Title: Phosphodiesterase-5 inhibitor use; a probably under-reported cause of profuse nasal bleeding.

Authors: 1) Petros V. Vlastarakos, MD, MSc, PhD, IDO-HNS (Eng.), Consultant, ENT Dept., MITERA Infirmary, Athens, Greece
2) Thomas P. Nikolopoulos, MD, DM, PhD, FEBEORL-HNS, Professor, ENT Dept., Attikon University Hospital, Athens, Greece

Corresponding author: Petros V. Vlastarakos.
E-mail address (preferred type of communication): pevlast@hotmail.com
Secondary e-mail address: pevlast@yahoo.gr
Country: Greece
City: Kallithea-Athens
Street address: 58 Laskaridou Str.
Postal code: 17676
Telephone number: 00302108577976
Mobile phone number (preferred phone of communication): 00306977803852
Fax number: 00302106869161
Hospital address: 6 Erythrou Stavrou Str.
Country: Greece
City: Marousi-Athens
Postal code: 15123

Running title: PDE-5 inhibitors and epistaxis
Phosphodiesterase-5 inhibitor use; a probably under-reported cause of profuse nasal bleeding

Abstract

**Background:** Phosphodiesterase (PDE)-5 inhibitors enhance penile erection and have gained popularity not only for erectile dysfunction, but also in more recreational settings. Nevertheless, adverse effects have been associated with their use, with nasal bleeding among them. That is because PDE-5 inhibitor action is materialized through the inhibition of the cyclic guanosine monophosphate (cGMP) enzyme. cGMP is present at several sites of the human body in addition to the corpus cavernosum, hence the adverse effects associated with its non-selective inhibition.

**Case-series:** Two male patients with severe epistaxis, who were taking PDE-5 inhibitors for erectile dysfunction, or recreational purposes, are discussed. Surgical intervention was required in both patients to control the nasal hemorrhage.

**Why should an emergency physician be aware of this?** Nasal bleeding in patients receiving PDE-5 inhibitors might represent an under-reported cause of epistaxis, because of the unwillingness of most male patients to discuss issues pertaining their use without hesitation. Yet such episodes are rather profuse. This is especially true when the venous engorgement caused in the nasal mucosa by the smooth-muscle relaxant effect of PDE-5 inhibitors is combined with a second event (i.e. specific drugs, blood dyscrasia etc.). Emergency physicians should be also aware of the possibility that in the next years the number of such cases might increase, due to the increased use of these medications for erectile dysfunction, or recreational purposes.
It is likely that these patients could not be managed conservatively, but would rather require referral to an ENT Department for a surgical intervention.

Keywords: epistaxis, nasal bleeding, phosphodiesterase-5 inhibitors
Introduction

Phosphodiesterase (PDE)-5 inhibitors (i.e. Viagra®) enhance penile erection by inducing smooth muscle relaxation in the corpus cavernosum. They have, hence, gained popularity not only for erectile dysfunction, but also in more recreational settings.

However, the enzyme inhibited by the drugs of this category, cyclic guanosine monophosphate (cGMP), is present at several sites of the human body in addition to the corpus cavernosum. Therefore, adverse effects such as intracranial hemorrhage, variceal and hemorrhoidal bleeding, vocal fold hemorrhage and epistaxis have been previously reported to follow its non-selective inhibition (1-6).

The aim of the present case-series is to discuss the occurrence of nasal bleeding in patients receiving PDE-5 inhibitors with emphasis in its management, since such episodes might represent an under-reported cause of epistaxis, because of the unwillingness of most male patients to openly discuss issues relating to PDE-5 inhibitor use.
Case series

Case 1

A 51-year old man was admitted in our Department, due to tenacious epistaxis from his left nostril of 10 days duration. On examination, there was severe septal deviation to the left. No specific bleeding site was identified. His past medical history included blood hypertension under amlodipine, and sildenafil overuse for recreational purposes. Bleeding control required anterior and posterior packing, however an attempt to remove the nasal packs resulted in bleeding recurrence.

The patient underwent a septoplasty and cautery to the inferior turbinates under general anesthesia. Anterior packing was placed postoperatively for two days. He was also given 500 mg of tranexamic acid per os for three days after the operation, due to mild bleeding leakage around the nasal packs. The patient was discharged four days after the septoplasty, and a year after his operation he has not experienced any further bleeding.

