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An Overview of Lipid-Lowering Drugs

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Summary

The long term use of lipid-lowering drugs in the treatment of patients with hyperlipoproteinaemia is aimed at reducing plasma concentrations of known atherogenic lipoproteins with a favourable effect on lipid deposition in the arterial wall. A less common aim is to prevent the adverse sequelae of hyperchylomicronaemia in patients with severe hypertriglyceridaemia. The decision to begin drug therapy should be made only after the exclusion of secondary factors and after an adequate trial of diet has failed to produce acceptable concentrations of plasma lipids and lipoproteins. The bile acid sequestrants (cholestyramine and colestipol), nicotinic acid, fenofibrate and inhibitors of hydroxymethylglutaryl coenzyme A (HMG CoA) reductase (e.g. lovastatin or simvastatin) are the most effective drugs for use in patients with primary hypercholesterolaemia; these agents reduce plasma concentrations of total and LDL-cholesterol by 15 to 45%. For those patients with concurrent hypertriglyceridaemia, nicotinic acid, lovastatin or simvastatin, or fenofibrate are the preferred drugs for initial use; bile acid sequestrants frequently exacerbate hypertriglyceridaemia in these patients. Fibric acid derivatives (e.g. clofibrate, gemfibrozil, bezafibrate or fenofibrate) are all effective in the therapy of patients with type III hyperlipoproteinaemia, as is nicotinic acid and I have found lovastatin to be effective also. Gemfibrozil or nicotinic acid are the most effective agents to use in the treatment of patients with severe hypertriglyceridaemia who are at increased risk of abdominal pain and pancreatitis. Combined therapy with drugs which have different mechanisms of action can be effectively used in the treatment of patients with severe hypercholesterolaemia or combined hyperlipidaemia; for the former group, combinations which use bile acid sequestrants, HMG CoA reductase inhibitors and nicotinic acid are the most effective.

The rationale for the identification and treatment of patients with hypercholesterolaemia is based on evidence that a reduction in plasma concentrations of known atherogenic lipoproteins will lead to a slower rate of progression of atherosclerosis, the arrest of this process altogether or potentially a reversal in previously developed arteriosclerotic lesions. The focus of drug treatment for patients with hypercholesterolaemia that is inadequately controlled on diet therapy alone is to reduce the plasma concentrations of low density lipoprotein (LDL) and very low density lipoprotein (VLDL) remnants. The use of lipid-lowering drugs is also appropriate in patients with hypercholesterolaemia in which triglyceride concentrations are severely elevated because of increased concentrations of chylomicrons and VLDL particles. For these patients, the aim of drug therapy is to reduce the concentrations of the triglyceride-rich lipoproteins and prevent the development of hepatomegaly, splenomegaly, eruptive xanthomas and pancreatitis as well as to reduce the long term risk

of atherosclerosis. Recent guidelines developed by the European Atherosclerosis Society (European Atherosclerosis Society Study Group 1987) and by the National Cholesterol Education Programs (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Expert Panel 1988) have provided frameworks for the evaluation of patients with hyperlipoproteinaemia and have defined certain guidelines for both diet and drug therapy in Europe and North America.

1. Drug Treatment of Primary Hypercholesterolaemia

A limited number of drugs are available for the treatment of hypercholesterolaemia, and the availability of individual agents differs between countries. For example, fibric acid derivatives such as fenofibrate and bezafibrate, which are more effective in lowering LDL-cholesterol concentrations than are gemfibrozil or clofibrate, are available in some European countries but not in the United States or Canada. In contrast, the hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitor lovastatin has recently been approved for use in the United States but is not currently approved in Europe or Canada. Simvastatin is pending release in several European countries. The bile acid-binding resins cholestyramine and colestipol, nicotinic acid and lovastatin are the drugs of first choice for initial therapy of most adult patients with primary hypercholesterolaemia; reductions in the concentrations of LDL-cholesterol of greater than 20% can be achieved with each of these agents. The bile acid sequestrants and nicotinic acid were advocated as drugs of first choice by the NCEP Adult Treatment Panel (Expert Panel 1988); both have been shown to reduce cardiovascular morbidity and mortality and have a long established record of clinical use. Lovastatin also warrants inclusion as a drug of first choice for the treatment of adult patients with primary hypercholesterolaemia (excluding women of child-bearing potential) because of its potent ability to lower LDL-cholesterol and relatively low incidence of side effects in short and moderately long term use (Illingworth et al. 1988).

