Simvastatin and taste disorders

Introduction

Simvastatin (Zocor®) is a HMG-CoA reductase inhibitor. HMG-CoA-reductase inhibitors (statins) are competitive inhibitors of 3-hydroxy-3methylglutargyl coenzyme-A reductase, which play a role in the synthesis of cholesterol. 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* [1]. Simvastatin is indicated for *hypercholesterolaemia and for prevention of cardiovascular mortality and morbidity* [2].
Taste and smell are critical components of a person's overall sense of well-being and quality of life. [3]. Various drugs have been reported to alter the ability to taste and smell. Drug-induced taste disorders are classified into several subtypes. Taste disorders can be described as ageusia (complete loss of taste), hypogeusia (diminished sense of taste) or hypergeusia (enhanced gustatory sensitivity). Dysgeusia is a qualitative gustatory disturbance relating to a distorted taste perception or to a persistent taste sensation in the absence of stimulation. Frequently, gustatory stimuli are reported to be different from what they used to be; they are perceived as bitter, sour, or metallic [4]. Neurological Review]. From the smell disorders anosmia describes the lack of ability to smell, hyposmia refers to a reduced ability to smell and hyperosmia to an enhanced ability to smell [3]. Dysosmia and parosmia are synonyms for distortion or perversion in the perception of an odorant; an unpleasant perception may occur when a normally pleasant odor is present, or the perception may occur when no odorant is present (olfactory hallucination) [5].

In July 2004, the Netherlands Pharmacovigilance Centre Lareb previously described a signal of dysgeusia associated with HMG-CoA-reductase inhibitors [6]. At that time the database of the Netherlands Pharmacovigilance Centre Lareb contained 21 reports of taste disorders associated with the use of HMG-CoA-reductase inhibitors. Of the reports of taste disorders, seven concerned simvastatin, six atorvastatin, three pravastatin, three fluvastatin and one cerivastatin. Since dysgeusia is at this moment not labeled in the SmPC of simvastatin, the current report gives an update of reports about the association between dysgeusia and simvastatin.

Reports

Between October 1990 and March 2017 Lareb received 25 reports of dysgeusia (table 1), twelve reports of ageusia (table 2) and one report of hypogeusia (table 2) associated with the use of simvastatin. One of the reports (patient W in table 1, patient L in table 2) mentions both: dysgeusia (taste alteration) and ageusia (taste loss).
22 reports concern males and fifteen reports females. The patient's ages were between 43 and 79 years, with a mean of 63.9 years. The age of two patients was not reported. The latency for the onset of taste disorder varied from almost immediately after start to two years. However, a majority of the cases describe a latency between a few days and a few weeks, with a median of fourteen days. In five reports a positive de-challenge was reported.

Table 1. Reports of dysgeusia associated with the use of simvastatin

Patient, number, sex, age, source	Drug, dosage, Indication	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome
A, 13225 M, 41-50 Pharmacist	simvastatin 20mg 1dd20mg fluoxetine 20mg	metoprolol diltiazem acetylsalicylic acid	Taste perversion	3 Hours Dose not changed Dose not changed Unknown
B, 15009 F, 61-70 Physician	simvastatin 10mg 1dd10mg	hydrochlorothiazide captopril	Taste perversion Unexpected therapeutic effect	3 Days Dose reduced Unknown
C, 22188 F, 51-60 Physician	simvastatin 10mg 1dd10mg Hypercholesterolemia	Insulin human	Taste perversion	18 Months Dose not changed Unknown

