

DRUG TREATMENT OF HYPERLIPIDAEMIA

SUMMARY

1. Recent research has clarified the role and value of lipid-lowering agents.
2. The availability of Statins has greatly simplified the use of such therapy.
3. Lipid-lowering therapy is of value in those who have hyperlipidaemia and established coronary heart disease (infarct, angina), those at high risk of coronary heart disease, familial hypercholesteremia and middle-aged men with significant hyperlipidaemia.
4. The value in treating low risk patients, particularly female, who have isolated hyperlipidaemia remains to be established.

INTRODUCTION

Following a decade of controversy, there is now more general agreement with regard to the appropriate use of lipid lowering drugs. The decision to prescribe lipid lowering drugs should depend on an assessment of the total risk of coronary heart disease (CHD) rather than an isolated elevated cholesterol as therapy is for life¹.

Recent evidence has clarified the indications in which treatment of hyperlipidaemia has proven beneficial. Lipid lowering drugs should be reserved for patients with CHD² and those at high risk of developing CHD³ on account of multiple risk factors or middle-aged men with significant hyperlipidaemia inadequately controlled by diet.

Concern has been expressed regarding the risks/benefits of treating patients with lipid lowering drugs who have medium risk of CHD³. The benefits of treating male middle-aged Scottish patients with cholesterol levels greater than 6.5mmol/L, who had no history of myocardial infarction and were otherwise healthy were recently published⁴. This study concluded that pravastatin taken for five years will reduce the incidence of myocardial infarction and death from cardiovascular disease by almost one third. The earlier "4S" study in men and women with a cholesterol greater than 5.5mmol/L and with coronary heart disease treated with simvastatin showed a 42% risk reduction in deaths from CHD. Contrary to some earlier studies with other types of drugs both studies showed no excessive deaths from non-cardiac causes and confirms the safety of the statins.

ASSESSING THE RISK OF CHD

Assessing the risk of CHD is the key to deciding whether or not treatment is required. While raised cholesterol is clearly associated with CHD⁵ its impact on CHD must be considered in the context of cholesterol, hypertension, smoking status (which can be modified) as well as consideration of age, family and past history of CHD, male sex and diabetes (which can not be modified).

While prescribers are aware of the risk factors for CHD, evidence suggests that it is difficult to estimate a patients absolute risk of CHD in the presence of these risk factors⁶. Guidelines¹ exist which help the prescriber to quantify the risk for CHD. When the ten year risk of developing CHD exceeds 20% then drug treatment of hyperlipidaemia may yield the greatest benefit in terms of risk reduction. This is the case for most patients with established CHD and middle-aged men who are hypertensive, diabetic or smokers or have a family history of premature CHD.

NON-PHARMACOLOGICAL OPTIONS

Initiatives^{7,8,9} to prevent CHD have advised patients to stop smoking, control weight, observe proper diet and increase exercise. In spite of the community preventative measures these initiatives had a limited effect on the level of smoking and had only a marginal reduction in cholesterol and weight. The optimal method of educating individual patients to control their risk factors for CHD remains elusive. Treating hyperlipidaemia without strict attention to these other factors is unlikely to alter the prevalence of CHD to an optimal degree as at best it reduces CHD rates by only 30-40%.

PHARMACOLOGICAL OPTIONS

Drug treatment should be reserved for at risk patients with diet resistant hyperlipidaemia. Commonly used drugs include statins (simvastatin, pravastatin), resins (cholecystyramine) and fibrates (gemfibrozil). Less commonly used drugs include nicotinic acid, probucol, clofibrate and colestipol. Fish oils have been advocated for the treatment of increased triglycerides (TG) but were found to raise low density lipoproteins (LDL). The statins have been used for almost a decade and have not produced untoward effects. Furthermore they are more efficacious than existing therapies and have a higher degree of patient acceptability.

WHEN TO USE LIPID LOWERING DRUGS

Hyperlipidaemia should be confirmed by repeat testing with at least one sample analysed by a reliable hospital laboratory. Before starting lipid lowering drugs the prescriber should rule out secondary causes of hyperlipidaemia such as hypothyroidism, nephrotic syndrome, diabetes and medications such as beta blockers, thiazides and the oral contraceptive pill. Drug treatment should begin after three to six months of dietary restrictions if hyperlipidaemia persists. Therapy should be selected on the basis of the predominant lipoprotein abnormality. Total cholesterol is the most easily measured lipid and reflects LDL. Triglycerides should be measured only following an overnight 14 hour fast and is rarely treated in isolation except at very high levels (> 10mmol/L). Patients with low (< 1mmol/L) HDL cholesterol levels are at increased risk of CHD. Diabetics with elevated TG and cholesterol with reduced HDL are best treated with gemfibrozil. Opinions vary with regard to the threshold for commencing drug therapy. Cholesterol greater than 5.5mmol/L in those with established CHD, and greater than 6.5mmol/L in high risk middle-aged men can be justified¹⁰.

Hypercholesterolaemia : The statins, pravastatin (Lipostat) and simvastatin (Zocor) are first choice. Alternatives are bile acid resins such as cholecystyramine (Questran).

Mixed hyperlipidaemia (elevated cholesterol and TG) :The statins or alternatively fibrates such as gemfibrozil (Lopid) may be used.

