

Hypothyroidism and simvastatin

To the Editor—The recent case report from Hung and Yeung¹ highlights the importance of checking for hypothyroidism before commencing lipid-lowering therapy, but a number of other points arising from this case are worthy of discussion.

Similar cases have been described before,² but attributing the myopathy to the use of simvastatin in this case may not be correct. The serum creatine kinase (CK) does not appear to have been checked prior to starting treatment and may have been elevated even before the drug was commenced. Asymptomatic elevation of CK with varying levels can occur spontaneously in hypothyroidism, whereas elevations in CK occurring with statin-induced myopathy normally resolve within a few days and do not recur once the drug is withdrawn, as was reported in this case. An early detailed review of hypothyroid myopathy from a former colleague at University College Hospital, London,³ reported cases with CK levels up to 4640 IU/L (normal range, 10-120 IU/L), and there have been other case reports of spontaneous rhabdomyolysis in hypothyroidism severe enough to cause acute renal failure.⁴

It is important to check for hypothyroidism in all patients with severe hyperlipidaemia but whether this should be checked in all subjects who are to be started on statins in Hong Kong could be debated as the 'pick-up rate' would be very low. We, however, consider it is essential to check the CK and liver enzymes before commencing therapy with statins or fibrates to provide a baseline and to identify potential problems, as in this case. Many lipid experts now consider that there is little point in checking the CK after starting statin therapy, (assuming appropriate investigations were performed before starting), as the risk of myopathy is so small unless there are other predisposing factors, such as potential drug interactions. Myopathy can occur suddenly at any time so that intermittent monitoring of CK may not provide a warning of impending problems. Our own practice is not to assess the CK level routinely, unless the patient is on the highest dose of the range for the statin used, or a combination of treatments is being used which increases the risk. Then, we consider it may be worth checking the CK level after 1 to 2 months, and periodically thereafter.

It is thought that hypothyroidism predisposes to the myopathy seen with statins but this impression

results mainly from retrospective case studies. Prospective data would be hard to obtain as hypothyroidism would normally be treated before embarking on lipid-lowering medication. The early detection and treatment of the thyroid problem in the patient described might also have avoided the need to undergo cardiac catheterization, as electrocardiogram changes are known to occur with hypothyroidism and resolve with thyroid replacement, as in this case.

The other main consideration arising from this case is the dose of simvastatin used. The average response to any particular dose of statin is predictable,⁵ and if it were assumed that the patient had coronary heart disease (CHD), the reduction in LDC-cholesterol required to achieve the more conservative European target of 3.0 mmol/L,⁶ would be 59% from the starting level of 7.38 mmol/L. The predicted dose of simvastatin to achieve this would, thus, be over 80 mg/d.⁷ Even if the target was the National Cholesterol Education Program goal of 4.1 mmol/L for patients with less than two other CHD risk factors,⁸ the reduction in LDC-cholesterol required would still be 44%, requiring an average simvastatin dose of 40 mg/d. The manufacturer's recommended starting dose of simvastatin is 20 mg/d, and the use of a 'homeopathic' dose of 5 mg/d in this case seems quite inappropriate. It is a common misconception that Asian patients show a greater response to statins than Caucasians. This probably arises because LDL-cholesterol values in patients with CHD are usually lower in Asian countries than in the west so the target levels determined from Western guidelines can be achieved with smaller doses. It could be argued that smaller doses will produce fewer side effects and the dose can be subsequently titrated upwards. The incidence of side effects with simvastatin, however, is virtually the same over the dose range of 5 to 20 mg/d,⁹ and doses of statins are often not titrated up to reach appropriate goals in everyday practice. It might also be argued that starting with a higher dose in this case may have caused a more severe myopathy, but this is unlikely, and one error should not be taken as an excuse for another.

