Iatrogenic profound hypoalphalipoproteinaemia: an unrecognised cause of very low HDL cholesterol

Michael J Murphy, Andrew Duncan, Barry D Vallance, Christopher J Packard, Denis St J O’Reilly

Summary
A significant reduction in plasma high density lipoprotein (HDL) cholesterol is a recognised consequence of treatment with probucol. By contrast, fibrate therapy in general has the opposite effect.

We report two cases where the combination of probucol and a fibrate led to profoundly reduced plasma levels of HDL cholesterol associated with very low levels of apolipoprotein A-I (apoA-I). In the first, bezafibrate was added to probucol, and in the second, probucol added to a combination of simvastatin and fenofibrate. In both cases, plasma levels of HDL and apoA-I returned towards normal after discontinuation of one or both drugs, indicating that the reduction was reversible.

Keywords: probucol, fibrates, hypoalphalipoproteinaemia

Case 1
A 57-year-old woman was referred to the cardiovascular risk factor clinic with hypercholesterolaemia (total cholesterol 9.35 mmol/l). She had no other prominent risk factors for cardiovascular disease and physical examination revealed no signs of hyperlipidaemia. For several years previously she had suffered from rheumatoid arthritis and was being treated with non-steroidal anti-inflammatory drugs. Baseline investigations included biochemical evaluation of thyroid, liver and renal function as well as fasting blood glucose and full blood count; no abnormalities were detected. Despite dietary intervention, total cholesterol remained elevated at 8.4 mmol/l (low density lipoprotein (LDL) cholesterol 6.55 mmol/l) and she was commenced on probucol 500 mg bid. Subsequently bezafibrate 400 mg nocte was added to her treatment regimen. Plasma high density lipoprotein (HDL) cholesterol before drug treatment was 1.0 mmol/l; it varied between 0.95 and 0.6 mmol/l after the introduction of probucol (normal > 1.0 mmol/l). Three months after the introduction of bezafibrate, HDL cholesterol had fallen to 0.1 mmol/l at which point the apoA-I level was 0.06 g/l (reference range 0.7–1.3 g/l). Within three months of stopping bezafibrate HDL cholesterol had returned to 0.7 mmol/l and apoA-I to 0.79 g/l. HDL rose further after probucol was discontinued. Cumulative results are shown in figure 1.

Case 2
An obese 36-year-old man with severe hypercholesterolaemia (total cholesterol 11.5 mmol/l; LDL cholesterol 8.55 mmol/l) and tendon xanthomata underwent coronary artery bypass grafting following recovery from a myocardial infarct. Investigations of thyroid, liver and renal function were carried out in addition to fasting blood glucose and full blood count; no causes of secondary hyperlipidaemia were identified. Over a period of several years his hypercholesterolaemia was treated with various lipid-lowering agents, either alone or in combination; they included colesterol, nicotinic acid, gemfibrozil and subsequently simvastatin, fenofibrate and probucol. While on treatment, the patient sustained a second myocardial infarct and underwent repeat bypass grafting. When probucol 500 mg bid was added to a combination of simvastatin 40 mg nocte and fenofibrate 200 mg tid, plasma HDL cholesterol fell within three months to 0.15 mmol/l (normal > 1.0 mmol/l); apoA-I at

![Figure 1](http://pmj.bmj.com/)

**Figure 1** Data points: 1, probucol 500 mg bid started; 2, bezafibrate 400 mg nocte started; 3, bezafibrate stopped; 4, probucol stopped; 5, measurements repeated off lipid-lowering treatment. Time intervals vary between data points shown. See text for details
Discussion

The basis for the reduction in HDL cholesterol normally seen with probucol probably relates to a decrease in the synthesis of apolipoprotein A-I (apoA-I), one of the principal protein components of HDL particles. However, there is evidence that it may be due in part to an increase in the plasma concentration and activity of cholesterol ester transfer protein. Although decreased lipoprotein lipase activity has been reported during probucol treatment, very low density lipoprotein (VLDL) catabolism does not appear to be affected. In contrast with probucol, bezafibrate is associated with concomitant rises in HDL cholesterol, apoA-I and apoA-II, both in patients with hypertriglyceridaemia and those with hypercholesterolaemia. Increased plasma apoA-I levels have also been described with fenofibrate, usually in association with a rise in plasma HDL cholesterol (see table).

The profound reduction in plasma levels of apoA-I and HDL seen in case 1 soon after bezafibrate was added to probucol made an interaction between the two drugs likely. This suspicion was strengthened when levels of both rose once bezafibrate was discontinued, returning in the case of apoA-I to normal and in the case of HDL to values similar to those seen prior to the introduction of bezafibrate (see figure 1). Case 2 was being treated with both fenofibrate and simvastatin when probucol was added, so the possibility of an interaction involving simvastatin cannot be ruled out. However, the development of profoundly reduced plasma levels of HDL cholesterol and apoA-I soon after the advent of another probucol–fibrate combination seems unlikely to have been coincidental, and an interaction between probucol and fenofibrate is therefore more likely.

