1.1. Latanoprost containing products and smell disorders

Introduction

Latanoprost eye drops are indicated for *the reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension*. It has been approved for the Dutch market since 1997 as a single agent (Xalatan® [1]), and since September 2001 in combination with timolol (Xalacom® [2]).

The active substance, a prostaglandin F2α analogue, is a selective prostanoid FP receptor agonist which reduces the intraocular pressure by increasing the outflow of aqueous humour. Most of the ADRs that occur after administration of latanoprost are ocular in nature and they are generally transient, with the exception of iris pigmentation, and occur on dose administration. Known ADRs of the nervous system are headache and dizziness.

Reports

On July 14, 2011, the database of the Netherlands Pharmacovigilance Centre Lareb contained seven reports concerning smell disorders with the use of latanoprost containing products.

Table 1. Reports of smell disorders associated with the use of latanoprost containing drugs

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 29097 M, 51 – 60 years Pharmacist	latanoprost eye drops 50mcg/ml	timolol eye drops	taste loss parosmia	several hours discontinued not recovered
B 29112 M, 51 – 60 years Pharmacist	latanoprost eye drops 50mcg/ml Glaucoma	azelastine budesonide salbutamol enalapril felodipine atorvastatin gliclazide	anosmia	several days unknown not reported
C 30449 M, 61-70 years Pharmaceutical Company	latanoprost eye drops 50mcg/ml		anosmia	not reported unknown unknown
D 38341 M, 61-70 years Specialist doctor	latanoprost eye drops 50mcg/ml Glaucoma		taste loss parosmia	16 days discontinued recovered
E 47556 F, 61-70 years Specialist doctor	latanoprost eye drops 50mcg/ml Glaucoma		anosmia taste loss	not reported discontinued recovered
F 62972 M, 51-60 years General practitioner	latanoprost eye drops 50mcg/ml Glaucoma	sildenafil	anosmia	3 months discontinued recovered
G 120014 M, 61-70 years Specialist doctor	latanoprost / timolol eye drops Ocular tension increased		ageusia anosmia	3 months no change not recovered

Details of the above mentioned reports are discussed below.

Patient A is a male aged 51-60 years with parosmia and taste loss following administration of latanoprost once daily (1 drop in both eyes) for an unknown indication with a latency of several hours. Eleven days after withdrawal of latanoprost, which had been used for approximately 3 months, and switching to dorzolamide, the patient had not recovered. Concomitant medication was timolol eye drops.
After withdrawal of latanoprost the patient was treated with amoxicillin because of a possible effect of a respiratory tract infection on the patient's smell and taste disorder.

Patient B, a male aged 51-60 years, experienced anosmia following administration of latanoprost once daily (1 drop in both eyes) for glaucoma with a latency of several days. It is not known whether latanoprost was withdrawn or continued, and the patent outcome was not reported. Concomitant medications were azelastine, budesonide, salbutamol, enalapril, felodipine, atorvastatin and gliclazide.

Patient C is a male aged 61-70 years years who experienced anosmia following administration of latanoprost (daily dose not reported). The outcome of the event and the action taken for latanoprost were not reported. The reporter assessed the events as serious, based on the criterion that they were disabling.

Patient D is a male aged 61-70 years with taste loss and parosmia following administration of latanoprost once daily (1 drop in both eyes) for glaucoma with a latency of 16 days. The patient recovered after withdrawal of latanoprost and re-experienced the symptoms when latanoprost was restarted.

Patient E, a female aged 61-70, experienced taste loss and anosmia following administration of latanoprost once daily for glaucoma with an unknown latency. The patient recovered immediately after withdrawal of latanoprost. Approximately 1 month after switching to travoprost the patient experienced similar symptoms, albeit less severe, which disappeared after withdrawal. The patient started treatment with timolol for her glaucoma.

