

# Efficacy of statin therapy: possible effect of phenytoin

M J Murphy, M H Dominiczak

## Summary

Statins are currently the most widely prescribed lipid-lowering drugs. Individual statins are known to be metabolised by the CYP3A4 isoform of the cytochrome P450 system. The effect of CYP3A4 inducers such as phenytoin on the metabolism and efficacy of these agents is unknown. We report a patient with familial hypercholesterolaemia and epilepsy in whom the introduction and subsequent discontinuation of phenytoin were associated with marked changes in the lipid response to treatment with simvastatin and atorvastatin. The serum activity of  $\gamma$ -glutamyl transpeptidase may have acted as a marker of microsomal induction by phenytoin, since it rose markedly when phenytoin was introduced and returned to normal after it was discontinued.

**Keywords:** statins; phenytoin; drug interaction

Statins are widely used in the treatment of hyperlipidaemia. Various drug interactions have been noted, the most frequently cited involving digoxin and warfarin. In the case of simvastatin and pravastatin, the potential for interactions involving hepatic microsomal enzymes has been identified; both have been found to cause statistically significant changes in the pharmacokinetics of substrates for specific cytochrome P450 isoforms.<sup>1</sup> Similarly, the manufacturer's data sheet for Lescol® (fluvastatin) mentions the possibility of interaction with drugs metabolised by the CYP2C family of isoforms.<sup>2</sup>

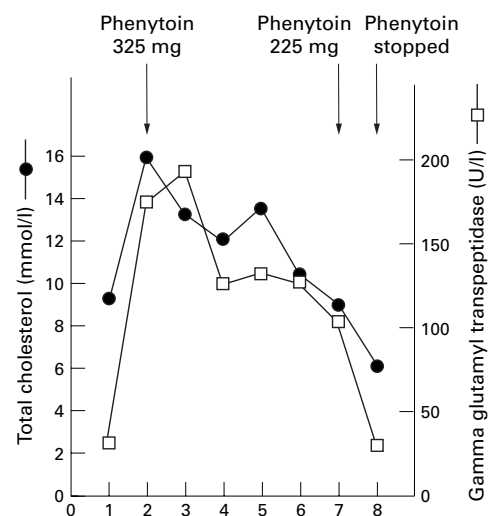
Statins are themselves metabolised by the cytochrome P450 system (specifically the CYP3A4 isoform), raising the possibility that other drugs may influence their metabolism, and, by extension, their efficacy. The manufacturer's data sheet for Lipitor® (atorvastatin) cautions against the concurrent use of inhibitors of the CYP3A4 isoform, such as macrolide antibiotics and azole antifungals, based on experience with other statins.<sup>3</sup> However, the effect of CYP3A4 inducers such as phenytoin or rifampicin on atorvastatin is unknown. We present strong circumstantial evidence that phenytoin may alter the efficacy of atorvastatin, and simvastatin, based on a patient with familial hypercholesterolaemia who was treated concurrently with phenytoin.

## Case report

A 50-year-old woman was referred to the Lipid Clinic in 1995. She was taking simvastatin 10 mg; her total cholesterol was 9.4 mmol/l and triglycerides 1.87 mmol/l. She had never smoked. Her father had died at 45 years of age from a myocardial infarct; one brother had coronary artery bypass grafting at 35 years of age. The patient had gross thickening of both Achilles tendons and a diagnosis of familial hypercholesterolaemia was made. Epilepsy had been diagnosed 6 years previously for which the treatment was sodium valproate 200 mg tid.

On review 3 months later, the patient's anti-convulsant medication had been changed to phenytoin 325 mg. Her total cholesterol was now 15.99 mmol/l; she claimed to be complying fully with simvastatin 10 mg. Serum activity of  $\gamma$ -glutamyl transpeptidase ( $\gamma$ GT), which had previously been normal, was 175 U/l (reference range 5–50 U/l). Significant alcohol intake was denied, and there was no other evidence of this; mean red cell volume was 85 fl (80–100 fl).

Successive subsequent changes to her lipid-lowering therapy included increasing the dose of simvastatin step-wise to 40 mg, switching to



**Figure** Changes in total cholesterol and  $\gamma$ GT levels during statin treatment. The numbers on the x-axis refer to the statins received: 1=simvastatin 10 mg, 2=simvastatin 20 mg, 3=simvastatin 40 mg, 4=fluvastatin 40 mg, 5=fluvastatin 80 mg, 6=atorvastatin 40 mg, 7=atorvastatin 80 mg, 8=atorvastatin 80 mg

Department of Biochemistry, Gartnavel General Hospital, 1053 Great Western Road, Glasgow G12 0YN, UK  
M J Murphy  
M H Dominiczak

Correspondence to M J Murphy, Derriford Combined Laboratory, Derriford Hospital, Plymouth PL6 8DH, Devon, UK