Hypertriglyceridaemia (elevated TG) : Use fibrates such as gemfibrozil as first line therapy, alternatively use the statins.

Lipid lowering drugs may be used in combination in severe hyperlipidaemia, particularly statins and resins. Care should be exercised when combining a statin and fibrate due to the risk of myopathy.

Critics³ of various authorities guidelines have pointed out that strict adherence to their policies would result in "over treatment" of hyperlipidaemia. The suggestion that having two CHD risk factors (male and smoker) require treatment would include 25% of the male population in the 40-50 yr. age group. Clearly further cost benefit analysis and further analysis of the recent Scottish study is required to determine the sub-groups most likely to benefit.

ADVERSE EFFECTS

Earlier fears regarding the ill effects of reducing cholesterol may not be valid^{11,12}. The apparent increase in mortality could be explained by the presence of pre-clinical cancer, chronic ill health, smoking and large alcohol intake..

Statins (pravastatin & simvastatin): May occasionally cause elevated liver function tests (LFT's), elevated creatinine phosphokinase (CPK), myopathy and rhabdomyolysis (rare).

Fibrates (gemfibrozil): May cause upper abdominal discomfort and myopathy.
Resins (cholecystyramine): Commonly cause GIT discomfort in the form of bloating, constipation and flatulence.

Nicotinic acid: May cause flushing, headaches, elevated LFT's and GIT upset.

DRUG INTERACTIONS

Statins (pravastatin & simvastatin): Generally regarded as low risk of serious interactions. Caution advised with concurrent administration of cyclosporin.

Fibrates (gemfibrozil): May interact with warfarin.

Resins (cholecystyramine): May reduce the absorption of digoxin, warfarin, thyroxine and thiazide diuretics if given concurrently. It is advised to administer these drugs one hour before cholecystyramine.

PREGNANCY

In view of the protection against CHD enjoyed by most pre-menopausal women treatment of hyperlipidaemia is rarely indicated. Cholecystyramine may be used if a woman of reproductive age requires treatment and may be continued through pregnancy if considered essential¹³, since it is not absorbed systematically¹⁴. In contrast simvastatin, pravastatin, gemfibrozil and clofibrate are all contraindicated during pregnancy. As atherosclerosis is a chronic process, discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolaemia.

SCREENING

A variety of recommendations for hyperlipidaemia screening have been promoted by various authorities¹⁵. Selective screening, using clinical judgement, is more rational and cost effective than total population screening for isolated raised cholesterol^{3,16}, although this may result in some cases of heterozygous familial hypercholesterolaemia being missed. Like hypertension, the diagnosis of hyperlipidaemia should not be based on a single recording.

CONCLUSION

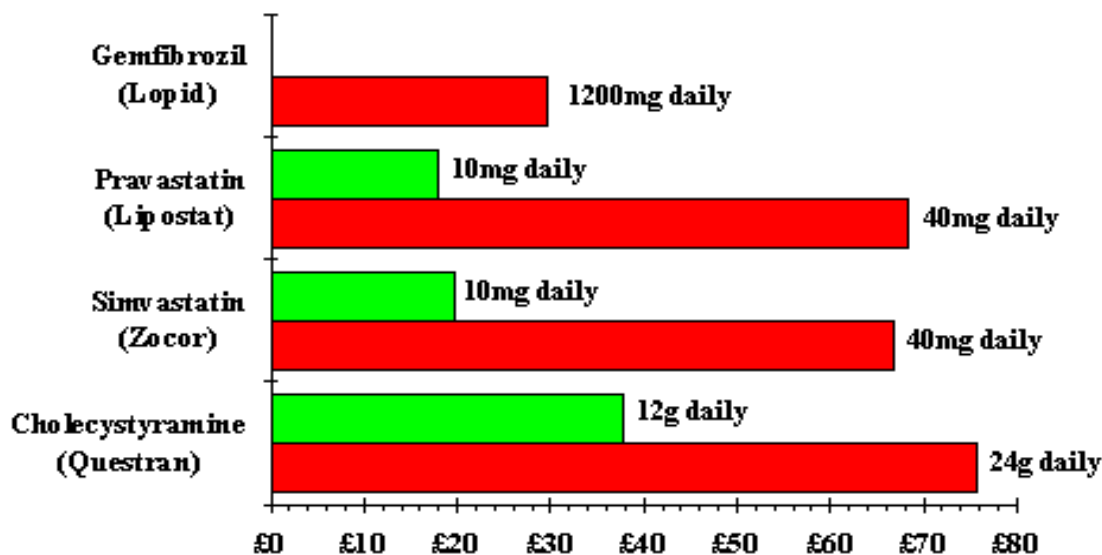
The benefits of reducing cholesterol are established beyond doubt. Prevention of CHD is still too large a problem to be accomplished with drugs alone. A population based strategy to decrease CHD further must focus on reducing the content of saturated fat and cholesterol in the diet and further reduce smoking.

COSTS

- Over 35,000 prescriptions for lipid lowering drugs were dispensed in 1994 costing the GMS almost £900,000.

COST OF DRUGS IN HYPERLIPIDAEMIA TREATMENT FOR 28 DAYS

Drug costs are based on data from GMS 1995



CORRECTION, VOLUME 1, NUMBER 5, 1995

The cost of 28 days supply of Lisinopril 5mg daily was incorrect. The price should read £10.86 and not £5.43 as stated.

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