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HMG CoA Reductase Inhibitors and Impotence

Two Case Series from the Spanish and French Drug Monitoring Systems

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Abstract

Objective: HMG CoA Reductase inhibitors, more commonly called statins, are used in the pharmacological management of hyperlipidaemia. At present, the use of these drugs is increasing worldwide. They have been linked to certain adverse drug reactions, including impotence. The aim of the present study is to explore the basis of the association between statin use and impotence using data from spontaneous reports.

Method: We analysed the cases of impotence associated with statins that were collected by the Spanish and French pharmacovigilance systems. We used cases of impotence as a numerator and consumption data as a denominator to estimate the cumulative reported incidence of impotence.

Results: Thirty-eight cases of impotence associated with statins have been identified in the database of the Spanish pharmacovigilance system; overall, there was a temporal sequence of events in all cases and the adverse reaction disappeared after drug withdrawal in 93% of the cases. Sixteen patients had also been treated with other drugs. In France, 37 cases were collected. In 85% of these cases recovery from the adverse reaction was observed after drug withdrawal; there was a positive rechallenge in five cases, and 15 patients were receiving other drugs at the same time. No significant differences among reported incidences with different statins were found.

Conclusion: Considering the widespread use of this drug class and the under-reporting of this particular reaction it could affect a large number of patients. The reaction seems to be reversible in most of the cases after drug withdrawal. Doctors should be aware of this potential adverse reaction when prescribing statins to their patients.

Introduction

HMG CoA reductase inhibitors, more commonly called statins, have an important role to play in the pharmacological management of hyperlipidaemias, including hypercholesterolaemias and combined hyperlipidaemia.[1] Accordingly, they are being increasingly used worldwide.[2] Long-term studies have provided evidence of significant reductions in morbidity and mortality in patients with ischaemic disease.[3] The most common adverse effects of statins are gastrointestinal disturbances, headache, skin rashes, dizziness, blurred vision, insomnia, dysgeusia, myopathy and increased aminotransferase levels.[1,4]

In addition, statins along with other lipid-lowering drugs, such as fibrates, have also been occasionally associated with impotence.[5-9] The aim of this study is to explore whether there is a rationale upon which the association of statin use and impotence could be based. The data used in this study originate from spontaneous reports.

Methods

Information from the French (1990–2004) and the Spanish (1989–2004) pharmacovigilance system databases was used; these databases include all the adverse drug reactions gathered from different sources from the French and Spanish regional pharmacovigilance centres since 1985 and 1982, respectively. Briefly, these are decentralised regional centres to which physicians and hospital pharmacists send spontaneous reports of suspected adverse drug reactions; events associated with the use of recently marketed drugs are specifically requested. By definition, cases of overdose are not included in the databases. *Ad hoc* committees evaluate all reports by using an algorithm to establish a causal relationship.[10] In both systems, all reports are included in the database regardless of causality and severity. All reactions were coded according to the WHO-ART dictionary.[11]

For the purpose of the study, only spontaneous reported cases of impotence associated with statins that were collected by the Spanish or French pharmacovigilance systems via the 'yellow card' system have been used; the terms 'impotence' and 'erectile dysfunction' were also used for retrieving cases.

Exposure information was gathered in Spain from the Especialidades Consumo de Medicamentos (ECOM) database of the Ministry of Health; this database contains information on community drug consumption through the Spanish National Health System, which covers virtually the whole population. In France, data were provided by the French National Health System database corresponding to drug sales for outpatients from 1999 to 2002. Drug consumption data were converted into defined daily doses (DDD)[12] and then into treated patients: a consumption of 365 DDD accounted for one patient treated in a year (DDD used values were those proposed by the WHO).[13] In this manner, the reported rate can be estimated as the quotient between the number of reported cases and the number of person-years.[14] The estimation of the rate was based on the assumption that the exposed population was large and the cases were scarce;[15] accordingly, the reporting of suspected adverse reactions associated with these drugs would follow a Poisson distribution and, based on its relation to the χ^2 distribution, confidence limits could be obtained.[16]

Results

In the Spanish database we identified a series of 38 cases of impotence associated with the use of statins during the period 1989–2004 (table I). The median age of case patients was 56 years (range 29–73); with regard to the reaction, the median induction period was 16.5 days (range 0–426) and the median recovery period was 27 days (range 6–215). Fifteen patients developed impotence in <15 days after treatment onset and 21 did so after 15 days (the induction period was unknown for two patients); 16 patients were receiving other drugs at the same time. There was a temporal sequence of events in all cases. Twenty-five of 27 patients in whom the drug was withdrawn improved; 1 of 25 patients improved after taking the drug on alternate days instead of taking it daily. In three patients in whom the medication was not withdrawn, the condi-

Table I. HMG CoA reductase inhibitor (statin)-induced impotence: main features of the cases detected from the Spanish pharmacovigilance system (1989–2004)

Case no.	Age (y)	Drug	Dose (mg)	Induction period[a] (d)	Recovery period (d)	Other drugs; comments
1	55	Atorvastatin	10	57	NS	
2	46	Atorvastatin	10	62	Continued	Indapamide, felodipine, aspirin (acetylsalicylic acid), isosorbide dinitrate
3	47	Atorvastatin	10	3	12	
4	55	Atorvastatin	10	16	NS	
5	50	Atorvastatin	10	0	8	Aspirin; history of impotence with pravastatin and fluvastatin
6	63	Atorvastatin	10	3	18	
7	66	Atorvastatin	20	42	8	Chlortalidone, diltiazem, allopurinol
8	44	Atorvastatin	10	166	Continued	Allopurinol, colchicine; heavy smoker
9	50	Atorvastatin	NS	1	NS	
10	71	Atorvastatin	10	47	NS	Acarbose; diabetes mellitus
11	68	Atorvastatin	20	183	Continued	Fenofibrate
12	73	Atorvastatin	10	5	NS	Ambroxol, simvastatin, doxazosin
13	62	Atorvastatin	10	13	28	
14	63	Atorvastatin	10	17	Continued	Metformin; diabetes mellitus
15	44	Atorvastatin	10	211	215	
16	54	Atorvastatin	20	117	53	
17	63	Cerivastatin	0.2	13	NS	
18	60	Fluvastatin	20	90	Continued	
19	38	Lovastatin	20	131	NS	
20	56	Lovastatin	20	7	NS	Nifedipine, chlordiazepoxide
21	38	Lovastatin	20	15	NS	
22	39	Lovastatin	20	4	NS	
21	64	Lovastatin	20	NS	NS	Ramipril, paracetamol (acetaminophen), codeine phosphate, aspirin
24	72	Lovastatin	20	25	Continued	
25	56	Lovastatin	20	NS	NS	Aspirin, verapamil
26	71	Pravastatin	10	16	NS	
27	60	Pravastatin	20	396	61	
28	56	Simvastatin	10	0	NS	Lovastatin
29	43	Simvastatin	20	426	NS	
30	57	Simvastatin	10	31	NS	Enalapril, nifedipine
31	56	Simvastatin	10	1	6	Folic acid, paracetamol, acenocumarol, interferon α-2a, prednisone
32	62	Simvastatin	20	375	Continued	
33	39	Simvastatin	40	91	NS	
34	64	Simvastatin	10	3	27	
35	44	Simvastatin	20	0	Continued	
36	62	Simvastatin	10	12	NS	Amlodipine
37	29	Simvastatin	20	155	NS	Ibuprofen, aceclofenac, pantoprazole
38	71	Simvastatin	10	0	32	

a The time between the start of treatment and clinical diagnosis of impotence as recorded on the yellow card.

NS = not stated.

tion continued and there was no further information about the progress in eight patients. In 22 of the patients, no other drugs or conditions were reported and in two cases the patients had diabetes mellitus. There was one patients with a history of impotence related to previous use of different statins.

A series of 37 cases were collected in the French database from 1990 to 2004 (table II). The median age of the patients was 52 years (range 36–71). The median induction period was 37.5 days (range 2–2190) and the median recovery period was 16 days (range 2–30). Nine patients developed impotence within 15 days after treatment onset and 21 did so after 15 days (the induction period was unknown in 7 patients); 15 patients were also receiving other drugs and three had diabetes. The reaction improved in 28 patients after drug withdrawal; in five patients the reaction continued after the drug was withdrawn; in one patient the drug was not withdrawn and the reaction continued; there was no information about the progress in three patients. In five patients a positive rechallenge was observed; a previous history of impotence was noted in one patient receiving nifedipine and fenofibrate and in three patients receiving other statins.

The reported incidence rates of impotence for the various statins are shown in table III and table IV. No clear correlation between reported rates and lipophilicity was observed.

Discussion

Impotence is a condition that is not commonly reported as an adverse drug reaction; several reasons could account for this under-reporting: (i) doctors usually do not ask about this type of problem; (ii) patients also usually do not complain about such a condition to their doctors; and (iii) it is sometimes difficult to attribute the condition to a particular cause as many factors could account for it. Also, there is no clear and reliable information on this particular topic for many drugs. This is the case for statins: no information at all on impotence can be obtained in this regard for all marketed statins in the summary of the product characteristics, except for atorvastatin.

Our data suggest an association between impotence and the use of statins. Although a causal relationship has not been – and cannot be – established on a case report basis, some of the features of the present series point to such a possibility; the two series from the Spanish and French pharmacovigilance systems are consistent.

In all cases there was a reasonable temporal relationship between the administration of the statins and the onset of the condition, in most of the cases impotence disappeared or improved after statin withdrawal, and, finally, in several cases there was a positive rechallenge that permitted confounding by indication to be ruled out. Notwithstanding, in a few patients the presences of diabetes or some other drugs might have contributed partially or totally to the condition.

No clear characteristics could be identified in patients developing impotence; spontaneous reports are often compounded with incomplete clinical information. The elapsed time of drug exposure to the development of impotence ranged from 1 day to several years, which agrees with other case series reported in the literature. This has probably more to do with the type of the reaction itself and the way this is perceived by patients than with the real induction period of the reaction.

Data from the literature seem to reinforce this association since two additional case series of 42 and 89 cases of presumably statin-induced impotence have been previously published.[18-21] In the first one, the Australian Adverse Drug Reactions Advisory Committee identified 42 reports of impotence in association with simvastatin; the ages of the men in the two series ranged from 43 to 72 years (median 57 years) and the onset occurred from 48 hours to 27 months (median 6 weeks) since the drug was first taken. Simvastatin was the only drug implicated in 35 of the reports and there was a positive rechallenge in four patients. Out of 29 patients in whom recovery was mentioned, 14 recovered after the drug was discontinued whereas no recovery was reported for the other 15 at the time. Similarly, in the UK, the Committee on Safety of Medicines identified 89 cases of impotence: 49 associated with

Table II. HMG CoA reductase inhibitor (statin)-induced impotence: main features of the cases detected from the French pharmacovigilance system (1990–2004)

Case no.	Age (y)	Drug	Dose (mg)	Induction period[a] (d)	Recovery period (d)	Other drugs; comments
1	44	Atorvastatin	NS	NS	NS	Lysine acetylsalicylate, diltiazem, dihydroergotamine
2	53	Atorvastatin	10	60	30	Furosemide, carvedilol
3	50	Atorvastatin	10	30	30	Fluticasone propionate, salmeterol
4	58	Atorvastatin	10	45	30	
5	65	Atorvastatin	20	2	Continued	Diltiazem, pentoxifylline, acenocumarol
6	52	Atorvastatin	10	270	15	Cetirizine
7	57	Atorvastatin	40	7	15	
8	50	Atorvastatin	NS	9	Continued	
9	50	Atorvastatin	40	14	NS	Positive rechallenge
10	48	Atorvastatin	10	2190	NS	Impotence history with pravastatin
11	58	Atorvastatin	NS	7	NS	Clopidogrel; positive rechallenge
12	52	Atorvastatin	10	152	NS	Metformin, levothyroxine, lithium; history of impotence with fenofibrate, diabetes mellitus
13	43	Atorvastatin	10	183	NS	Valproic acid
14	59	Cerivastatin	0.4	21	7	
15	40	Cerivastatin	NS	30	25	
16	51	Cerivastatin	0.4	NS	NS	Metformin, acebutolol, glimepiride, hydrochlorothiazide, losartan; diabetes
17	59	Fluvastatin	20	150	NS	
18	52	Fluvastatin	20	30	NS	
19	47	Pravastatin	20	14	NS	History of importence with cerivastatin
20	63	Pravastatin	20	75	15	Celiprolol; history of impotence with nifedipine
21	47	Pravastatin	10	30	2	
22	71	Pravastatin	20	NS	NS	Positive rechallenge
23	38	Pravastatin	10	NS	Continued	
24	69	Simvastatin	20	730		Positive rechallenge
25	62	Simvastatin	10	NS	Continued	Betaxolol, clorazepate, diltiazem, bromazepam
26	55	Simvastatin	NS	12	NS	
27	63	Simvastatin	20	NS	NS	Perindopril; history of impotence with pravastatin, diabetes
28	42	Simvastatin	NS	NS	NS	Allopurinol
29	56	Simvastatin	10	90	NS	Captopril
30	41	Simvastatin	10	548	NS	
31	60	Simvastatin	20	90	NS	Carbasalate calcium, bepridil
32	51	Simvastatin	10	6	NS	
33	44	Simvastatin	10	11	NS	
34	46	Simvastatin	20	30	17	
35	52	Simvastatin	5	60	NS	
36	NS	Simvastatin	20	180	NS	Positive rechallenge
37	36	Simvastatin	20	90	NS	

a The time between the start of treatment and clinical diagnosis of impotence as recorded on the yellow card.

NS = not stated.

simvastatin, 26 with atorvastatin, 10 with pravastatin, 3 with fluvastatin and 1 with cerivastatin. The age range was 25–76 years (median 56). Other case series of statin-related sexual dysfunction have also been published recently.[22] Furthermore, in the 4S (Scandinavian Simvastatin Survival Study), 37 of

Table III. Reported incidences of HMG CoA reductase inhibitor (statin)-induced impotence in Spain[a]

Drug	No. of cases[a]	No. of DDDs[b]	Reporting rate per 1 000 000 male patient-years (95% CI)	Lipophilicity, C log P (octanol/water)[17][c]
Atorvastatin	12	489 082 015	8.96 (4.63, 15.64)	4.1
Cerivastatin	1	61 778 233	5.91 (0.15, 32.92)	1.5
Fluvastatin	1	58 646 859	6.22 (0.16, 34.68)	3.2
Lovastatin	7	228 064 124	11.20 (4.50, 23.08)	4.3
Pravastatin	2	270 912 190	2.69 (0.33, 9.73)	−0.2
Simvastatin	11	488 637 533	8.21 (4.10, 14.7)	4.7

a Periods considered (vary due to year of market introduction): simvastatin, 1990–2003; lovastatin, 1989–2003; pravastatin, 1991–2003; fluvastatin, 1995–2003; atorvastatin, 1998–2003; cerivastatin, 1998–2003.

b Data from drug sales to the Spanish National Health System. WHO DDD value: simvastatin 15mg; lovastatin 30mg; pravastatin 20mg; fluvastatin 40mg; atorvastatin 10mg; cerivastatin 0.2mg.

c Logarithm of the partition coefficient based on octanol/water phase.

DDDs = defined daily doses.

1814 men (2.04%) from the simvastatin group versus 28 of 1803 (1.55%) from the placebo group reported impotence;[23] although the difference was not significant because of the sample size (Fisher's exact test, p = 0.32), this difference would account for an attributable risk for simvastatin of 24.02% in the setting of this randomised clinical trial.

Since the pathways for their actions and the structures of the various types of lipid-lowering drugs are different and the result of the use of these drugs is a decrease in the cholesterol levels, testosterone synthesis may be affected.[24,25] This mechanism could explain the association between impotence and all types of lipid-lowering drugs since libido is closely related to serum testosterone levels. In addition, in familial hypercholesterolaemia, the low density lipoprotein receptor malfunctions,[26] which makes the Leydig cell more dependent on *de novo* synthesis of cholesterol; statins are found in small quantities in the testes, where they can inhibit this *de novo* synthesis of cholesterol.

Since reported rates underestimate the real rates of adverse effects, the true risk for this particular reaction is likely to be higher. Although atorvastatin and simvastatin seem to point to a higher rate, no significant differences were observed between these figures.

Conclusion

In summary, these series further emphasise the possible association between statins and impotence. Doctors should be aware of this potential adverse reaction, which could affect a large number of patients, considering the wide use of this medication and the potential under-reporting of this particular reaction.

Table IV. Reported incidences of HMG CoA reductase inhibitor (statin)-induced impotence in France[a]

Drug	No. of cases[a]	No. of DDDs[b]	Reporting rate per 1 000 000 male patient-years (95% CI)	Lipophilicity, C log P (octanol/water)[17][c]
Atorvastatin	6	329 662 525	6.64 (2.43, 14.46)	4.1
Cerivastatin	3	98 285 010	11.14 (2.30, 32.56)	1.5
Fluvastatin	1	77 336 200	4.72 (0.12, 26.30)	3.2
Pravastatin	2	323 972 540	2.25 (0.27, 8.14)	−0.2
Simvastatin	4	320 971 510	4.55 (1.24, 11.64)	4.7

a Period considered: 1999–2002.

b Data from the French National Health System corresponding to drug sales for outpatients. WHO DDD value: simvastatin 15mg; pravastatin 20mg; fluvastatin 40mg; atorvastatin 10mg; cerivastatin 0.2mg.

c Logarithm of the partition coefficient based on octanol/water phase.

DDDs = defined daily doses.

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