Case 2

A 67-year old man was again admitted in our Department, due to persistent epistaxis from his left nostril of 10 days duration. Over the aforementioned time period the patient underwent three nasal cauterizations under local anesthesia and endoscopic guidance in another hospital. On examination, the patient had a 4-cm nasal pack
lodged between the middle turbinate and the nasal septum, but reported intermittent posterior bleeding every four hours despite its presence and the previous cauterizations. Upon pack removal, the patient started to experience profuse nasal bleeding, which was only partially controlled by antero-posterior nasal packing. His past medical history included irradiation for prostate cancer 8 years before, with occasional use of tadalafil for erectile dysfunction. He had also been recently diagnosed with leukemoid reaction of his white cell lineage (WBC~30,000), pending bone marrow biopsy to determine the exact nature of the problem.

The patient underwent endoscopic ligation of the left sphenopalatine artery under general anesthesia, following the endoscopic discovery of a bleeding site between the attachment of the left middle turbinate and the lateral nasal wall (Figures 1a & 1b, 2a & 2b, 3). The patient was not packed postoperatively, and was discharged the next day. Six months after his operation, he remains free of bleeding recurrence.
Discussion

Epistaxis is thought to affect 10–12% of the population, among which 10% require medical attention (7). Epistaxis can be triggered by local (i.e. trauma, mucosal inflammation, septal deviation, tumors), systemic (i.e. blood dyscrasias, arteriosclerosis, hereditary hemorrhagic telangiectasia), and idiopathic causes. Although most cases are self-limited, some do not resolve without intervention.

PDE-5 inhibitors, on the other hand, have gained popularity due to their erectile properties, which are materialized through the inhibition of the cGMP enzyme. However, in addition to the presence of the inhibited enzyme at several sites of the human body, in-vitro research suggests that sildenafil may inhibit collagen-induced platelet aggregation (8). Furthermore, anti-hypertensive drugs metabolized in cytochrome p450 could affect the pharmacokinetics of PDE-5 inhibitors, which share the same metabolic pathway, rendering hemorrhage more likely (9).

The nasal turbinates also demonstrate erectile properties (10), and nasal stuffiness during sexual activity is an acknowledged phenomenon (11). Although nasal bleeding in patients receiving PDE-5 inhibitors has been reported in the past (5, 6, 9, 12-14), it might represent an under-reported cause of epistaxis, because of the unwillingness of most male patients to discuss issues pertaining their use without hesitation.

The patients in our series demonstrated PDE-5 inhibitor-induced severe epistaxis for different reasons. The first presumably because of the combined amlodipine-sildenafil intake, and the second due to the additionally impaired coagulation properties of his...
platelets, resulting from his underlying disease (which was demonstrated two months postoperatively with platelet function testing).

Although packing has historically been the workhorse of nasal bleeding management, it seems that such episodes in patients receiving PDE-5 inhibitors are rather profuse, and surgical management is very often required. This is especially true when the venous engorgement caused in the nasal mucosa by the smooth-muscle relaxant effect of PDE-5 inhibitors is combined with a second event (i.e. specific drugs, blood dyscrasia etc.). Nevertheless, the number of patients who experience this complication is probably limited, taking into account that the use of the agent is quite widespread. Yet, it is likely that these patients would require referral to an ENT Department for surgical control of their hemorrhage. Surgical interventions in these patients not only control the nasal hemorrhage, but may also be associated with improved cost-effectiveness and patient comfort.

Why should an emergency physician be aware of this?

Nasal bleeding in patients receiving PDE-5 inhibitors might represent an under-reported cause of epistaxis, because of the unwillingness of most male patients to openly discuss issues relating to erectile dysfunction. Emergency physicians should be aware of the possibility that in the next years the number of such cases might increase due to the increased use of these medications. Episodes of nasal bleeding in patients receiving PDE-5 inhibitors are rather profuse, and surgical management is very often required. It is hence likely that these patients would require referral to an ENT Department.


Figures

Figure 1a                                               Figure 1b
Patient N° 2. Bleeding in the left middle meatus (left image) and identification of bleeding site underneath the left middle turbinate (right image)

Figure 2a                                                   Figure 2b
Patient N° 2. Main trunk of the left sphenopalatine artery (left image), and descending branch (right image)

Figure 3
Patient N° 2. Left sphenopalatine artery completely diathermized