1.1 Bile Acid Sequestrants, Cholestyramine and Colestipol

The bile acid sequestrants cholestyramine and colestipol have been extensively evaluated in well-conducted clinical trials, and, in compliant patients, these drugs lower plasma concentrations of LDL-cholesterol by 20 to 35% (Glueck et al. 1972; Levy et al. 1973; Spengel et al. 1981). The dose-response curves for both cholestyramine and colestipol are non-linear, and in adult patients 10 to 20% decreases in plasma LDL-cholesterol concentrations can be achieved with doses of 10 g/day of colestipol or 8 g/day of cholestyramine. In addition to lowering plasma concentrations of LDL-cholesterol, therapy with bile acid sequestrants often results in 3 to 8% increases in the plasma concentrations of HDL-cholesterol and a small rise in plasma triglycerides, which, in patients with normal triglyceride levels, is small and inconsequential (5 to 30% increase). However, this effect is greater in patients with mild hypertriglyceridaemia, which commonly occurs in individuals with familial combined hyperlipidaemia (Illingworth 1987).

The bile acid-binding resins are 'non-systemic' in that their mechanism of action is based on their ability to bind bile acids in the intestinal lumen, interrupt the enterohepatic circulation of bile acids and consequently cause an increase in the faecal excretion of steroids. Depletion of the hepatic sterol pool then results in compensatory increases in both cholesterol biosynthesis and the expression of high affinity LDL receptors on liver-cell membranes; it is the latter effect which is responsible for the increased catabolism of LDL particles from plasma (Shepherd et al. 1980). The increase in hepatic cholesterol biosynthesis is believed to be accompanied by parallel increases in the synthesis and secretion of VLDL and potentially LDL particles from the liver; it is this increase in VLDL production that is responsible for the rise in plasma tri-

glycerides which commonly occurs in patients treated with cholestyramine or colestipol.

Since these drugs are free from systemic actions, they do not require detailed monitoring for unwanted biochemical effects. Common side effects observed with these drugs include changes in bowel function and a potential to exacerbate pre-existent haemorrhoids (Illingworth 1987).

1.2 Nicotinic Acid

Nicotinic acid, a first-choice drug for the treatment of patients with primary hypercholesterolaemia, exerts its actions through a decrease in the hepatic synthesis of VLDL and LDL (Grundy et al. 1981; Levy & Langer 1972). The hypocholesterolaemic effects of nicotinic acid are well established (Carlson 1984; Grundy et al. 1981; Levy & Langer 1972) and its long term use has been associated with a reduction in cardiovascular morbidity and mortality (Canner et al. 1986).

When used at doses of 3 to 6 g/day, nicotinic acid reduces plasma concentrations of LDL-cholesterol by 20 to 33% and concurrently raises the levels of HDL-cholesterol by 10 to 20% and reduces plasma triglycerides by 20 to 40% (Illingworth & Gowen 1987). Side effects occur commonly in patients treated with nicotinic acid to the extent that it cannot be tolerated by some patients. Although the predictable cutaneous flushing can be minimised by starting with a low dosage, several other side effects are common, including nausea, abdominal discomfort, dryness of the skin and, rarely, blurred vision. Laboratory abnormalities are more common in patients treated with doses greater than 3 g/day and include increases in the serum concentrations of uric acid, glucose, transaminases and alkaline phosphatase. Nicotinic acid is contraindicated in patients with active liver disease, hyperuricaemia or a history of peptic ulcer disease. In general, successful use of nicotinic acid requires considerable skill on the part of the prescribing physician and motivation on the part of the patient; it is, however, an effective and inexpensive medication for use in the therapy of hypercholesterolaemia or combined hyperlipidaemia.

