1).

Increased plasma concentrations of triglyceride-rich lipoproteins (VLDL and chylomicrons) can result from increases in the rate of hepatic production of VLDL particles (which accumulate in plasma and ultimately result in delayed catabolism of intestinal-derived chylomicron particles), or from decreases in the rate of removal of both of these triglyceride-rich lipoproteins from plasma. The use of triglyceride-lowering drugs in patients with severe hypertriglyceridaemia aims to reduce hepatic triglyceride production and/or enhance the rate of triglyceride hydrolysis by lipoprotein lipase in peripheral tissues. Cholesterol-rich VLDL and chylomicron remnant particles accumulate in the plasma of patients with type III hyperlipoproteinaemia; most patients with this disorder are homozygous for one form of apoprotein E (E2) which has a reduced binding affinity for specific hepatic receptors which facilitate the catabolism of VLDL and chylomicron remnant (Mahley & Angelin 1984). In addition, most patients with type III hyperlipoproteinaemia overproduce VLDL, and therapy of this disorder is directed at enhancing the rate of conversion of VLDL to LDL and concurrently reducing the rate of VLDL production.

In humans most of the LDL in plasma is de-

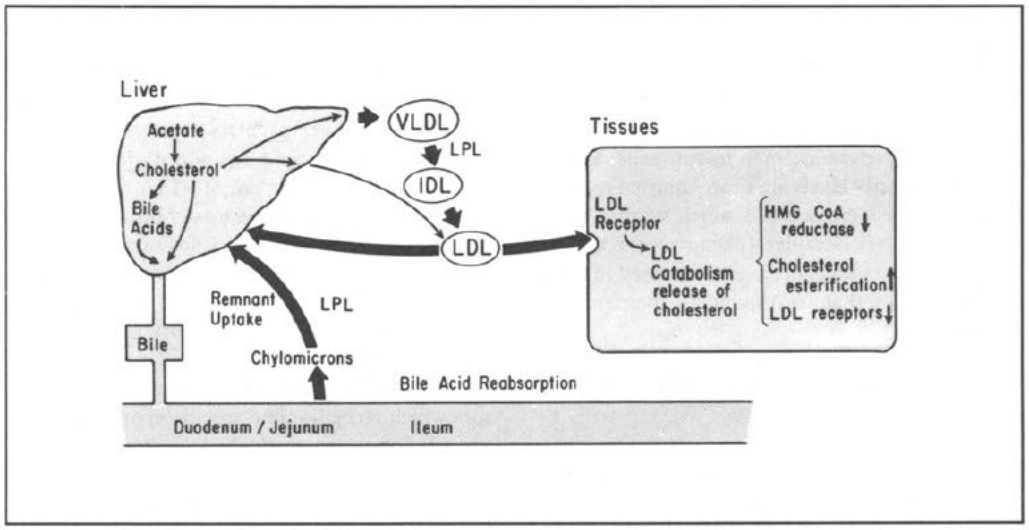

Fig. 1. Metabolism and transport of lipoproteins in humans and the cellular changes that result from receptor-mediated uptake of low density lipoproteins.

rived from intravascular catabolism of VLDL, and LDL may therefore be regarded as the end-product of VLDL metabolism (fig. 1). Catabolism of LDL occurs in both peripheral cells and the liver (the latter being the major site of removal) and is facilitated by both receptor- and non-receptor-mediated pathways. The uptake of LDL by high affinity LDL receptors results in suppression of endogenous cholesterol biosynthesis, an enhanced rate of intracellular cholesterol esterification and a reduction in the number of high affinity LDL receptors expressed on the cell surface (fig. 1). Functional high affinity LDL receptors are absent from the cells of most patients with homozygous familial hypercholesterolaemia and are reduced by approximately 50% in patients heterozygous for this disorder (Goldstein & Brown 1983). Because the expression of high affinity LDL receptors on hepatocyte membranes is subject to metabolic regulation, factors which deplete the liver of cholesterol (for example, bile acid depletion or partial inhibition of cholesterol biosynthesis) stimulate production of an increased number of LDL receptors on the hepatocyte membrane. This in turn stimulates the liver to catabolise LDL particles from plasma at a faster rate and concurrently reduces the plasma concentrations of this lipoprotein. Increased plasma concentrations of LDL can result from an inherent reduction in the number of high affinity LDL receptors (as occurs in patients with familial hypercholesterolaemia) or can be due to an enhanced hepatic production of VLDL and LDL (as occurs in patients with familial combined hyperlipidaemia).