Accepted 7 December 1998

fluvastatin 40 mg, and finally to atorvastatin, the dose of which was increased step-wise to 80 mg. During this period, the patient developed angina; coronary angiography revealed the presence of significant coronary heart disease. Her total cholesterol remained in excess of 10 mmol/l throughout. Finally, phenytoin was discontinued, in two steps: initially the dose was reduced to 225 mg (simultaneously, the dose of atorvastatin was increased from 40 to 80 mg); phenytoin was then withdrawn altogether. A marked reduction in her total cholesterol (to 6.24 mmol/l) coincided with a return to normal of the serum activity of  $\gamma$ GT. Total cholesterol has remained less than 7 mmol/l since the discontinuation of phenytoin; the patient remains on atorvastatin 80 mg. Selected results are shown in the figure.

### Discussion

The evidence presented here that phenytoin may affect the efficacy of some statins is important for several reasons. Firstly, the deterioration in total cholesterol that accompanied the introduction of phenytoin was clinically significant. The risk of coronary heart disease in familial hypercholesterolaemia and the role of statins in its treatment have both long been recognised.<sup>4-5</sup> Secondly, such an interaction has not previously been described, despite the fact that phenytoin is known to be an inducer of the isoform CYP3A4 which is involved in statin metabolism.<sup>6</sup> Thirdly, phenytoin appeared in this case to alter the efficacy of both atorvastatin and simvastatin, two of the statins with the greatest cholesterol-lowering potency. Fluvastatin 40 mg was no better in this regard, raising the possibility of a class effect.

Alternative explanations for the initial unexpected deterioration in our patient's total cholesterol (and marked rise in serum  $\gamma$ GT) were sought. There was no other evidence of liver dysfunction, although it is possible that the rise in serum  $\gamma$ GT was the sole manifestation of this. Stated compliance with simvastatin was 100%, and alcohol intake was denied. These findings did not, of themselves, provide strong evidence that phenytoin was responsible for the observed deterioration. As we could not test our hypothesis by discontinuing phenytoin, alternative approaches to lipid-lowering were tried. Successively, we increased the dose of simvastatin step-wise to 40 mg daily, switched to fluvastatin 40 mg, and finally introduced atorvastatin, starting at the lowest dose of 10

### Learning point

Prescribers should exercise caution when concurrently prescribing statin agents and inducers of hepatic microsomal enzymes

mg and increasing step-wise to the maximum dose of 80 mg. Despite these changes, the total cholesterol remained unacceptably high. When finally phenytoin was discontinued, in two steps, there was a marked improvement in total cholesterol; simultaneously, the serum activity of  $\gamma$ GT returned to normal. These findings provide stronger circumstantial evidence that phenytoin alters the efficacy of atorvastatin at least.

Demonstration of pharmacokinetic interactions between phenytoin and the individual statins has not been possible: in the case of simvastatin, the possibility of an interaction only came to light long after the pre-phenytoin sample had been discarded, while the cost of assaying atorvastatin in the presence and absence of phenytoin is prohibitive. Phenytoin levels remained within the therapeutic range while our patient remained on this agent, and were undetectable following discontinuation.

It is not clear what extra information would be provided by pharmacokinetic studies involving statins. The relationships between serum concentrations of individual statins and concentrations within the hepatocyte (the site of action of statins) are not fully understood. Although the relative activities of some metabolites of individual statins are known,<sup>7-8</sup> our understanding of statin metabolism, and of the ability of enzyme-inducing drugs to influence it, is likewise far from complete.<sup>9</sup>

In conclusion, we are currently not in a position to test our hypothesis that phenytoin induced CYP3A4 to metabolise atorvastatin and simvastatin (and possibly also fluvastatin) to less active metabolites, thereby reducing their cholesterol-lowering efficacy in our patient. However, we believe that the circumstantial evidence presented here makes such an interaction the most plausible explanation for the sequence of events described.

The authors would like to thank Ms Kathy McFall of the Department of Medical Illustration, West Glasgow Hospitals University NHS Trust, for her help in the preparation of the figure.

1 Horsmans Y, Deager JP, Van den Berge V, Abrassart M, Harvengt C. Effects of simvastatin and pravastatin on  $6\beta$ -hydroxycortisol excretion: a potential marker of cytochrome P450 3A. *Pharmacol Res* 1993;28:243-7.

2 Sandoz Limited. *Lescol® Data Sheet*. December 1993.

3 Parke-Davis & Co. *Lipitor® Data Sheet*. December 1996.

4 Slack J. Risks of ischaemic heart disease in familial hyperlipoproteinaemia states. *Lancet* 1969;ii:1380-2.

5 Mol MJTH, Erkelens DW, Leuvan JAG, Schouten JA, Stalenhoef AFK. Effects of synvinolin (MK-733) on plasma lipids in familial hypercholesterolaemia. *Lancet* 1986;i:936-9.