Patient, number, sex, age, source	Drug, dosage, Indication	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome
D, 22205 M, 51-60 Pharmacist	simvastatin 20mg simvastatin 10mg 1dd1tabl.	acetylsalicylic acid amitriptyline ispaghula	Taste peculiar	Dose not changed Dose not changed Unknown
E, 28237 F, 41-50 Pharmacist	simvastatin 20mg 1dd100mg	beclomethasone rabeprazole	Taste perversion Flatulence Oedema	4 Days Drug withdrawn Unknown
F, 35734 F, 61-70 Pharmacist	simvastatin 20mg 1dd10mg Hypercholesterolemia	atenolol nifedipine carbasalate calcium thiamazole triamterene/epitizide	Taste bitter	Unknown Dose not changed Not recovered/not resolved
G, 41115 M, Unknown Pharmacist	simvastatin 20mg 1dd20mg Hypercholesterolemia	paracetamol indapamide diltiazem tamsulosin pantoprazole	Taste metallic Mouth dry Therapeutic response unexpected with drug substitution	8 Days Drug withdrawn Recovered/resolved
H, 63312 F, 71 years and older Pharmacist	simvastatin 20mg 1dd20mg Hypercholesterolemia mirtazapine 15mg acetylsalicylic acid 80mg dipyridamole 200mg	non specified drug enalapril salbutamol fluticasone/salmeterol ipratropium/albuterol	Taste metallic Mouth dry	Unknown Dose not changed Recovering/resolving
I, 76915 M, 61-70 Physician	simvastatin 20mg 1dd20mg		Taste perversion	2 Months Unknown Unknown
J, 83957 M, 71 years and older Pharmacist	losartan 50mg acetylsalicylic acid 80mg pantoprazole 40mg simvastatin 40mg 1dd40mg verapamil 120mg	mometasone furoate Vaseline lanette cream	Dysgeusia	3 Months Unknown Unknown
K, 84307 M, 61-70 Consumer	simvastatin 20mg 1dd20mg Hypercholesterolemia	carbasalate calcium	Dysgeusia	15 Days Dose not changed Recovered/resolved
L, 85085 M, 71 years and older Pharmacist	simvastatin 40mg 1dd40mg Angina pectoris	isosorbide dinitrate nebivolol doxazosine hydrochlorothiazide acetylsalicylic acid	Taste perversion Tearing eyes	2 Days Unknown
M, 110146 F, 51-60 Pharmacist	simvastatin 40mg 1dd40mg		Taste disturbance Heavy feeling in arms & legs	3 Weeks Drug withdrawn Unknown
N, 115987 M, 51-60 Pharmacist	simvastatin 40mg 1dd40mg Hypercholesterolemia	fluticasone enalapril/hydrochlorothiazide rabeprazole	Dysgeusia Parosmia	1 Months Drug withdrawn Recovered/resolved
O, 128272 M, 51-60 Pharmacist	simvastatin 40mg 1dd40mg Hypercholesterolemia		Dysgeusia Pain mouth	1 Day Drug withdrawn Recovered/resolved
P, 129902 F, 61-70 Pharmacist	sotalol 160mg simvastatin 10mg dosage unknown Cardiovascular disorder nos	oxazepam acenocoumarol pantoprazole	Dysgeusia	14 Days Dose not changed Drug withdrawn Recovering/resolving

Patient, number, sex, age, source	Drug, dosage, Indication	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome
Q, 175130 M, 61-70 Pharmacist	interacting - simvastatin 40mg 1dd40mg Hyperlipidaemia interacting - gemfibrozil 900mg		Dysgeusia Drug interaction	Dose not changed Unknown Not recovered/not resolved
R, 187803 M, 51-60 Pharmacist	simvastatin 40mg 1dd40mg	tramadol cinnarizine beclometasone/ formeterol ipratropium enalapril diclofenac-sodium	Taste disturbance	1 Days Dose not changed Recovered/resolved
* S, 205853 F, 51-60 Pharmacist	simvastatin 20mg 1dd20mg Hypercholesterolemia		Taste peculiar Pharmaceutical product complaint	6 Months Dose not changed Unknown
T, 206236 M, 71 years and older Pharmacist	interacting - simvastatin 40mg 1dd40mg Cardiovascular event prophylaxis interacting - pazopanib 400mg interacting - omeprazole 20mg	metformin prednisolon bumetanide beclomehtasone/ formoterol telmisartan insulin glargine hydrochlorothiazide acenocoumarol	Taste disturbance Alanine aminotransferase increased Appetite lost Headache Drug interaction Fatigue	5 Weeks Dose not changed Dose reduced Unknown Recovered/resolved
*U, 213438 M, 61-70 Consumer	simvastatin 20mg 1dd20mg Hypercholesterolemia		Taste peculiar	1 Minute Not applicable Recovered/resolved
V, 230202 F, 41-50 Physician	simvastatin 40mg 1dd40mg Hypercholesterolemia	fluticason- nose spray lisinopril levothyroxine fluticason aerosol hydrochlorothiazide	Dysgeusia Dysosmia	1 Month Drug withdrawn Recovered/resolved
W, 230302 M, 71 years and older Consumer	hydrochlorothiazide diclofenac-sodium simvastatin dose unknown Prostate cancer nos omeprazole perindopril 2,5mg acetylsalicylic acid		Taste loss Taste alteration	Several months Dose not changed Dose not changed Dose not changed Dose not changed Dose not changed Dose not changed Not recovered/not resolved
X, 230564 M, 51-60	simvastatin 40mg	Omeprazole	Dysgeusia Cramps in legs Disturbance in attention Headache Fatigue Oppositional defiant disorder Nausea Malaise	Uknown Drug withdrawn Not recovered/not resolved