The exact nature of this interaction between probucol and fibrates remains speculative. Potentiation of probucol by the fibrates seems more likely, a priori, than alteration of the properties of bezafibrate and fenofibrate by probucol. Fibrate-induced changes in the structure and composition of HDL particles may have rendered them more susceptible to the effects of probucol on apoA-I synthesis, or may have made them more unstable, thereby resulting in an increased fractional catabolic rate. Alternatively, displacement of probucol by fibrates from binding sites on plasma proteins may have enhanced the bioavailability of probucol, thereby potentiating its actions on HDL synthesis and/or breakdown. Alterations in the absorption and/or excretion of probucol induced by the fibrates are less plausible explanations.

Further characterisation of this interaction will require detailed examination of sequential fasting lipid profiles in each patient, initially off and subsequently on treatment with the agents involved, separately and in combination. (Wash-out periods between profiles would need to take account of the long half-life of probucol in the body.) Studies might usefully include analysis of the associated changes in HDL composition and subclasses, as well as turnover studies of apoA-I synthesis. As the patients were given different fibrates, it would in addition be of interest to compare the results obtained in each patient with bezafibrate and fenofibrate.

The possibility of inducing profound hypoalphalipoproteinaemia, and a commensurate reduction in plasma HDL cholesterol, should be borne in mind if probucol is to be combined with fibrate therapy. Although in both of these cases the alteration in lipoprotein metabolism reversed following discontinuation of the combination, it cannot be assumed that this will always occur. Finally, the potential effects on cardiovascular risk of iatrogenic profound hypoalphalipoproteinaemia are unknown.

Table Effect of drug treatment on lipid levels

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total cholesterol</th>
<th>LDL cholesterol</th>
<th>HDL cholesterol</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probucl</td>
<td>↓5–20%,</td>
<td>↑10–15%,</td>
<td>↑20–25%,</td>
<td>++</td>
</tr>
<tr>
<td>Fibrates</td>
<td>↓15–30%,</td>
<td>↓5–35%,</td>
<td>↑10–30%,</td>
<td>↓40–50%,</td>
</tr>
</tbody>
</table>

Learning point

Prescribers should be aware that combining probucol with a fibrate may result in very low levels of HDL.
Polymyalgia rheumatica, temporal arteritis and malignancy

CA Speed, I Haslock

Summary
The use of steroid therapy in polymyalgia rheumatica and temporal arteritis is necessary and usually effective, but may mask coexisting disease. The importance of early consideration of other disorders in such patients is illustrated by three case histories.

Keywords: polymyalgia rheumatica, temporal arteritis, malignancy, Waldenstrom’s macroglobulinaemia

Polymyalgia rheumatica (PMR) and temporal arteritis (TA) are disorders which are usually steroid responsive and easily monitored by the clinical picture and acute phase parameters such as the erythrocyte sedimentation rate (ESR). The clinical features are often non-specific and steroid therapy may mask features of coexisting diseases. We describe three cases of PMR/TA, in which an apparent flare of the disease was in fact an initial presentation of another disease – in two cases, a malignancy. The importance of maintaining a high degree of clinical suspicion in the management of such patients is emphasised and the association of PMR/TA with other disorders is discussed.

Case histories

Case 1
A 60-year-old male smoker presented with a two-month history of bilateral temporal headaches. Examination revealed pulsatile, thickened temporal arteries. An ESR was 97 mm/h; a temporal artery biopsy confirmed cranial arteritis. A chest X-ray performed at the time was consistent with chronic obstructive Airways disease, with no focal lesions. His symptoms and ESR responded dramatically to oral steroids.

Eighteen months later, he was re-referred by his general practitioner with letheragy and an ESR of 84 mm/h. This had failed to respond to increasing his steroids from 5 to 40 mg daily. A right supraclavicular lymph node was palpable. A chest X-ray revealed an enlarged right hilum and right lower lobe collapse. A lymph node biopsy confirmed adenocarcinoma.

Case 2
A 60-year-old male smoker presented to his general practitioner with a seven-month history of temporal headaches, scalp tenderness and proximal myalgia. An ESR was 116 mm/h. A diagnosis of temporal arteritis was made and he responded dramatically to steroids. One month later, whilst on 40 mg prednisolone daily, he returned to his doctor complaining of lethargy. An ESR was 107 mm/h. He failed to respond to increasing his steroid dosage and was referred to the rheumatology clinic. A chest X-ray was performed and revealed consolidation and collapse of the right lower and middle lobes. Bronchoscopy confirmed squamous cell carcinoma.

Case 3
A 53-year-old woman presented to her general practitioner with a two-month history of proximal muscle stiffness and non-specific headaches. Examination was unremarkable; an ESR was 65 mm/h. A diagnosis of polymyalgia rheumatica was made. Her symptoms responded to prednisolone (30 mg/day) within two days. However, her ESR remained elevated, varying between 45 and 62 mm/h, so she was referred for a specialist opinion. Further investigations revealed an IgM kappa paraproteinaemia; urinary Bence Jones proteins were absent. Her plasma viscosity was 1.89 cp; full blood count and C-reactive protein were normal, apart from a mild neutrophilia. A bone marrow biopsy was consistent with a diagnosis of Waldenström’s macro-

References
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