6 Nation RL, Evans AM, Milne RW. Pharmacokinetic drug interactions with phenytoin (part I). *Clin Pharmacokinet* 1990;18:37-60.

7 Vickers S, Duncan CA, Vyas KP, *et al*. In vitro and in vivo biotransformation of simvastatin, an inhibitor of HMG-CoA reductase. *Drug Metab Dispos* 1990;18:476-83.

8 Pan HY, DeVault AR, Wang-Iverson D, *et al*. Comparative pharmacokinetics and pharmacodynamics of pravastatin and lovastatin. *J Clin Pharmacol* 1990;30:1128-35.

9 Garnett WR. Interactions with hydroxymethylglutaryl-coenzyme A reductase inhibitors. *Am J Health-Syst Pharm* 1995;52:1639-45.

# Pentazocine-induced fibromyositis and contracture

C P Das, A Thussu, S Prabhakar, A K Banerjee

## Summary

**We report a case of myopathy, accompanied by widespread contractures predominantly involving the elbow and knee joints, following long-standing pentazocine abuse.**

**Keywords:** pentazocine; myopathy; contractures

Complications of parenteral narcotic abuse such as focal tissue damage (localised sclerosis of skin and subcutaneous tissue, indurations and nonseptic ulcerations) are well documented.<sup>1,2</sup> There are a few reports of myopathy following chronic pentazocine administration,<sup>3,4</sup> but the association with contractures around the shoulder and hip joints is still rare.<sup>5,6</sup> We report a patient with myopathy, accompanied by widespread contractures predominantly involving the elbow and knee joints, following long-standing pentazocine abuse. A detailed electrophysiological study of different muscle groups and biopsies from involved and healthy sites was also carried out.

## Case report

A 38-year-old doctor (figure 1) presented with a painless and progressive restriction of flexion around both the knee joints for 4 years. This had been followed by a similar problem involving both the elbow joints a year later. His main complaints were inability to squat, difficulty in dressing/undressing and generalised stiffness. Over the last 6 months he had mild limitation at the extremes of abduction of the right shoulder, and bilateral hip extension for which he had developed a compensatory lumbar lordosis. He had no complaints of any muscle weakness within the limited range of possible movements. He had been addicted to injection

of Fortwin (pentazocine) 1–2 ml intramuscular bid for the past 18–20 years. The site of injection was the right deltoid for the first 8 years, followed by sequential use of both glutei, quadriceps and the left deltoid. He had a history of frozen shoulder on the right side which subsequently improved. He was non-diabetic and non-hypertensive. There was no family history of any neuromuscular disorder.

Physical examination revealed a well-built man with marked contractures involving both the knee and elbow joints and mild limitations of abduction of right shoulder and extension of both hip joints. He walked with a lordotic gait and had marked woody indurations of the deltoids, biceps, glutei and quadriceps. Both elbows were semi-flexed with a 20° range of movement on either side. The knees could not be flexed beyond 80° and the right hand could not be abducted beyond 90°. Distal joints were normal. Muscle power was normal within the limited range of movements, and there was no sensory deficit. Laboratory studies disclosed the following values: haemoglobin 15.0 g/dl; white cell count  $6.0 \times 10^9/l$  (neutrophils 67%, lymphocytes 20%, monocytes 3%, eosinophils 10%); platelets  $275 \times 10^9/l$ ; erythrocyte sedimentation rate 2 mm 1st hour; serum urea 8.9 mmol/l; serum creatinine 0.09 mmol/l; aspartate transaminase 27 U/l; alanine transaminase 9 U/l; alkaline phosphatase 56.8 U/l; creatine kinase 324 U/l. Radiography revealed normal joint architecture. Electromyography (EMG) of the deltoids, triceps and quadriceps showed a reduced number of potentials, low in amplitude and of short duration. Polyphasias were increased (>40%) with a full recruitment pattern. EMG of the supraspinati was normal. Muscle biopsy showed a normal right soleus, whereas there was extensive fibrosis involving the left quadriceps (figure 2).

It was explained to the patient that his drug addiction was responsible for the condition, and he received drug rehabilitation treatment as well as vigorous physiotherapy with passive and active stretching exercises. At 6 months follow-up he had successfully overcome his addiction, but there was no change in his deformity apart from some increase in range of mobility around both the elbow joints to 40–45°, from the previous range of 20°.

## Discussion

Cutaneous complications of pentazocine injections were first described by Schlicher *et al.*<sup>1</sup> Swanson *et al.*, in their study of psychiatric aspects of pentazocine abuse,<sup>7</sup> noted a 33%

Postgraduate Institute  
of Medical Education  
& Research,  
Chandigarh, India  
160012  
Department of  
Neurology  
C P Das  
A Thussu  
S Prabhakar  
Department of  
Pathology  
A K Banerjee

Correspondence to Anil  
Thussu

Accepted 17 December 1998



**Figure 1** The patient (reproduced with his permission)