Tamsulosin and dry mouth

Introduction

Tamsulosin hydrochloride (Omnic®) is an antagonist of alpha1A adrenoceptors in the prostate. Tamsulosin is indicated for *the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)*. It has been approved for the Dutch market since April 1995 [1].
The symptoms associated with benign prostatic hyperplasia (BPH) are related to bladder outlet obstruction, which is comprised of two underlying components: static and dynamic. The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. The dynamic component is a function of an increase in smooth muscle tone in the prostate and bladder neck leading to constriction of the bladder outlet. Smooth muscle tone is mediated by the sympathetic nervous stimulation of alpha1 adrenoceptors, which are abundant in the prostate, prostatic capsule, prostatic urethra, and bladder neck. Blockade of these adrenoceptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in urine flow rate and a reduction in symptoms of BPH.
Tamsulosin, an alpha1 adrenoceptor blocking agent, exhibits selectivity for alpha1 receptors in the human prostate. At least three discrete alpha1 adrenoceptor subtypes have been identified: alpha1A, alpha1B, and alpha1D; their distribution differs between human organs and tissue. Approximately 70% of the alpha1 receptors in the human prostate are of the alpha1A subtype [2].

Other selective alpha1-antagonists for the treatment of BPH on the Dutch market are alfuzosin (Xatral®), doxazosin (Cardura®), silodosin (Silodyx®) and terazosin (Hytrin®).

There are several causes of dry mouth, also called xerostomia. Dehydration can be an important factor in the development of a dry mouth. Xerostomia can also be drug-induced, for instance by anti-cholinergic medication [3].

The current observation describes the association between tamsulosin and dry mouth.

Reports

On October 19th 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained six reports of dry mouth associated with the use of tamsulosin. The reports are listed in Table 1.

Table 1. Reports of dry mouth associated with the use of tamsulosin.

Patient, Sex, Age, Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 49388 M, 61-70 years general practitioner	tamsulosin 1 dd 0,4mg prostate cancer NOS		mouth dry	3 days no change recovered with sequelae
B 73619 M, 61-70 years pharmacist	tamsulosin 1 dd 0,4mg		orthostatic hypotension, movement disorder, mouth dry	not reported discontinued recovered

Patient, Sex, Age, Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
C 77380 M, 31-40 years pharmacist	tamsulosin 1 dd 0,4mg		dizziness, mouth dry	1 day discontinued recovered
D 106103 M, 51-60 years pharmacist	tamsulosin 1 dd 0,4mg benign prostatic hyperplasia		epistaxis, dizziness, throat dry, nasal congestion, mouth dry	7 days discontinued recovered
E 109313 M, 51-60 years pharmacist	tamsulosin 1 dd 0,4mg micturition frequency quinapril/hydrochloro-thiazide hypertension, hydrochlorothiazide hypertension, amlodipine hypertension, omeprazole dyspepsia	rosuvastatin, losartan	xerostomia	7 days no change not recovered
F 134524 M, 71 years and older consumer	tamsulosin 1 dd 0,4mg prostatic disorder	carbasalate calcium, hydrochlorothiazide	dry mouth, pruritus generalised	4 days discontinued recovering

Some of the characteristics of the reports are described below:
Patient D withdrew tamsulosin after three years and restarted after some time. The dry mouth reoccurred after restart of tamsulosin.
Patient E had been using the other suspect drugs for more than four years.

Other sources of information

SmPC

The Dutch SmPC of tamsulosin does not mention dry mouth [1]. This is also the case for the US SmPC [2].
The UK patient information leaflet mentions dry mouth as an adverse drug reaction of tamsulosin with unknown frequency [4].

Literature

Yanai-Inamura et al. [5] studied the effects of alpha1-adrenoceptor antagonists on phenylephrine-induced salivary secretion and intraurethral pressure elevation in anesthetized rats. They showed that tamsulosin inhibited phenylephrine-induced salivary secretion in a dose-dependent fashion. These results suggest that tamsulosin inhibits not only urethral contraction but also salivary secretion which may contribute to the incidence of dry mouth [5].
In a randomized, double-blind, placebo-controlled trial in men 40 years or older with lower urinary tract symptoms and overactive bladder patients were randomly assigned to receive placebo (n=222), 4 mg of tolterodine extended release (ER) (n=217), 0,4 mg of tamsulosin (n=215), or both tolterodine ER plus tamsulosin (n=225) for 12 weeks. The most frequent adverse event reported in patients receiving active treatment was dry mouth. Two patients taking tamsulosin and 5 patients taking tolterodine ER plus tamsulosin stopped treatment because of dry

mouth. The incidence of dry mouth was 7% in the tolterodine ER and tamsulosin group, 21% in the tolterodine ER plus tamsulosin group and 2% in the placebo group [6].
In a 12-week, double-blind, placebo controlled trial assessing the safety and tolerability of solifenacin plus tamsulosin in 398 men with residual overactive bladder symptoms who had received prior therapy with tamsulosin monotherapy it was shown that dry mouth was the most frequent adverse event (7% in the solifenacin plus tamsulosin group and 3% in the tamsulosin monotherapy group) [7].
In a single-blind, randomized study in 98 Korean patients with benign prostatic hyperplasia in which tamsulosin (fixed dose 0,2 mg) was compared to terazosin (increasing dose 1-5mg), the adverse reactions most frequently reported were dry mouth and dizziness (18 patients on terazosin and one patient on tamsulosin) [8].

Databases

On October 19th 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained six reports of dry mouth associated with the use of tamsulosin, which was not reported disproportionally. The Reporting Odds Ratio (ROR) is 1.3 (95% CI 0.6-3.0). Furthermore, the Lareb database contained two reports of dry mouth for doxazosin, one report for silodosin and one report for terazosin.
The WHO database of the Uppsala Monitoring Centre contained 77 reports of dry mouth associated with the use of tamsulosin. This association is disproportional. Table 2 shows the number of reports of dry mouth associated with the use of tamsulosin and other selective alpha1-antagonists in the WHO database.

Table 2. Reports of dry mouth for the selective alpha1-antagonists in the WHO database.

Drug	Number of reports	ROR (95% CI)
tamsulosin	77	1.5 (1.2-1.9)
doxazosin	190	4.4 (3.9-5.1)
terazosin	88	2.7 (2.2-3.3)
alfuzosin	28	1.7 (1.2-2.5)
silodosin	5	1.8 (0.8-4.4)
selective alpha1-antagonists total	388	2.7 (2.4-3.0)

On December 5th 2012, the Eudravigilance database contained 12 reports of dry mouth in association with tamsulosine, which was not reported disproportionally (ROR = 1.2, 95% CI: 0.7 – 2.0). The number of reports of dry mouth for all selective alpha1-antagonists is given in Table 3.

Table 3. Reports of dry mouth for the selective alpha1-antagonists in the Eudravigilance database.

Drug	Number of reports	ROR (95% CI)
tamsulosin	12	1.2 (0.7 – 2.0)
doxazosin	13	2.9 (1.7 – 5.1)
terazosin	2	1.5 (0.4 – 6.2)
alfuzosin	4	1.4 (0.5 – 3.8)
silodosin	2	3.4 (0.8 – 13.5)
selective alpha1-antagonists total	33	1.7 (1.2 – 2.4)

Prescription data

The number of patients using tamsulosin in the Netherlands is shown in Table 4.

Table 4. Number of patients using selective alpha1-antagonists in the Netherlands between 2007 and 2011 [9].

Drug	2007	2008	2009	2010	2011
tamsulosin	146,670	162,100	172,950	186,450	194,980
doxazosin	38,578	40,016	39,767	40,922	41,862
terazosin	2,537	2,172	1,951	1,731	1,590
alfuzosin	64,048	62,833	60,572	59,916	57,235
silodosin	-	-	-	-	1,289

Mechanism

Tamsulosin binds selectively and competitively to postsynaptic alpha1-adrenoceptors, mostly subtype alpha1A. This causes relaxation of the smooth muscle in the prostate and urethra. Postsynaptic alpha1A-adrenoceptors are also present in the salivary glands. Blockade of alpha1-adrenoceptors in the salivary glands causes diminished excretion of water and potassium. This can lead to dry mouth [10].

Class effect

The Lareb database contains two reports of dry mouth for doxazosin, one report for silodosin and one report for terazosin. The WHO database contains numerous reports of dry mouth associated with the use of selective alpha1-antagonists. All associations are reported disproportionally, except for silodosin (Table 2). Since all the selective alpha1-antagonists have the same mechanism of action it would seem plausible that dry mouth is a class effect.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received six reports of dry mouth associated with the use of tamsulosin. Latency periods ranged from one to seven days. This is in accordance with the proposed mechanism. Of the six cases three had a positive dechallenge and one patient continued the medication and did not recover. One patient had a positive rechallenge.

Various studies report dry mouth as the adverse reaction most frequently seen in patients receiving tamsulosin. In addition the association of tamsulosin with dry mouth is supported by a statistically significant disproportionality in the database of the WHO. This is also the case for the other selective alpha1-antagonists. Therefore, further investigation of the information of the marketing authorization holders is advisable.

- New signal of dry mouth associated with tamsulosin
- Further investigation of the information of the marketing authorization holders is advisable.

References

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This signal has been raised on February 2013. 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).