Amlodipine and epistaxis

Introduction

Amlodipine is a dihydropyridine calcium channel antagonist. Amlodipine was granted marketing authorization in the Netherlands in 1990 and is indicated for *hypertension, chronic stable angina pectoris and vasospastic (Prinsmetal) angina* (1).

Epistaxis, or nose bleed, is estimated to occur in 60% of persons during their lifetime with a higher incidence during the winter months. The prevalence is increased for children less than 10 years of age, is lower for adolescents and young adults and then rises again after the age of 35 years. Nose bleeds are more common in older patients; a mean age of 64 is mentioned (2). The female-to-male ratio is also age dependent. A study investigating patterns of hospital attendance with epistaxis found that in the group aged between 20 to 49 years twice as many males as females were admitted, where no sex difference was expected from the population data (3). Approximately 6% of the patients with nose bleeds seek medical treatment. More than 90% of episodes of epistaxis originates from the anterior nasal septum, at a site called Kiesselbach's area (2). Epistaxis or nose bleed has no clear cause in about 75% of the cases. The most common causes of epistaxis are dry mucosal membrane in the nose, common cold, trauma, hypertension, nose deformities, drug use such as nasal sprays or the use of anticoagulants. A relatively rare genetic cause is hereditary hemorrhagic telangiectasia (4).

Reports

From 3 October 1996 until 15 October 2019 The Netherlands Pharmacovigilance Centre Lareb received 8 reports of epistaxis (MedDRA PT epistaxis) in association with the use of amlodipine.

Table 1: Reports of epistaxis in association with to the use of amlodipine

Patient, Number, Sex, Age (years), Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
NL-LRB-15246 male, 50-60 physician, pharmacist	amlodipine,10mg, unknown, fluvastatine, 40mg, hypercholesterolaemia	prazepam, nitroglycerin spray	Sinus congestion Nasal bleeding	3 days, dose not changed, unknown
NL-LRB-70122 female, 70 years and older pharmacist	amlodipine, 5mg, hypertension	acetylsalicylic acid, enalapril, simvastatin	Recurrent epistaxis	2 days, dose not changed, unknown
NL-LRB-118937 female, 60-70 pharmacist	amlodipine, 10mg, hypertension, alfacalcidol, vitamin B deficiency		Epistaxis	3 days, unknown, unknown
NL-LRB-167747, female, 70 years and older pharmacist	amlodipine, 5mg, unknown		Epistaxis	2 days, dose not changed, unknown
NL-LRB-232612 male, 60-70 physician	amlodipine, 5mg, hypertension		Epistaxis	13 days, drug withdrawn, recovered
NL-LRB-00274774 man, 40-50 physician	amlodipine, 5mg, hypertension	enalapril	Epistaxis	3 weeks, drug withdrawn, recovered

NL-LRB-00280597 male, 70 years and older consumer	amlodipine, 5mg, hypertension	nebivolol, paracetamol, zopiclon, mesalazine, macrogol laxans	Oedema Blurred vision, Epistaxis	2 days, dose not changed, not recovered
NL-LRB-00332110 male, 70 years and older other health care professional	amlodipine, 5mg, hypertension		Epistaxis	2 days, drug withdrawn, recovered

The reports concern 5 males and 3 females. The indication for amlodipine, where reported, was hypertension. The latency varies from 1-3 days in 6 of the reports to a latency of 2-3 weeks in 2 of the reports.
The duration of the nosebleeds is not known from the cases. Of the 8 reports received, there was a positive dechallenge in 3 of the cases. In these cases, recovery was quick, within a few days. We interpreted this as the patient having multiple nosebleeds, which did not occur any more after drug cessation. The reports which had a positive dechallenge are described in more detail below.
In none of the reports information was available whether the patients had experienced epistaxis in the past before the start of amlodipine.
One patient used acetylsalicylic acid, which could be a factor in the occurrence of epistaxis.

NL-LRB-00332110
This non-serious spontaneous report from another health professional concerns a male aged 70 years and older, with epistaxis (heavy nose bleedings, in short succession) following administration of amlodipine tablet 5mg (action taken: withdrawn after 2 days of use) for hypertension. The patient recovered within 24 hours. At time of reporting (about 3 weeks after withdrawal) the reporter indicated that the patient hasn't had any more nose bleeds.

NL-LRB-00274774
This non-serious spontaneous report from a physician concerns a male aged 40-50 years, with epistaxis following administration of amlodipine tablet 5mg for hypertension with a latency of 3 weeks after start. The patient recovered 1 week after withdrawal.

