DOI:10.1111/j.1365-2125.2004.02128.x

Is decreased libido associated with the use of HMG-CoA-reductase inhibitors?

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Keywords
Hydroxymethylglutaryl-CoA Reductase Inhibitors, decreased libido, decreased testosterone

Received
29 August 2003
Accepted
5 February 2004

Aims and methods
To describe patients with decreased libido during use of a HMG-CoA-reductase-inhibitor, and to discuss causality and pharmacological hypotheses for this association by analysis of the adverse drug reactions (ADR) database of the Netherlands Pharmacovigilance Centre Lareb.

Results
Eight patients were identified as having decreased libido during use of statins. In two of these cases testosterone levels were determined and appeared to be decreased.

Conclusion
Decreased libido is a probable adverse drug reaction of HMG-CoA-reductase-inhibitors and is reversible. The ADR may be caused by low serum testosterone levels, mainly due to intracellular cholesterol depletion.

Introduction

Hydroxymethylglutaryl-coenzyme-A-reductase (HMG-CoA-reductase) inhibitors, or statins, are widely used for the treatment of hypercholesterolaemia. The most severe adverse drug reactions associated with HMG-CoA-reductase inhibitors are myopathy and disturbances in hepatic function. Meanwhile, there is increasing evidence in the literature that sexual disorders may also occur during therapy with these drugs [1].

The Netherlands Pharmacovigilance Centre Lareb, which maintains the spontaneous reporting system for adverse drug reactions in the Netherlands, received eight reports of decreased libido during the use of statins.

Reports

Patient A is a 46-year-old male with symptomatic familial hypercholesterolaemia (increased α lipoprotein), with a serum cholesterol of 7.1 mmol l^{-1}. The patient started treatment with fluvastatin, initially 20 mg daily, increased to 40 mg daily. Shortly after initiation of

therapy, the patient noticed a decrease in libido. His testosterone value was measured and determined at 7.2 nmol l^{-1} (morning value, normal range for adult men 12–35 nmol l^{-1}). At this time his cholesterol level had decreased to 5.9 mmol l^{-1}. Fluvastatin was withdrawn and 5 days later testosterone had increased to 13.2 nmol l^{-1} (morning value). The patient's libido had also returned to normal. The man concomitantly used aspirin 80 mg daily.

Patient B, a 54-year-old male, started treatment with pravastatin for nonfamilial hypercholesterolaemia (cholesterol 6.1 mmol l^{-1}). Within days after initiation of this therapy, he experienced a decrease in his libido. His testosterone level was determined at 5.8 nmol l^{1} (morning value), while his total cholesterol level had decreased to 4.5 mmol l^{-1}. Pravastatin was discontinued 7 months later, and after a few days his libido returned to normal. Four months later, testosterone level was determined again and had risen to 22.8 nmol l^{-1} (morning value). The patient used concomitantly aspirin 80 mg daily, diltiazem 200 mg daily, ramipril 1.25 mg daily and isosorbidemononitrate 60 mg daily.

Lareb received six more reports concerning a decreased libido in association with the use of statins, one of them concerning a woman (Table 1). In none of the reports on men were testosterone levels determined. In three cases the outcome is known: two patients recovered after withdrawal of the suspected drug and one recovered after switching to another HMG-CoA-reductase inhibitor.

Discussion

Libido is related to serum testosterone levels: lower testosterone levels decrease male libido [2]. Testosterone in males is produced mainly in the Leydig cells, where cholesterol is the main substrate. The Leydig cells can absorb cholesterol from the blood via the LDL-receptor, but are also capable of *de novo* cholesterol synthesis [3]. Statins may interfere with the synthesis of testosterone in three ways.

First, by decreasing plasma LDL-cholesterol, HMG-CoA-reductase inhibitors lower the total amount of cholesterol offered to the Leydig cell. Taking into account the amount of cholesterol in the blood, it is unlikely that this decrease will have a significant effect. In familial hypercholesterolaemia (patient A), the LDL-receptor is malfunctioning [4, 5], which makes the Leydig cell more dependent on *de novo* synthesis of cholesterol. Statins are rather liver selective, but are found in small quantities in the testes, where they can inhibit the*de novo* synthesis of cholesterol out of acetate by HMG-CoA-reductase [6].

Finally, high-dose simvastatin, and possibly other statins, directly suppress testosterone synthesis by inhibiting the 17-ketosteroid-oxidoreductase catalysed conversion from dehydroepiandrosterone and dehydroandrostenedione to androstenediol and testosterone, respectively [7].

Since cholesterol is necessary for the synthesis of testosterone, the effects of statins on testosterone levels have been the subject of several investigations. Most of these studies could not demonstrate a significant decrease

Table 1
Characteristics of reports of decreased libido in association with the use of HMG-CoA-reductase inhibitors in the Lareb database of adverse drug reactions

Patient	Sex/age	Drug, action	Concomitant medication	Latency	Outcome
A	M/46	Fluvastatin, withdrawn (described in text)	Aspirin 80 mg	Shortly after initiation	Recovered
B	M/54	Pravastatin, withdrawn (described in text)	Aspirin 80 mg, diltiazem, ramipril, isosorbidedinitrate	Within days after initiation	Recovered
C	M/47	Simvastatin, withdrawn		4 days	Unknown
D	F/58	Pravastatin, continued		Several months	Unknown
E	M/64	Simvastatin, continued	Diltiazem, isosorbidedinitrate, calciumcarbasalate, amiodarone, nitroglycerin	4 months	Unknown
F	M/53	Atorvastatin, withdrawn	Diclofenac, doxyxcyclin, amoxicilin	Several days	Recovered
G	M/67	Atorvastatin, switched to pravastatin	Acetylsalicylic acid, dipyridamol	Several weeks	Recovered after switch to pravastatin
H	M/50	atorvastatin, withdrawn		Unknown	Recovered

of free or total testosteron [5, 8, 9]. However, Azzarito *et al*. did find a mild but significant decrease of both basal and human chorionic gonadotrophin (hCG)-stimulated free testosterone levels in patients receiving treatment with simvastatin for polygenic (nonfamilial) hypercholesterolaemia [6]. We suggest that, for example by genetic polymorphism, 17-ketosteroid-oxidoreductase may be more vulnerable to interference of statins. The libido decrease seems to be reversible.

The cases presented above are spontaneous reports from practitioners, which often implies that clinical information is incomplete. In our cases testosterone values were measured only once or were not determined at all. However, despite lacking clinical information and the small number of patients described, spontaneous reports or case series of spontaneous reports have shown great value in generating hypotheses about new adverse effects of drugs [10].

Our reports on fluvastatin, pravastatin, simvastatin and atorvastatin and the suggested pharmacological explanation generate the hypothesis that decreased libido may be associated with the use of statins.

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