Patient, number, sex, age, source	Drug, dosage, Indication	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome
Y, 235543 M, 61-70 Consumer	simvastatin 40mg 1dd40mg Hypercholesterolemia	calcium carbonate/ colecalciferol metformin valsartan/hct	Taste bitter Appetite absent Anger Thinking slow Forgetfulness Backache, unspecified Muscle spasms Agitation Walking difficulty Restless legs Fatigue Listless Stomach ache Nausea	2 Weeks Drug withdrawn Recovered/resolved

Table 2. Reports of ageusia associated with the use of simvastatin

Patient, number, sex, age, source	Drug, dosage, smoking at time of event	Concomitant medication	Suspected adverse drug reaction	Time to onset, drug outcome
A, 666 F,unknown Physician	simvastatin 20mg 2dd20mg	metoprolol	Taste loss	10 Weeks Unknown Unknown
B, 51222 M, 61-70 Physician	simvastatin 10mg 1dd10mg Hypercholesterolemia		Taste loss	5 Days Drug withdrawn Not recovered/not resolved
C, 61142 M, 71 years and older Pharmacist	lamotrigine 100mg simvastatin 20mg 1dd20mg ranitidine 150mg metoprolol 100mg		Taste loss	1 Month Unknown Unknown
D, 75053 F, 71 years and older Physician	simvastatin 20mg dosage unknown Hypercholesterolemia	metoprolol/hct losartan lercanidipine	Taste absent Mouth dry	Drug withdrawn Unknown Not recovered/not resolved
E, 80154 M, 41-50 Pharmacist	simvastatin 40mg 1dd40mg	acetylsalicylic acid	Taste loss	Unknown Drug withdrawn Recovered/resolved
F, 88358 M, 61-70 Pharmacist	simvastatin 40mg 1dd40mg Cardiac arrest clopidogrel 75mg bisoprolol 2,5mg carbasalate calcium 100mg losartan 100mg	levothyroxine	Taste loss	2 Days Drug withdrawn Dose not changed Dose not changed Dose not changed Dose not changed Not recovered/not resolved
G, 108531 F, 71 years and older Pharmacist	simvastatin 40mg 1dd40mg	carbasalate calcium metoprolol	Ageusia Swollen tongue	2 Weeks Drug withdrawn Not recovered/not resolved