High density lipoproteins (HDL) constitute the fourth class of lipoproteins. HDL particles are derived from direct hepatic secretion and during the intravascular lipolysis of chylomicron particles (Nicoll et al. 1980). Clinical and epidemiological studies have shown an inverse correlation between plasma concentrations of HDL cholesterol and atherosclerosis (Gordon et al. 1977). Thus, high levels of HDL may enhance removal of cholesterol from tissues and protect against the development of atherosclerosis, whereas low levels of HDL cholesterol appear to be an independent risk factor. It is currently unclear whether measures which raise HDL cholesterol have any long term therapeutic

benefit, and thus the primary aim of drugs used in the treatment of hyperlipoproteinaemias is to reduce the concentrations of known atherogenic lipoproteins, rather than to increase HDL concentration.

2. *Criteria for the Diagnosis of Hyperlipoproteinaemia*

Accurate determination of cholesterol and triglyceride levels in plasma represents the basic test necessary for the diagnosis of most hyperlipoproteinaemias. Concentrations of plasma triglycerides increase postprandially, and for this reason reliable determinations require the patient to have fasted 12 to 16 hours prior to venipuncture. Patients with elevated levels of both cholesterol and triglyceride often require further lipoprotein characterisation by ultracentrifugation to distinguish between those patients with combined elevations of VLDL and LDL (phenotypic type IIB hyperlipoproteinaemia), and those individuals with type III hyperlipoproteinaemia, in which VLDL remnants accumulate. In most other patients with hypercholesterolaemia it is desirable to determine the concentrations of LDL and HDL cholesterol.

In evaluating the results of lipid determinations, it is important to consider the age of the patient and appropriate normal values for that individual (with the reservation that values which are classified as 'normal' in Western societies may, in fact, be too high). Data from the Lipid Research Clinic's programme which documents the mean and 95th percentile values of plasma lipid and lipoproteins are presented in table I.

The question 'what level of plasma cholesterol and/or LDL cholesterol warrants therapy with lipid lowering drugs?' is one of considerable importance. Although no absolute values can be applied to every patient, a more aggressive approach is warranted in males, in young people with a strong family history of early deaths from coronary artery disease, and in patients with concurrent other risk factors or atypically low concentrations of HDL cholesterol. Patients with concentrations of total and LDL cholesterol which exceed the 75th percentile for age should receive dietary advice and, in selected cases, drug therapy, whereas those patients with total and LDL cholesterols exceeding the 90th to 95th percentile should be strongly considered for drug treatment, if diet alone does not substantially reduce the magnitude of hypercholesterolaemia (Consensus Conference 1985). Results from 2 recently reported randomised clinical trials have demonstrated that reduction in LDL cholesterol by diet plus cholestyramine reduced the incidence of fatal and non-fatal coronary heart disease in a primary prevention trial (Lipid Research Clinics Coronary Primary Prevention Trial 1984a,b), and a second study (Brensike et al. 1984) showed a reduction in the angiographic progression of coronary artery disease in hypercholesterolaemic patients with pre-existent coronary artery disease. These studies support the view that if the premature development of coronary atherosclerosis in patients with primary hypercholesterolaemia is to be pre-

Table I. Normal values (mg/dl) for lipids and lipoproteins in American men and women[a]

Age (y)	Total plasma cholesterol	LDL cholesterol	HDL cholesterol	Total plasma triglyceride
Men				
20-24	162 (212)	103 (147)	45 (63)	89 (165)
25-29	179 (234)	117 (165)	45 (63)	104 (204)
30-34	193 (258)	126 (185)	46 (63)	122 (253)
35-39	201 (267)	133 (189)	43 (62)	141 (316)
40-44	205 (260)	136 (186)	44 (67)	152 (318)
45-49	213 (275)	144 (202)	45 (64)	143 (279)
50-54	213 (274)	142 (197)	44 (63)	154 (313)
Women				
20-24	162 (-)	98 (-)	52 (-)	68 (-)
25-29	174 (222)	106 (151)	56 (81)	71 (128)
30-34	174 (220)	109 (148)	55 (75)	74 (138)
35-39	186 (251)	119 (173)	56 (82)	89 (174)
40-44	196 (253)	125 (174)	57 (87)	92 (179)
45-49	205 (267)	130 (188)	58 (86)	105 (192)
50-54	222 (292)	145 (214)	60 (89)	112 (214)
55-59	231 (296)	150 (212)	60 (86)	132 (280)

a Data obtained from 11 communities across the United States. Values given are means (and 95th percentiles) in mg/dl for White males and females (data from the Lipid Research Clinics Population Studies Data Book 1980).

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