Patient F is a male aged 51-60 years with a medical history of chronically increased ocular pressure, who experienced anosmia following administration of latanoprost once daily for glaucoma with a latency of three months. Two weeks after withdrawal of latanoprost the patient recovered. Concomitant medication was sildenafil on a sporadic basis.

Patient G is a male aged 61-70 with taste loss and anosmia following administration of timolol/latanoprost once daily with a latency of three months. The treatment with timolol/latanoprost was continued and the patient had not recovered at the time of reporting.

Other sources of information

SmPC

None of the SmPCs of latanoprost containing products mention smell disorders as a possible ADR.

Literature

Smell disorders have not been found in the literature in association with latanoprost or any of the other prostanoid FP receptor agonists.

Databases

For the purpose of these disproportionality analyses, a smell disorder was defined as any report containing the MedDRA Preferred Terms, anosmia or parosmia.
On July 20, 2011, the database of the Netherlands Pharmacovigilance Centre Lareb contained seven cases of smell disorder in association with latanoprost containing products, which was reported disproportionally (ROR = 10.8, 95% CI: 5.1 – 23.2).

On July 20, 2011, the WHO database of the Uppsala Monitoring Centre contained 22 reports of smell disorder. The reports concern 14 females and 7 males, and in one case the sex was not reported. The median age of the patients was 66 years (range 43 - 87). The association was disproportionally present in the database (ROR = 2.7, 95% CI: 1.8 – 4.1).

On July 20, 2011, the Eudravigilance database contained five reports of smell disorder associated with the use of latanoprost which was reported disproportionally (ROR = 3.4, 95% CI: 1.4 – 8.1). It concerns three females and two males. The median age of the patients was 68 years (range 53 – 77). Although three reports were classified as serious, in one of them this was due to a hospitalization for gallbladder surgery.

Prescription data

The number of patients using latanoprost containing products in the Netherlands is shown in table 2.

Table 2. Number of patients using latanoprost containing products in the Netherlands between 2006 and 2010 [3]

Drug	2006	2007	2008	2009	2010
Latanoprost	71,108	68,885	69,203	69,551	69,403

Data for timolol/latanoprost were not available

Mechanism

Latanoprost is a prodrug (isopropyl ester) which becomes biologically active as a free acid after hydrolysis [1]. In addition to being a selective prostanoid FP receptor agonist, in vitro research has shown that the free acid of latanoprost is a non-competitive inhibitor of the enzyme carbonic anhydrase (CA) I/II [4]. In the nasal mucosa, CA is necessary for the depolarisation of the olfactory receptor neurons during olfactory transduction [5], and CA II is one of the most abundant in the human nasal mucosa [6].
The CA inhibitor dorzolamide has been associated with anosmia in a case report describing a 49-year-old male, who experienced anosmia during treatment with dorzolamide. During his treatment the patient was subjected to several changes in treatment, which occurred in a blinded manner and resulted in several positive dechallenges and rechallenges [7].

Since the eyes and nasal cavity are directly connected by the (naso)lacrimal ducts, excess eye drops could flow into the nasal cavity, possibly resulting in smell disorders as a result of the above described mechanism.

It is well known that the perception of smell and taste are linked, and this may explain why four of the patients described above, also reported taste disorders.

However, since taste disorders are generally secondary to a loss of smell and not vice versa, the association described here is limited to smell disorders only

Discussion and conclusion

Lareb received seven cases of smell disorders associated with the use of latanoprost containing products. In three of these a positive dechallenge was reported, with a positive rechallenge in one of them.
The association of smell disorders with the use of latanoprost was supported by a statistically significant disproportionality in all three databases. In addition, there is a plausible pharmacological mechanism for this association, based on the carbonic anhydrase inhibiting properties of latanoprost. This enzyme has a role in olfactory functioning and its inhibition by the carbonic anhydrase inhibitor dorzolamide has been associated with anosmia.
Based on the above, a causal relationship between smell disorders and the use of latanoprost containing products seems probable.

- New signal of latanoprost containing products associated with smell disorders

References
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This signal has been raised on November 2011. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).