Patient, number, sex, age, source	Drug, dosage, smoking at time of event	Concomitant medication	Suspected adverse drug reaction	Time to onset, drug outcome
H, 137278 F, 61-70 Pharmacist	macrogol with electrolytes citalopram 40mg simvastatin 40mg 1dd40mg esomeprazole 40mg		Ageusia Anosmia	2 Hours Drug withdrawn Dose not changed Dose not changed Dose not changed Recovered/resolved
I, 143751, M, 71 years and older Pharmacist	furosemide 40mg simvastatin 40mg 1dd40mg Prophylaxis	acetylsalicylic acid prednisolone sotalol oxazepam colecalciferol metformin pantoprazole fenprocoumon	Ageusia	2 Months Dose not changed Dose not changed Not recovered/not resolved
J, 211987 M, 71 years and older Other health profession al	metoprolol 25mg insulin detemir 100e/ml simvastatin DM type 2 insulin aspart 100e/ml metformin	multivitamins	Ageusia	Unknown Not applicable Not recovered/not resolved
K, 228476 F, 61-70 Consumer	levothyroxine 50mcg metformin 500mg amitriptyline 25mg simvastatin 20mg Hypercholesterolemia (drug induced)	tocilizumab	Ageusia Pruritus Palpitations Burning sensation Diarrhoea Headache Feeling jittery Dry mouth Restlessness Muscle spasms Condition aggravated Dyspnoea	Not applicable Dose not changed Not applicable Dose not changed Dose not changed Not recovered/not resolved
L, 230302 M, 71 years and older Consumer	simvastatin prostate cancer nos hydrochlorothiazide diclofenac-sodium acetylsalicylic acid perindopril 2,5mg omeprazole		Taste loss Taste alteration	Unknown Dose not changed Not recovered/not resolved
M,75077 F, 61-70 Physician	simvastatin 10mg Dosing unknown Hypercholesterolemia		Taste diminished Haematoma Dizziness Eyelid oedema Myalgia Difficulty sleeping	2 years Drug withdrawn Recovered

Other relevant information:
Two of the reports (cases S and U in table 1) concern peculiar taste occurring after use of simvastatin 20mg from the manufacturer Accord. Lareb wrote a report in September 2016 about this issue, concerning in total five reports received from 14 October 2015 until 12 January 2016 [7]. This signal describes a remarkable taste of the film-coated tablets simvastatin 20 mg from the manufacturer Accord in which in four reports it was mentioned that the tablets themselves tasted remarkable. So there is a possibility that there was a specific badge related problem, possibly due a change in the composition of coating which caused the remarkable taste itself or it might be less effective as coating, exposing the core to the surface. An investigation by the marketing authorization holder revealed no quality issues.
Captopril, reported as a co-medication in the patient B and enalapril in patients H, N and R could be considered as a confounder since the ACE-inhibitors are also known to introduce taste disturbance.
The patient K used also amitriptyline and reports also a dry mouth as an adverse drug effect. This ADR, a well-known side effect of amitriptyline, can also be a reason for the taste disturbance.
Three patients experienced beside the taste also a smell disturbance. The patients M and V in the table 1 report parosmia and dysosmia respectively. The patient H in the table 2 reports beside ageusia also a total loss of the smell sensation (anosmia).

Other sources of information

SmPC

The Dutch SmPC of simvastatin does not mention taste or smell disorders as adverse drug reaction [2]. Also the SmPC's of pravastatin, fluvastatin and rosuvastatin do not mention taste or smell disorders [8,9,10].
Dysgeusia is mentioned as an possible adverse drug reaction in the SmPC of atorvastatin [11].

Literature

In a review article several lipid-lowering drugs like cholestyramine, clofibrate and gemfibrosil were reported to alter taste and smell function. Lovastatin was reported to induce a metallic phantogeusia in 1% of the patients [6]. In one case report pravastatin was reported to induce dysgeusia [12].
Altered taste perceptions like dysgeusia and ageusia are also described in association with atorvastatin, simvastatin and lovastatin [13].

Databases

Table 3. Reports of dysgeusia associated with the use of simvastatin in the Lareb database [14].

Drug	PT	Number of reports	ROR (95% CI)
Simvastatin	Dysgeusia	25	1.1 [0.7-1.6]
Simvastatin	Ageusia	12	0.9 [0.5-1.7]
Simvastatin	Hypogeusia	1	Number of reports too low to calculate ROR

Table 4.Reports of taste disorders associated with the use of simvastatin in the WHO database [15].