1.3 HMG CoA Reductase Inhibitors

The recent development of specific competitive inhibitors of HMG CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis, has provided a new therapeutic approach to the treatment of primary hypercholesterolaemia. Lovastatin was recently approved for prescription use in the United States, and several other drugs in this class are currently in clinical trials or pending approval by regulatory agencies, including simvastatin, pravastatin and SR62320. Of these, lovastatin has been the most extensively investigated; this drug is effective in patients with primary hypercholesterolaemia which is attributable to either heterozygous familial hypercholesterolaemia or familial combined hyperlipidaemia (Havel et al. 1987; Hoeg & Brewer 1987; Hunninghake et al. 1986; Illingworth & Sexton 1984). The comparative efficacy of lovastatin, simvastatin and pravastatin in reducing plasma concentrations of LDL-cholesterol in patients with heterozygous familial hypercholesterolaemia is shown in table I. Single-drug therapy with each of these drugs has also been associated with a 20 to 30% decrease in the plasma concentrations of triglycerides and an overall tendency for HDL-cholesterol to rise by 2 to 15%.

At the cellular level lovastatin inhibits the conversion of HMG CoA to mevalonic acid and thus the cellular synthesis of cholesterol, leading to compensatory increases in the number of high affinity LDL receptors on the cell membrane and a stimulation of LDL catabolism. Lovastatin acts primarily in the liver; it is believed that the ability of this drug to reduce LDL concentrations results both from the increase in LDL catabolism and a reduction in VLDL and LDL production (Bilheimer et al. 1983; Grundy & Vega 1985). Reported side effects of the HMG CoA reductase inhibitors include changes in bowel function, headaches, nausea, fatigue, insomnia, skin rashes and a myopathy. The latter is potentially the most serious of the adverse effects reported with lovastatin and appears to be potentiated by concurrent therapy with cyclosporine, gemfibrozil and possibly nicotinic acid (East et al. 1988; Norman et al. 1988; Tobert 1988).

A more detailed discussion of the clinical efficacy and side effects of simvastatin are presented elsewhere in these proceedings.

1.4 Fibrates

Several drugs in the fibric acid class have been developed, but considerable variation exists among the individual drugs which have been approved for prescription use by regulatory authorities in different countries. Thus, clofibrate and gemfibrozil are at present the only 2 fibrates available for prescription use in the United States and Canada, whereas bezafibrate, fenofibrate and ciprofibrate are available in a number of Western European countries and Australia. Bezafibrate, fenofibrate and ciprofibrate are more effective in the treatment of primary hypercholesterolaemia than are gemfibrozil or clofibrate (table II), and the former 3 drugs could be considered as first-line agents in the treatment of this disorder. The fibric acid derivatives all reduce plasma triglyceride concentrations more than they reduce total and LDL-cholesterol and concurrently raise plasma concentrations of HDL-cholesterol by 10 to 20%. The lipid-lowering effects of the fibrates result from several different mechanisms, including an increased activity of lipoprotein lipase, an enhanced rate of catabolism of LDL and a reduction in VLDL synthesis. Side effects observed with these drugs include changes in bowel function, abdominal pain and occasional nausea. Biochemical side effects are relatively uncommon, but all drugs in this class have the potential to increase biliary lithogenicity, with a predicted increase in the incidence of gallstones (Illingworth 1987). As gemfibrozil and clofibrate reduce LDL-cholesterol concentrations by less than 10%, they cannot be considered as first-line agents for the therapy of primary hypercholesterolaemia (table III).

Table I. Changes in plasma concentrations of LDL-cholesterol in patients with heterozygous familial hypercholesterolaemia treated with HMG CoA reductase inhibitors

Reference	Drug	No. of patients	Dose (mg/day)[a]	Change in LDL-cholesterol (%)
Havel et al. (1987)	Lovastatin	20	10	−17
			20	−25
			40	−31
			80	−40
Illingworth & Bacon (1987)	Simvastatin	10	20	−38
			40	−44
			80	−48
Illingworth & Sexton (1984)	Lovastatin	13	10	−20
			20	−28
			40	−35
			80	−38
Kajinami et al. (1986)	Pravastatin	35	10	−22
			20	−31
Mol et al. (1986)	Simvastatin	8	10	−28
		4	20	−30
		7	40	−37
		4	80	−44

a Given as twice-daily dosage.