NL-LRB-232612
This non-serious spontaneous report from a general practitioner concerns a male aged 60-70 years, with epistaxis following administration of amlodipine for hypertension with a latency of 13 days after start. The drug amlodipine was withdrawn. The patient recovered 5 days later.

Other sources of information

SmPC

The Dutch Summary of Product Characteristics (SmPC) of amlodipine does not mention epistaxis as an adverse drug reaction. It mentions thrombocytopenia and rhinitis as adverse drug reactions (1).

In the US SmPC, epistaxis is described as an adverse drug reaction (5).

In the Dutch SmPC of nifedipine, which also belong to the group of dihydropyridine calcium channel antagonist, epistaxis is being described as an adverse drug reaction with a frequency of 0.1-1% of the uses (6).

Literature

Literature on the association between amlodipine and epistaxis is scarce. A case of epistaxis in patients treated with amlodipine/benazepril occurred in a study comparing this combination therapy for hypertensive patients nonresponsive to benazepril monotherapy. No epistaxis occurred in the monotherapy group (7).
A case-report describes a 79-year-old man with epistaxis and gum bleeding while on amlodipine therapy for 10 years due to immune thrombocytopenia. Initially, his platelet count increased owing to treatment with prednisolone and intravenous immunoglobulin G, but decreased shortly after

discontinuation of this treatment. The patient's serum was found to contain amlodipine-dependent antibodies to platelets, and he recovered after stopping the drug (8). A 78-year-old female hypertensive patient was described to suffer from acute severe thrombocytopenia occurring after a 2-week course of amlodipine. Her platelet count normalized after the amlodipine was discontinued. She had a similar reaction to simvastatin (9).
Several articles describe the association between nifedipine and epistaxis (10, 11) or thrombocytopenia (12, 13).

Databases

Table 2. Reports of alopecia associated with the use of amlodipine in the Lareb, WHO and Eudravigilance database (14-16)

Database	Number of reports	ROR (95% CI)
Lareb	8	1.4 (0.7-2.7)
WHO	274	0.8 (0.7-0.9)
Eudravigilance	130	0.9 (0.8-1.1)

The reports in the WHO database originate from 29 countries. In 122 cases amlodipine was the single suspect drug, in 39 cases a positive dechallenge was reported and in 3 cases a positive rechallenge.

Table 3. Prescription data (users) (17).

Drug	2014	2015	2016	2017	2018
Amlodipine	467,490	499,040	529,890	558,760	584,010

Mechanism

Thrombocytopenia, which is a known adverse drug reaction of amlodipine, could manifest itself in epistaxis (18). Amlodipine is also known to cause rhinitis, which in turn can cause epistaxis (19). Amlodipine-induced vasodilatation could possibly also play a role in the occurrence of epistaxis. In the cases reported to Lareb, there is no information on thrombocytopenia as a cause, in one case sinus congestion was reported.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 8 reports of epistaxis with the use amlodipine of which 3 had a dechallenge with recovery within a week after stopping. It is not always clear from the reports if there was a single episode of epistaxis or if the nosebleeds were occurring more often. One case clearly describes heavy nose bleedings, in short succession.
Epistaxis can have many other causes than drug use. Hypertension itself can cause epistaxis. This is especially a cause of epistaxis to be considered in the cases where a short latency is reported, as within this short time interval the blood pressure lowering effects of amlodipine might not have reached it optimal effect.
The background incidence of epistaxis is high. Epistaxis is more prevalent during the colder months as in this time period the nasal mucosa gets drier. When looking at the occurrence of the epistaxis, 4 of the cases occurred in Jan-March, 2 reports in April-June and 1 report each in the other two quarters showing no clear seasonal pattern.

Rhinitis is a well-known adverse drug reaction (1), but considering the short latency in many of the cases (1-3 days), it is less likely that rhinitis is the cause of the epistaxis In addition, only 1 report contains symptoms which could be related to rhinitis, namely sinus congestion.

Thrombocytopenia is also a well-known adverse drug reaction of amlodipine (1) but in the cases with the shorter latency (1-3 days), it is unlikely that thrombocytopenia is the cause since drug induced thrombocytopenia usually occurs within 1-2 weeks after start of the drug (20).

Epistaxis is labelled in the US SmPC of amlodipine (5). Epistaxis is also mentioned in the Dutch SmPC of nifedipine (6), another dihydropyridine calcium channel antagonist, with a frequency of 0.1-

1%. Based on 8 cases of epistaxis in relation to the use of amlodipine received by Lareb, Lareb highlights this association as a signal for further review.

Literature

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This signal has been raised on November 20, 2019. 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