PT	Number of reports EV	ROR EV (95% CI)	Number of reports WHO	ROR WHO (95% CI)
Dysgeusia	77	1.2 [0.8-1.7]	213	0.79 [0.69-0.90]
Ageusia	27	1.0 [0.8-1.3]	83	1.15 [0.93-1.42]
Hypogeusia	1	Number of reports too low to calculate ROR	4	0.84 [0.31-2.23]

Prescription data

Table 3. Number of patients using simvastatin in the Netherlands between 2011 and 2015 [16].

Drug	2012	2013	2014	2015	2016
Simvastatin	1,043,000	1,064,000	1,077,000	1,081,000	1,084,000

Mechanism

Gustatory receptor cells are located within taste buds, which are contained in the papillae, approximately 250 buds per circumvallate papilla. The perception of taste results from the interplay of at least three sensory channels, namely taste, smell and the trigeminal system. The gustatory system (N. glossopharyngeus,N. facialis, N. vagus) recognizes the basic tastes: sweet, sour, salty, bitter and umami (glutamate). The olfactory nerve recognizes a wide range of odorants. When eating the odour molecules are passed to the olfactory epithelium via the retronasal pathway. A connoisseur of taste therefore also has a fine sense of smell. The N. trigeminus identifies sensations such as sharpness, cooling or tingling effect. As almost all odours can cause a trigeminal sensation, the trigeminal nerve plays a key role in the perception of odours [3].

Drugs can induce taste disturbances by various mechanisms. The commonest type of drug-induced taste disorder dysgeusia occurs when there is dysfunction of taste buds or neurons involving the ion channels that sense sourness and saltiness or due to the alteration of the second messenger system involving the cyclic nucleoside and inositol triphosphate [13].
The exact mechanism of taste disorders induced by statins is still unclear. Terbinafine is a drug for which taste alterations are well documented in the medical literature. In fungal cells, terbinafine inhibits squalene epoxidase, which is responsible for the production of sterols needed for maintaining the integrity of cell membrane. Since, in humans, this enzyme is involved in cholesterol biosynthesis, it has been suggested that terbinafine can alter the structure or function of neurons deputed to taste sensing by interference with cholesterol pathway. This hypothesis is supportive for the taste dysfunctions caused by HMG-CoA reductase inhibitors ('statins'), which are known to disrupt synthesis of cholesterol [17].

Discussion and Conclusion

Taste disorders associated with the use of HMG-CoA-reductase inhibitors are rarely reported in literature. The Netherlands Pharmacovigilance Centre Lareb received 37 reports of taste disorders associated with the use of simvastatin. The mean age of the patients in our report is 70 years. The elderly patients often have multiple comorbidities which require a high number of concurrent medications. Besides, since simvastatin is one of the preference statins among the other drugs within the cardiovascular risk management guidance [18] simvastatin is often administered in combination with other drugs. Also some conditions, like diabetes mellitus, hypothyroidism, major depression, Parkinson's disease, infections like herpes simplex, HIV, upper respiratory infections, acute viral hepatitis and older age are associated with taste disorders[13]. Therefore the recognizing and endorsing of the association between statins and taste disorder is complicated. Seven out of 37 Lareb cases describe taste disorders where no other medication but simvastatin was used and no underlying confounding conditions were reported. The information about the latency for the drug induced taste disorders is rare in the literature. The median latency time for dysgeusia and ageusia in association with simvastatin in Lareb reports is fourteen days. For comparison, in terbinafine the median latency time for the taste disorders is 35 days [20] and the median latency for this association in the Lareb database is 30,5 days [21]. In five of the reports recovery took place after discontinuation of the simvastatin. Since the recovery process from the taste disorders is slow and may take many months [13], probably more patients recovered in the period after reporting of the ADR at the Pharmacovigilance Centre Lareb.
Despite the lack of disproportionality in the databases of Lareb and WHO the reports support a causal relationship between simvastatin and taste disorders. Dysgeusia is already mentioned in the SmPC of atorvastatin [11]. Attention for taste disorders due to the use of simvastatin is therefore warranted.

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This signal has been raised on February 1, 2018. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl