Fluvastatin and diarrhoea

Introduction

Fluvastatin (Lescol®) is a synthetic, competitive 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. HMG-CoA reductase is an enzyme involved in cholesterol synthesis. Fluvastatin is indicated for *dyslipidemia, hypercholesterolemia and secondary prevention for patients with coronary heart disease*. Fluvastatin was granted marketing authorization in the Netherlands in 1995 (1). Diarrhoea is a labelled adverse drug reaction of fluvastatin in the SmPC of the FDA (2) but not in the Dutch SmPC. Diarrhoea is a labelled adverse drug reaction in the Dutch SmPCs for the other HMG-CoA-reductase inhibitors atorvastatin, simvastatin, pravastatin and rosuvastatin (3-6).

Reports

From 17 July 1996 to 20 September 2017 the Netherlands Pharmacovigilance Centre Lareb received ten reports of diarrhoea associated with the use of fluvastatin. The reports are listed in table 1. Six cases involved females and four cases involved males. The ages varied between 56 and 78 years, with an average of 66 years. In most cases (eight cases) the latency varied from one day to four weeks and in one case the latency was five months. The latency was unknown in one case. A positive dechallenge was seen in five cases (cases B, C, D, H and I) and a positive rechallenge was reported in two cases (cases C and H). In case B fluvastatin was withdrawn 5 days after the onset of diarrhoea, in case D a dose was skipped 1 week after onset and in case I fluvastatin was withdrawn 7 months after onset. The period of continuing fluvastatin after onset is unknown in case C and H. Rechallenges were done with unknown outcomes in four cases (cases A, B, D and G). In one case (case J) the reaction improved after changing the time of administration from morning to evening. This patient had experienced diarrhoea while using atorvastatin before. In one case (case C) the patient experienced vomiting at the same time as diarrhoea and in one case (case A) cystitis was also reported as adverse event, which was treated with trimethoprim. In one case (case E) the patient also experienced diarrhoea with the use of acenocoumarol, digoxin and enalapril. In case F the patient started an antibiotic course of roxithromycin at the same time as fluvastatin. Diarrhoea started two days after the antibiotic course was finished. In nine out of ten cases a daily dose higher than 40 mg was used. In two cases (case I and J) fluvastatin extended release tablets were used.

Table 1. Reports of diarrhoea associated with the use of fluvastatin.

Patient, Sex, Age, (years), Source	Drug, Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, Outcome
A 14502 F, 71 years and older General practitioner	Fluvastatin 40 mg, 2dd1, pure hyperglyceridaemia	Oxazepam Metoprolol Nitroglycerin Amitriptyline Enalapril Paracetamol	Nausea Bladder infection Diarrhoea Muscle pain	2 weeks Drug withdrawn 4 months after onset Outcome unknown
B: 16705 M, 61-70 Pharmacist	Fluvastatin 40 mg, 1dd1, lipoprotein (a)	Acetylsalicylic acid Amlodipine	Diarrhoea	5 days Drug withdrawn 5 days after onset Drug restarted Positive dechallenge
C: 16853 F, 71 years and older General practitioner	Fluvastatin 40 mg, 1dd1, pure hypercholesterolaemia	Isosorbide mononitrate Carbasalate calcium Metoprolol	Diarrhoea Vomiting	3 days Drug withdrawn Positive rechallenge
D: 17062 M, 61-70 Pharmacist	Fluvastatin 20 mg, 1dd1, indication unknown	Metoprolol Acetylsalicylic acid	Diarrhoea	4 weeks Unknown Positive dechallenge after skipping 1 dose which was 1 week after onset

Patient, Sex, Age, (years), Source	Drug, Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, Outcome
E: 17134 M, 61-70 General practitioner	Fluvastatin 40 mg, 1dd1, indication unknown	Enalapril Sotalol Acenocoumarol Digoxine Bumetanide	Diarrhoea Malaise	Unknown weeks Drug withdrawn 3 weeks after onset Outcome unknown
F: 18620 F, 61-70 General practitioner	Fluvastatin 40 mg, 1dd1, indication unknown	Diazepam Roxithromycin	Diarrhoea	Unknown weeks Drug withdrawn on the day of onset Outcome unknown
G: 19089 F, 71 years and older General practitioner	Fluvastatin 40 mg, 1dd1, indication unknown	Levothyroxine Lormetazepam	Diarrhoea	1 day Drug withdrawn and restarted Outcome unknown
H: 34624 M, 51-60 General practitioner	Fluvastatin 40 mg, 1dd1, hypercholesterolaemia after myocardial infarction	Acetylsalicylic acid Metoprolol	Depressed reaction Diarrhoea	Unknown Drug withdrawn Recovered Positive rechallenge
I: 42283 F, 51-60 Physician, report received via the MAH	Fluvastatin 80 mg extended release, 1dd1, hyperlipidaemia	Quinapril Amlodipine Hydrochlorothiazide	Diarrhoea	5 months Drug withdrawn 7 months after onset Recovered
J: 247357, F, 61-70 General practitioner	Fluvastatin 80 mg extended release, 1dd1, prophylaxis (cardiovascular risk)	Hydroxocobalamin Leflunomide Vaseline Cetomacrogol Metformin Lisinopril Insuline glargine Colecalciferol	Diarrhoea	1 day Dose not changed Not recovered (improvement after change in administration time)