B Tomlinson, MD, FRCP (Edin)
W Lan, MB, PhD
Department of Medicine and Therapeutics
The Chinese University of Hong Kong
Prince of Wales Hospital
Shatin, Hong Kong

References

1. Hung YT, Yeung VT. Hypothyroidism presenting as hypercholesterolaemia and simvastatin-induced myositis. *HKMJ* 2000;6:423-4.
2. al-Jubouri MA, Briston PG, Sinclair D, Chinn RH, Young RM. Myxoedema revealed by simvastatin induced myopathy. *BMJ* 1994;308:588.
3. Khaleeli AA, Griffith DG, Edwards RH. The clinical presentation of hypothyroid myopathy and its relationship to abnormalities in structure and function of skeletal muscle. *Clin Endocrinol (Oxf)* 1983;19:365-76.
4. Sekine N, Yamamoto M, Michikawa M, et al. Rhabdomyolysis and acute renal failure in a patient with hypothyroidism. *Intern Med* 1993;32:269-71.
5. Roberts WC. The rule of 5 and the rule of 7 in lipid-lowering by statin drugs. *Am J Cardiol* 1997;80:106-7.
6. Pyorala K, De Backer G, Graham I, Poole-Wilson P, Wood D. Prevention of coronary heart disease in clinical practice. Recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. *Eur Heart J* 1994;15:1300-31.
7. Dujovne CA. New lipid lowering drugs and new effects of old drugs. *Curr Opin Lipidol* 1997;8:362-8.
8. National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation* 1994;89:1333-445.
9. Plosker GL, McTavish D. Simvastatin. A reappraisal of its pharmacology and therapeutic efficacy in hypercholesterolaemia. *Drugs* 1995;50:334-63.

Author's reply

To the Editor—Contrary to attributing the myopathy to the use of simvastatin, our case report aimed at advocating the importance of excluding underlying causes of hypercholesterolaemia before contemplating lipid-lowering therapy. As a matter of fact, we stated in the discussion that the “elevated CK level was wrongly attributed to the use of simvastatin”. Our case served to illustrate the fact that raised CK levels, when detected only after initiation of statin therapy, could be wrongly attributed to an adverse drug reaction and result in further delay in diagnosis.

As stated in our paper, a Dutch group reported a 4.2% prevalence of hypothyroidism in patients referred for dyslipidaemia.¹ We are aware of the fact that there is no such data in Hong Kong and have not suggested routine thyroid function tests for all patients with dyslipidemia. As mentioned in the discussion, however, it is necessary for clinicians to obtain a meticulous history, and to perform a careful physical examination to search for symptoms and signs of underlying metabolic disorders, including hypothyroidism. This can be followed by measurement of the thyroid stimulating hormone (TSH) levels for confirmation of suspected hypothyroidism. After all, the cost of performing a TSH test should be minimal when compared to that of life-long statin therapy, let alone any potential side effects from therapy.

We agree that higher doses of statins have been advocated to achieve target lipid levels in more recent international publications. One, however, has to bear in mind that the patient was seen several years ago (1998). Further, it is not uncommon to commence a statin at a smaller dose, and titrate the dosage up in clinical practice, particularly if the therapy is for primary prevention in patients without multiple risk factors. In fact, the starting dose of simvastatin quoted in the *Manual of Lipid Disorders* is given as 5 to 10 mg/d.²

YT Hung, MB, ChB, FHKAM (Medicine)
VTF Yeung, MD, FRCP
Department of Medicine and Geriatrics
Our Lady of Maryknoll Hospital
118 Shatin Pass Road
Wong Tai Sin
Hong Kong

References

1. Diekman T, Lansberg PJ, Kastelein JJ, Wiersinga WM. Prevalence and correction of hypothyroidism in a large cohort of patients referred for dyslipidaemia. *Arch Intern Med* 1995;155:1490-5.
2. Gotto A, Powall H. *Manual of lipid disorders*. 2nd ed. Baltimore: Williams and Wilkins; 1999:304.