Table II. Reductions in plasma LDL-cholesterol concentrations in patients with heterozygous familial hypercholesterolaemia treated with fibric acid derivatives

Drug	Dose (mg/day)	No. of patients	Baseline LDL-cholesterol (mmol/L) [mg/dl]	Decrease in LDL-cholesterol (%)	Reference
Clofibrate	2000	10	7.38 [285]	4.6	Levy et al. (1972)
Gemfibrozil	1200	9	7.98 [308]	9.6	Meinertz (1986)
Bezafibrate	600	12	8.03 [310]	28	Eisenberg et al. (1987)
	600	18	6.74 [260]	18.3	Curtis et al. in press
Ciprofibrate	100	10	7.56 [292]	24	Illingworth et al. (1982)
	100	20	8.65 [334]	19.5	Rouffy et al. (1985)
	200	20	8.65 [334]	27	
Fenofibrate	300	9	7.95 [307]	24	Weisweiler et al. (1984)
	300	21	8.01 [309]	25	Rouffy et al. (1985)
	400	21	8.01 [309]	31	

1.5 Second-Line Drugs for Hypercholesterolaemia

Several other hypolipidaemic agents are available in addition to those previously discussed, but because of their lower hypocholesterolaemic efficacy these agents are best regarded as second-line drugs for the therapy of primary hypercholesterolaemia. Drugs in this category include probucol, neomycin, gemfibrozil, clofibrate and d-thyroxine. Probucol 500mg twice daily reduces plasma concentrations of LDL-cholesterol by 8 to 15% and has no effect on plasma triglycerides but reduces the plasma concentrations of HDL by 15 to 25% (Durrington & Miller 1985; Mellies et al. 1980). It has been shown to increase the fractional catabolic rate of LDL and may also stimulate non-receptor-mediated LDL clearance from plasma. Probucol may have other potentially beneficial effects on lipoproteins, including inhibition of LDL oxidation, and, when used in patients with heterozygous familial hypercholesterolaemia, it has been shown to result in the regression of tendon xanthomas (Steinberg 1986; Yamamoto et al. 1986).

Neomycin is a poorly absorbed aminoglycoside antibiotic, which, at a dose of 1g twice daily, reduces LDL-cholesterol concentrations by 10 to 15% in patients with primary hypercholesterolaemia (Hoeg et al. 1984) but does not affect plasma concentrations of HDL-cholesterol or triglycerides. Neomycin has the potential for serious ototoxicity and nephrotoxicity and frequently causes gastrointestinal side effects. Neomycin cannot be generally recommended as a hypocholesterolaemic agent because of its high frequency of clinical side effects and relatively poor hypocholesterolaemic efficacy. Similarly, d-thyroxine cannot be generally recommended as a hypocholesterolaemic drug; although it reduces plasma concentrations of LDL-cholesterol by 10 to 15%, it does so at the expense of making the patient moderately hyperthyroid (Bantle et al. 1981).

2. Drug Therapy of Combined Hyperlipoproteinaemia

Drug therapy of patients with combined hyperlipoproteinaemia, in which plasma concentrations of VLDL and LDL are increased, is directed primarily at reducing the concentrations of LDL-cholesterol, with a secondary aim being to reduce plasma concentrations of triglycerides and VLDL-cholesterol and to potentially exert a favourable effect on HDL-cholesterol levels. Nicotinic acid, the drug of first choice for patients with combined hyperlipoproteinaemia, reduces VLDL-cholesterol concentrations by 30 to 80% in doses of 3 to 6 g/day, with a concurrent reduction of 10 to 40% in the plasma concentrations of LDL-cholesterol. HDL-cholesterol concentrations frequently rise by

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