1.1. Tamsulosin and epistaxis

Introduction

Tamsulosin (Omnic®) is an α1-receptor antagonist and is indicated for the *treatment of lower urinary tract symptoms (LUTS) related to benign prostate hyperplasia (BPH)*. In 2008, the number of patients using tamsulosin was about 165,320 [1]. A frequent Adverse Drug Reaction (ADR) of tamsulosin is dizziness [2]. 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 [3]. Among hospitalized patient with nose bleeds, male patient are more presented in the age of 20-49 years. From the age of 50, no sex differences were found [4]. Approximately 6% of the patients with nosebleeds seek medical treatment. More than 90% of episodes of epistaxis occur along the anterior nasal septum, at a site called Kiesselbach's area [3]. Epistaxis is not mentioned in the SmPC of tamsulosin [2].
This report describes the occurrence of epistaxis with the use of tamsulosin.

Reports

Up to July 7, 2009, Lareb received eight moderately documented reports of epistaxis associated with the use of tamsulosin (see Table 1).
Latency time varied from 1 day to 1 year and is mostly within a few months after start. Patient G also mentioned nose dryness and patient A also mentioned tinnitus as other ADRs. Three patients (A, D and E) did not use any concomitant medication.
The outcome was reported in five patients. In one of these reports (patient H), frequency of the bleedings reduced after tamsulosin was replaced by alfuzosin. This patient also had a medical history of xylometazolin abuse and nose bleeding which required electric cautery.
Three patients (B, C, D) recovered (with sequel for patient D) on ongoing therapy with tamsulosin. For patient A, the action with the drug is not known. Patient E visited an ear, nose and throat specialist, who diagnosed an inflammation of the upper blood vessel of the nose. After electric cautery, the patient recovered.
Patient C and F used acenocoumarol and beclometasone as concomitant medication, which can induce epistaxis. Patient H used metoprolol, which has rhinitis as well known ADR due to its vasodilatation effects.

Table 1. Reports of epistaxis with the use of tamsulosin.

Patient, sex, age	Drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
A 56008 M, 60	tamsulosin 0.4mg 1dd benign prostatic hyperplasia		epistaxis tinnitus	3 months, March action unknown recovered
B 75117 M, 56	tamsulosin 0.4mg 1dd prostatic hypertrophy	escitalopram	epistaxis	2 days, February no change recovered
C 83555 M, 73	tamsulosin 0.4mg 1dd benign prostatic hyperplasia	acenocoumarol verapamil digoxin	epistaxis	within the same month, May no change recovered
D 82420 M, 61	tamsulosin 0.4mg 1dd benign prostatic hyperplasia, ciprofloxacin prophylaxis for biopsy		epistaxis	1 year (tamsulosin), 3 days (ciprofloxacin), November Ciprofloxacin withdrawn, tamsulosin ongoing recovered with sequel
E 31672 M, 64	tamsulosin 0.4mg 1dd		nosebleed	3 weeks, April no change unknown
F 22177 M, 77	tamsulosin 0.4 1dd hyperplasia of prostate	salmeterol nitrazepam beclometasone (nasal) ketokonazole	epistaxis	1 day, October discontinued not reported
G 14030 M, 59	tamsulosin 0.4 mg 1dd	doxycyclin heparinoid creme amoxicillin/ clavulanic acid	nosebleed, nose dryness	2 days, May drug withdrawn before the event occurred. not reported
H 48827 M, 69	tamsulosin 0.4mg 1dd dutasteride 0.5mg 1dd	doxazosin enalapril/ hydrochloro-thiazide metoprolol	epistaxis	6 weeks, November tamsulosin replaced by alfuzosin. frequency bleedings reduced

Other sources of information

Literature

Epistaxis is not mentioned in the SmPC of tamsulosin. Other symptoms which can manifest itself in the form of epistaxis, such as thrombocytopenia, are also not mentioned. Rhinitis, a risk factor for epistaxis, is a well known ADR [2].
The SmPC of terazosin, another α1-antagonist (brand name, Hytrin®), does not mention epistaxis [5]. However, the SmPC of terazosin generic mentions epistaxis as an ADR seen in clinical setting with an unknown causal relationship [6]. In this SmPC, thrombocytopenia is also mentioned as ADR seen in post marketing setting [6]. In literature, we found no cases of epistaxis with the use of tamsulosin or α-blockers.

Databases

In the Lareb database the association between tamsulosin and epistaxis is disproportionally present. On July 7, 2009, the Lareb database contained eight reports of epistaxis and tamsulosin, with an odds ratio of 4.8 (95% CI 1.9 - 6.7). In the database of the World Heath organization (WHO) there were 17 reports of epistaxis with the use of tamsulosin with an odds ratio of 1.6 (95% CI 0.96 - 2.5).
On July 24, 2009, the Eudravigilance database - that contains mainly reports of serious ADRs - contained 15 reports of tamsulosin associated epistaxis. Thirteen were rated serious, of which ten due to hospital admission, two due to disability and one due to other non-specified reasons. Thrombocytopenia was reported once, atrial fibrillation - without mention of coumarine use - three times. In six cases a drug interaction was reported. All 15 patients were of male sex, ages ranging from 39 to 75 years.

Mechanism

Alpha-1-agonists such as xylometazolin or oxymetazolin cause decongestion of the nose due to vasoconstriction, and these drugs are indicated for treatment of epistaxis [3]. Alpha-1-receptor antagonists, like tamsulosin, cause vasodilatation [7]. Hypothetically, vasodilatation increases the risk of nose bleeds.
Additionally, vasodilatation of the nose also leads to swelling of the mucosa and nose congestion. Swelling of the mucosa and nose congestion can lead to rhinitis, a well known side effect of tamsulosin. Rhinitis is a risk factor for the occurrence of epistaxis [3].

Discussion and conclusion

There are several factors associated with nose bleeds. These include rhino sinusitis, systemic conditions associated with coagulopathy, septal perforations, dry mucosa and neoplasm [3]. Of the eight reports Lareb received, three patients had additional factors such as nasal dryness, the use of acenocoumarol or nasal corticosteroids and the concomitant use of antibiotics. Another patient received antihypertensive drugs as concomitant medication. Hypertension may also contribute to epistaxis, although this theory is controversial [3].
There is an increased incidence of nose bleeds during winter months, probably due to dehumidification of the nasal mucosa [3]. However, since only two of the eight reports concern patients who experienced epistaxis in the winter months (December to March) this cannot be the explanation in all cases. Remarkably, all reports concerned males while no sex difference was found after the age of 50 in literature [4].

Although other factors for nose bleeds cannot fully be excluded, the number of the reports and the pharmacological properties of tamsulosin supports the relation between epistaxis and tamsulosin. The association between epistaxis and tamsulosin is disproportionally present in the Lareb database. For another α1-antagonist, terazosine, epistaxis is described in the SmPC. Epistaxis should be mentioned in the SmPCs of all tamsulosin containing products.

References

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6. Dutch SmPC terazosin pch. (version date: 5-3-2002, access date: 7-7-2009) http://db.cbg-meb.nl/IB-teksten/h26356.pdf.
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This signal has been raised on October 2009. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbg-meb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).