Other sources of information

SmPC

Diarrhoea is not mentioned as an adverse drug reaction in the Dutch SmPCs of fluvastatin. Concerning gastrointestinal reactions, abdominal pain, nausea and dyspepsia are labelled adverse drug reactions of fluvastatin (1). Diarrhoea is a labelled adverse drug reaction of fluvastatin in the SmPC of the FDA. An incidence of diarrhoea was reported for 4.9% of patients with fluvastatin (n=2326) and 3.3% of patients using fluvastatin extended release tablets (n=912) compared to 4.2% of patients with placebo (n=960). It is also mentioned that diarrhoea is among the most common adverse reactions that led to treatment discontinuation with an incidence higher than placebo. Discontinuation incidence due to diarrhoea was 0.2% for patients with fluvastatin and 0.5% for patients with fluvastatin extended release (2).
Diarrhoea is a labelled adverse drug reaction in the Dutch SmPCs for the other HMG-CoA-reductase inhibitors atorvastatin, simvastatin, pravastatin and rosuvastatin (3-6).

Mechanism

The mechanism for diarrhoea as an adverse drug reaction of fluvastatin is not known. Diarrhoea could possibly be a class effect of HMG-CoA-reductase inhibitors since it is a labelled adverse drug reaction for four other statins.

Databases

Table 3. Reports of the Preferred Term (PT) “diarrhoea” associated with fluvastatin, in the Lareb (7), WHO (8) and Eudravigilance database (9) with Reporting Odds Ratios (ROR).

Database	MedDRA PT	Drug	Number of reports	ROR (95% CI)

Database	MedDRA PT	Drug	Number of reports	ROR (95% CI)
Lareb	Diarrhoea	Fluvastatin	10	1.2 (0.6-2.3)
WHO	Diarrhoea	Fluvastatin	263	1.3 (1.1-1.5)
Eudravigilance	Diarrhoea	Fluvastatin	166	1.16 (1.0-1.4)

Prescription data

Table 4. Number of patients using fluvastatin in the Netherlands between 2012 and 2016 (10).

Drug	2012	2013	2014	2015	2016
Fluvastatin	21,450	20,564	19,604	18,633	18,228

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received ten cases of diarrhoea associated with the use of fluvastatin. There were five cases with positive dechallenges. A positive rechallenge was reported in two of these cases.
Diarrhoea is described as an adverse drug reaction in the SmPC of fluvastatin of the FDA, but is not described in the Dutch SmPC of fluvastatin. It is also a labelled adverse drug reaction in the Dutch SmPC of atorvastatin, simvastatin, pravastatin and rosuvastatin (3-6). Diarrhoea could possibly be a class effect of HMG-CoA-reductase inhibitors, suggesting further attention to this association is warranted.

References

(1) SmPC Lescol capsules 20 mg. (Version date: 19-3-2009, access date: 10-1-2018) https://db.cbg-meb.nl/IB-teksten/h18719.pdf.
(2) FDA SmPC Lescol/Lescol XL. (Version date: 2012, access date: 19-1-2018) https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021192s019lbl.pdf.
(3) SmPC Lipitor filmonhulde tabletten 10/20/40/80 mg. (Version date: 13-11-2016, access date: 19-1-2018) https://db.cbg-meb.nl/IB-teksten/h21081.pdf.
(4) SmPC Zocor filmonhulde tabletten 10/20/40 mg. (Version date: 9-4-2017, access date: 19-1-2018) https://db.cbg-meb.nl/IB-teksten/h13193.pdf.
(5) SmPC Selektine tabletten 10/20/40 mg. (Version date: 8-6-2017, access date: 19-1-2018) https://db.cbg-meb.nl/IB-teksten/h13755.pdf.
(6) SmPC Crestor filmomhulde tabletten 5/10/20/40 mg. (Version date: 5-12-2016, access date: 19-1-2018) https://db.cbg-meb.nl/IB-teksten/h26872.pdf.
(7) Lareb Database. (Version date: 2017, access date: 11-10-2017) www.lareb.nl.
(8) WHO Global Individual Case Safety Reports database (Vigilyze). (Version date: 2017, access date: 1-12-2017) http://www.vigiaccess.org/.
(9) Eudravigilance database. (Version date: 2017, access date: 1-12-2017) http://bi.eudra.org.(access restricted).
(10) GIP database - Drug information System of the Dutch Health Care Insurance Board. (Version date: 21-11-2017, access date: 10-1-2018) http://www.gipdatabank.nl/.

This signal has been raised on April 9, 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