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HMG-CoA-reductase inhibitors and taste disorders

Introduction

HMG-CoA reductase inhibitors (statins) are widely used in primary and secondary prevention of cardiovascular diseases because of their effects on both the total cholesterol level and the LDL-cholesterol level. HMG-CoA-reductase inhibitors are competitive inhibitors of 3-hydroxy-3-methylglutargyl coenzyme-A reductase, which plays a role in the synthesis of cholesterol. The adverse drug reactions most frequently associated with the use of HMG-CoA-reductase inhibitors are gastrointestinal complaints, myalgia and slight elevation of the liver-enzymes. More rarely, severe adverse drug reactions like myopathy and rhabdomyolysis may occur [1].
The Netherlands Pharmacovigilance Centre Lareb received 21 reports of taste disorders associated with the use of HMG-CoA-reductase inhibitors. Taste disorders are not mentioned in the SPC of any of these drugs currently marketed in the Netherlands [2-6].
The chemosensory systems of the body (like taste and smell) play roles in maintaining normal metabolic body functions. Pathology of taste may result in two major functional abnormalities: loss of acuity, which can be either diminished (hypogausia) or a total loss of the ability to taste (ageusia), or the distortion of taste (parageusia). Various drugs, like penicillamine, clarithromyin and aspirin have been reported to alter the ability to taste [7]. Although not life-threatening, persisting loss of taste may have severe impact on the patient's well being and should be considered as a disabling condition.

Reports

On June 5, 2004 the database of the Netherlands Pharmacovigilance Centre Lareb contained 21 reports of taste disorders associated with the use of HMG-CoA-reductase inhibitors. Four reports refer to taste loss, five reports to a 'bitter taste', two reports to a metallic taste, five reports mention the sensation of non-specified altered taste perceptions (parageusia), five reports mention non-specified taste disorders. Only one report also mentions a smell disorder.
From the reports of taste disorders, seven concerned simvastatin, three pravastatin and six atorvastatin, three fluvastatin and one cerivastatin.
In four cases the suspect HMG-CoA-reductase inhibitor has been discontinued and in these cases the patient (partially) recovered. The mean time to onset is 31 days (range 1 day to 18 months). Table 1 shows an overview of all reports concerning taste disorders associated with the use of HMG-CoA-reductase inhibitors.

Table 1. reports of taste disorders associated with the use of HMG-CoA-reductase inhibitors

Patient sex, age	Suspected drug, dosage	Concomitant medication	Adverse drug reaction	Time to onset
A, F, 63	simvastatin, 2 dd 20 mg	metoprolol	taste loss	10 weeks after start
B, M, 47	simvastatin 1 dd 20 mg	fluoxetine, acetyl salicylic acid, metoprolol, diltiazem	taste perversion	not specified
C, F, 69	simvastatin 1 dd 10 mg	captopril, hydrochlorthiazide	taste perversion	not specified
D, F, 74	pravastatin 1dd 10 mg clarithromycine 500 mg 1dd	cetirizine, calcium-carbonate	bitter taste	1 day
E, F, 56	pravastatin 20 mg 1dd1	none reported	tast loss and loss of smell	14 weeks
F, F, 59	fluvastatin 20 mg 1dd1	gemfibrozil, enalapril	taste bitter gastro-intestinal disorder	not specified
G, F, 73	atorvastatin 20 mg 1dd1	acetyl salicylic acid, dipyridamol	taste bitter mylagia	3 days

Patient sex, age	Suspected drug, dosage	Concomitant medication	Adverse drug reaction	Time to onset
H, F, 53	simvastatin 20 mg 1dd1	insulin	salty taste	18 months
I, M, 58	simvastatin 10 mg 1dd1	psyllium fibres, acetyl salicylic acid, amitryptiyline	taste disorder	23 days
J, F, 52	atorvastatin 20 mg 1dd1	acetyl salicylic acid	sweet taste	1 week
K, F, 58	cerivastatin 0.2 mg 1dd1	paracetamol, diclofenac/miso-prostol, omeprazol, levothyroxine	taste loss	1 week
L, F, 43	atorvastatin 10 mg 1dd1 captopril 50 mg 3dd1l	acetyl salicylic acid, sotalol, amlodipine	taste loss, peculiar taste	19 days
M, M, 66	fluvastatin 40 mg 1dd1 clopidogrel 75 mg 1dd1	acetyl salicylic acid, sotalol	taste loss, peculiar taste	6 weeks
N, F, 46	simvastatine 20 mg 1dd1	paracetamol, beclomethason	bitter taste, flatulence, edema	4 days
O, F, 69	fluvastatin 40 mg 1dd1	famotidin, acenocoumarol, flecainide, triamcinolon, hydrochlorothiazide	taste perversion, glossitis	2 weeks
P, M, 67	pravastatin 20 mg 1dd1	paroxetine, furosemide, nitroglycerine spray, bisoprolol, tildiazem, carbasalate calcium	taste loss	not specified
Q, M, 81	atorvastatin 10 mg 1dd1	phenprocoumon	taste and smell alteration (increased)	1 week
R, F, 69	simvastatin 20 mg 1dd1	thiamazol, triamterene/chloramphe-nicol, nifidepine, carbasalate calcium, atenolol	taste bitter	not specified
S, M, 55	atorvastatin 20 mg 1dd1	acenocoumarol, oxazepam	taste metallic	not specified
T, M, 71	simvastatin 20 mg 1dd1	tamsulosine, pantoprazol, indopamine, paracetamol	taste metallic	not specified
U, F, 64	atorvastatin 20 mg 1dd1	bisoprolol, acenocoumarol,	taste perversion	not specified

Other sources of information

Literature

According to Henkin several lipid-lowering drugs like cholestyramine and clofibrate and gemfibrozil have been reported to alter taste and smell function. Lovastatin has also been reported to induce a metallic phantogeusia in 1% of the patients according to this review article [8]. Pravastatin has been reported to induce dysgeusia in one case report [9].

Databases

On June 10, 2004, the database of the Netherlands Pharmacovigilance Centre contained 2360 ADRs associated with the use of HMG-CoA-reductase inhibitors. The reporting odds ratio among these reports was 0.77 (95% CI 0.50-1.19), indicating that taste disorders associated with HMG-CoA-reductase inhibitors are not disproportionally present in the Lareb database.

The database of the WHO contained 382 ADRs concerning taste disorders associated with the use of HMG-CoA-reductase inhibitors. These ADRs are not disproportionally present in the database.

Mechanism

It has been suggested by Henkin that HMG-CoA-reductase inhibitors may affect the ability to taste by affecting bile acid formation and fatty acid metabolism, which may affect olfactory receptor growth and development. Since smell contributes to the taste to a large extend, this may explain the occurrence of taste alterations. It is not clear if this also plays a role in the reports submitted to Lareb. Only one of the 21 reports also mentions smelling disorders.

Conclusion

Taste disorders associated with the use of HMG-CoA-reductase inhibitors are rarely reported in literature. Despite the lack of disproportionality in the databases, the number of reports in our database, together with a possible pharmacological explanation supports a causal relationship. Taste disorders should be included in the SPCs of all HMG-CoA-reductase inhibitors.

References

1. Aursnes I. Dukes MNG, Aronson JK, editors. Meyler's Side Effects of Drugs. 14 ed. Amsterdam: Elsevier; 2000; 44, Drugs affecting lipid metabolism. p. 1527-37.
2. Dutch SPC of Zocor®. (version date 15-12-2000) http://www.cbg-meb.nl/IB-teksten/13192-13193-13194-13195-23457.pdf.
3. Dutch SPC of Lescol® (version date 30-1-2004). http://www.cbg-meb.nl/IB-teksten/18719-18720.pdf.
4. Dutch SPC of Crestor® (version date 9-2-2004). http://www.cbg-meb.nl/IB-teksten/26872-26873-26874.pdf.
5. Dutch SPC of Lipitor® (version date 31-1-2003). http://www.cbg-meb.nl/IB-teksten/21081.pdf.
6. Dutch SPC of Selektine® (version date 23-1-2003). http://www.cbg-meb.nl/IB-teksten/13755-13756-20665.pdf.
7. Seymour RA. Davies DM, Ferner RE, de Glanville H, editors.Davies's Textbook of Adverse Drug Reactions. 5 ed. London: Chapman & Hall Medical; 1998; 11, Oral and dental disorders. p. 234-58.
8. Henkin RI. Drug-induced taste and smell disorders. Incidence, mechanisms and management related primarily to treatment of sensory receptor dysfunction. Drug Saf 1994;11(5):318-77.
9. Abdollahi M, Radfar M. A review of drug-induced oral reactions. J Contemp.Dent.Pract 2003;4(1):10-31.