1.1. Inhaled fluticasone and epistaxis

Introduction

Fluticasone is a locally acting potent corticosteroid and is registered in the Netherlands since 1990. It is marketed as nasal drops and nasal spray (Flixonase®, Avamys®) for the indications *vasomotor and allergic rhinitis, nasal polyps,* and as inhalation corticosteroid (ICS) (Flixotide®) in both an inhalation dosisaerosol and a powder inhalation form for indications *asthma and chronic obstructive pulmonary disease (COPD).*

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 [1]. 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 [2]. 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 [1].

Systemic adverse drug reactions can occur during nasal and inhaled administration of fluticasone. Epistaxis is a well known ADR during nasal use of fluticasone [3], but it is not mentioned in the Dutch SmPCs of orally inhaled fluticasone products [4-6].

Reports

On July 29, 2010, the database of the Netherlands Pharmacovigilance Centre Lareb contained eight reports of epistaxis associated with the use of orally inhaled fluticasone. These reports concerned male as well as female patients in varying ages. The reports are listed in Table 1.

Table 1. Reports of epistaxis associated with the use of fluticasone

Patient, Number, Sex, Age	Drug (daily dose) Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 19187 F, 8 – 10 years	fluticasone dose unknown asthma	salbutamol	epistaxis	several hours discontinued recovered, positive de- and rechallenge
B 23740 F, 70 years and older	fluticasone 2 dd 500 mcg asthma	ipratropium, salmeterol, nifedipine, nedocromil, ranitidine	epistaxis	unknown discontinued recovered, positive de- and rechallenge
C 24936 M, 70 years and older	fluticasone 2 dd 500 mcg	ipratropium, famotidine, captopril, salbutamol	epistaxis (3 to 4 times a day)	7 days discontinued recovered
D 26684 M, 5 – 7 years	fluticasone 2 dd 250 mcg	loratadine, salbutamol, salmeterol	epistaxis	unknown continued not recovered
E 48448 M, 61 – 70 years	fluticasone chronic bronchitis 2 dd 250 mcg	losartan	epistaxis (one sided)	several hours unknown unknown similar symptoms during nasal use of fluticasone

Patient, Number, Sex, Age	Drug (daily dose) Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
F 82593 F, 31 – 40 years	fluticasone dose unknown respiratory disorder	-	epistaxis	several days continued recovered
G 82930 M, 41 – 50 years	fluticasone asthma 2 dd 250 mcg	-	epistaxis	several days continued recovering
H 107529 M, 11 – 20 years	fluticasone 2 dd 250 mcg asthma	-	epistaxis; blood in snot after noose blowing	1 day discontinued recovered, positive de- and rechallenge

Time to onset varied from several hours to several days. In four cases a positive dechallenge was reported, two of them with positive rechallenge as well.
In five cases the nose bleeds occurred in the winter (B, D-G).

Other sources of information

Literature

Epistaxis is mentioned as a possible adverse reaction of orally inhaled fluticasone in the US SmPC of Flovent® discus [7]. To the best of our knowledge, there are no other publications on a possible association between orally inhaled fluticasone and epistaxis.
In Micromedex [8] and Pubmed publications epistaxis is only described in association with the use of nasal administration of fluticasone.
The relationship between *skin bruising* and inhaled corticosteroid (ICS) therapy is described in several studies. In a large double-blind, randomized, placebo-controlled clinical trial with 1116 participants (544 ICS, 542 placebo) it was found that a significantly higher proportion of ICS than placebo participants reported easy bruising (11.2% vs 3.5%, respectively) and the slow healing of skin cuts or sores (2.4% vs 0.5%, respectively) [9].
Lareb previously described the association between inhaled fluticasone and *haematoma* in a quarterly report [10] and a publication [11]. By now, bruising is mentioned as a possible adverse drug reaction in the SmPCs of inhaled fluticasone, but epistaxis is not described.

Databases

The eight Lareb reports of epistaxis during use of orally inhaled fluticasone lead to a reporting odds ratio (ROR) of 6.3 (95% CI 3.1-12.9). It should be noted that this ROR includes the cases that occurred during the winter.

On July 29, 2010, the WHO database of the Uppsala Monitoring Centre contained 573 reports of epistaxis and orally inhaled fluticasone. This resulted in a disproportional ROR of 26.2 (95% CI 24.1-28.6). This ROR also includes the cases that occurred during the winter.

On August 3rd the Eudravigilance database contained six reports of epistaxis associated with use of inhaled fluticasone. All six cases were rated serious (one report of a life threatening event due to a combined nose and throat bleeding, three additional reports of hospital admission, other in two cases). There are three Portuguese cases which all concern 65-year old women. However, the reported clinical event differs in each three cases, which most plausibly implies that these cases concern separate events.

Prescription data

The number of patients using inhaled fluticasone in the Netherlands is shown in Table 2.

Table 2. Number of users of inhaled fluticasone in the Netherlands between 2005 and 2008 [12]

Drug	2006	2007	2008	2009
Fluticasone	302,320	295,140	276,110	281,660

Mechanism

Thinning and bruising of the skin may occur while taking inhaled corticosteroids, with evidence of a dose-response effect [13]. The presence of skin bruising can be considered a visible marker of the adverse effects of corticosteroids on collagen turnover in connective tissue, and serial skin examinations therefore can be used to monitor potential systemic adverse effects in patients taking high-dose therapy [14].
Inhaled corticosteroids most probably repress skin collagen synthesis. In a small study with 18 asthma patients, both types I and III procollagen propeptide concentrations decreased significantly after 6 weeks of even a low dose of inhaled corticosteroids [15].
Epistaxis caused by inhaled corticosteroids may well be caused by the same mechanism; repressed skin collagen synthesis, resulting in an increased vulnerability of the skin and the cutaneous blood vessels.

Discussion and conclusion

Epistaxis is associated with several factors, including rhino-sinusitis, systemic conditions associated with coagulopathy, septal perforations, dry mucosa, Osler-Weber-Rendu syndrome and neoplasm [1]. The eight Lareb cases may all be more susceptible to epistaxis due to their asthmatic condition, which is often attended with or induced by (allergic) rhinitis [16].
Furthermore, the concomitant medication of three patients (B, C and E) is most probably indicated for hypertension. Hypertension may also contribute to epistaxis, although this theory is controversial [1]. It should also be considered that there is an increased incidence of nose bleeds during the winter months, probable due to dehumidification of the nasal mucosa [1]. Since five of the eight case reports occurred during the winter months (December to March), the contribution of this factor cannot be excluded.
However, the positive de- (and re-)challenge in four cases - including cases B and C - strongly supports the causal relation with use of fluticason.

The association between inhaled fluticasone and epistaxis is supported by the disproportional number of reports both in the Lareb and WHO database, the known effects of inhaled corticosteroids on skin haematoma, and the fact that epistaxis is a known adverse drug reaction for nasal administration of fluticasone.

- Possible signal of epistaxis in association with orally inhaled fluticasone

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This signal has been raised on November 2010. 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).