

1.1. Phosphodiesterase 5 inhibitors and pulmonary embolism

Introduction

Phosphodiesterase 5 (PDE5) is the predominant phosphodiesterase in the corpus cavernosum of the penis. It is involved in the cyclic guanosine monophosphate (cGMP) pathway that mediates smooth muscle relaxation and vasodilatation through nitric oxide, resulting in penile erection. Inhibition of the breakdown of cGMP by PDE5 inhibitors leads to prolongation of the vasodilator effects of nitric oxide and thus of the erection [1].

PDE5 inhibitors marketed in the Netherlands are sildenafil (Viagra[®]), tadalafil (Cialis[®]) and vardenafil (Levitra[®]). They are registered for the treatment of *erectile dysfunction in men* [2-4]. Because of their vasodilator and endothelial antiproliferative effects, they are also used in pulmonary hypertension [5].

Reports

In 2008, two cases of pulmonary embolism in association with the use of the PDE5 inhibitor vardenafil were reported to the Netherlands Pharmacovigilance Centre Lareb. The reporters were both medical specialists and were unaware of a colleague reporting a similar event. The reports are described in detail below.

Patient A (report number 75088) is a male aged 57, with a medical history of hypertension. He was examined by the specialist doctor because of dyspnea that existed for weeks, since the first use of vardenafil for impotence. He had used it three times, each time he also had chest pressure during 30 minutes, starting shortly after vardenafil intake. He had never used vardenafil without these symptoms, it was withdrawn after the 3rd episode. A CT-scan angiography showed a pulmonary embolus in the right upper lobe. The patient had no history or family history of thrombo-embolic events, he is a non-smoker and was not immobilized prior to the event. He was treated with anticoagulant therapy.

Patient B (report number 75473) is a male aged 62, with a medical history of vasectomy, polymyalgia rheumatica, osteoporosis, papillary urothelium carcinoma grade 1-2 (September 2005, TUR bladder was done, no signs of recurrence). He had a deep venous thrombosis of the leg in 2006 and was now – February 2008 - hospitalized for pulmonary embolism. The patient mentioned that both episodes he had used vardenafil shortly before the events and with short therapy duration. It is not clear how many times he had used vardenafil and what the exact latency was. The patient was treated with anticoagulant therapy and advised not to restart vardenafil.

Other sources of information

Literature

The symptoms of pulmonary embolism can vary from almost none to various non-specific symptoms, like acute dyspnea, chest pain, haemoptysis, hypoxia, tachycardia and in severe cases acute cardiac death. Further adverse events that could point to a venous hypercoagulation state are deep venous thrombosis of the extremities and venous thrombosis of the retina. Myocardial infarction is mentioned as adverse reaction for all PDE5 inhibitors, but this is considered of arterial origin. Furthermore, the SmPC of sildenafil and tadalafil mention CVA and TIA. The SmPC of vardenafil mentions dyspnea [4]. The SmPC of sildenafil mentions: retinal vessel occlusion, sudden cardiac death and chest pain [2]. The SmPC of tadalafil mentions retinal vessel occlusion and sudden cardiac death [3].

Two case-reports concerning pulmonary thrombosis associated with PDE5 inhibitors are described in the literature. Rufa et al. describe a 57-year-old man who experienced deep venous thrombosis of the leg, severe thrombosis of the haemorrhoid plexus and cerebral venous sinus thrombosis over a 12 month period during which he was taking sildenafil regularly twice a week. Each episode of venous thrombosis occurred within 24 hours of drug use. A slight reduction in

antithrombin III and free protein S levels were found. After withdrawal of sildenafil and six months of anti-coagulant therapy, clinical improvement was obtained [6].

Chen et al. describe a 54-year-old male who developed pulmonary embolism within one hour of taking tadalafil and before any sexual exercise. Laboratory testing showed reduced plasma levels of protein C. He was treated with anticoagulant therapy and has completely recovered after six months [5].

Databases

the number of reports are insufficient to calculate a reliable reporting odds ratio (ROR). The database of the Netherlands Pharmacovigilance Centre Lareb does not contain additional reports of venous thromboembolism in association with the use of PDE5 inhibitors. Adverse reactions reported as “occlusions” are one report of coronary artery occlusion and two reports on retinal artery occlusion.

On February 13, 2009, the Eudravigilance database contained five serious reports (three men, two women) of pulmonary embolism associated with sildenafil. In two cases the patient died. In two patient’s sildenafil was used for pulmonary hypertension, in one case for vasodilatation in scleroderma. In one fatal case, sildenafil was used for erectile dysfunction. In the fifth case the indication for use was specified.

Tadalafil was associated with pulmonary embolisms in four cases. All were men with ages ranging from 53 to 80. The pulmonary embolism was reported to be life threatening in one case, led in two additional cases to hospitalisation and was considered serious due to other reasons in one case.

In three cases pulmonary embolisms were associated with vardenafil. All patients involved were men (age 57, 62 and in one case not specified). One case was rated as a serious reaction because of hospitalisation, in two cases the reason for considering this case serious was non-specified.

On the same date, the database of the WHO contained several reports on embolism and thrombotic processes in association with PDE5 inhibitors. An overview is provided in table 1.

Table 1. Number of reports concerning embolism and thrombosis in the database of the WHO Collaborating Centre for International Drug Monitoring.

	Sildenafil	Tadalafil	Vardenafil
Pulmonary embolism	13	1	3
Embolism NOS	22	1	
Thrombosis NOS	33	5	
Venous Trombosis	5		

Prescription data

Since PDE5 inhibitors are not being reimbursed in the Netherlands, the Drug Information System of the Dutch Health Care Insurance Board (GIP) can not provide data on the number of users.

Mechanism

PDE5 inhibitors are not only abundant in the penile corpus cavernosum, but also in pulmonary tissue [5]. Sildenafil has no known effects on prothrombin or bleeding times, or direct effect on platelets. PDE5 inhibitors potentiate the inhibitory function of the nitric oxide donor, nitroprusside, on adenosine diphosphate–induced platelet aggregation ex vivo, and are therefore anticipated to be antithrombotic agents [6].

There are four mechanisms that could explain thrombotic events in patients using PDE5 inhibitors. First, under the vasodilatory mechanism, transient hypoperfusion of the lung may occur, especially when acquired or hereditary prothrombotic risk factors exist, [5]. Second, in chronic use, high concentrations of cGMP could interfere with several phosphokinases, and thus with normal endothelial function [6]. Third, cGMP may also stimulate phosphodiesterase E2 and E4, which may promote endothelial adhesion events that lead to thrombus formation[6]. Finally,

sildenafil is known to interact with bivalent ions like Ca⁺ that are also very important in the coagulation cascade [6].

Discussion

The clinical diagnosis of pulmonary embolism is difficult and can be easily missed. Furthermore, adverse reactions in patients using PDE5 inhibitors are probably less likely to be reported than in the normal situation of spontaneous reporting. Patients sometimes acquire these drugs through different channels (e.g. internet) and for an indication that may lead to shame. Therefore, events of pulmonary embolism might not be related to use of PDE5 inhibitors by health care professionals.

However, we conclude that the two reports are sufficient to provide a pharmacovigilance signal, because the reports are well documented and because there is support from case reports in literature. Reports in the Eudravigilance and WHO databases support our hypothesis.

Conclusion

Pulmonary embolism might be a new adverse reaction associated with the use of PDE5 inhibitors. Continued vigilance and further exploration of this signal in other databases and by special attention of the marketing authorization holders is recommended.

References

1. Corbin JD, Francis SH, Webb DJ. Phosphodiesterase type 5 as a pharmacologic target in erectile dysfunction. *Urology*. 2002;60(2 Suppl 2):4-11.
2. European SmPC of sildenafil (Viagra[®]). (version date: 13-11-2008) <http://www.emea.europa.eu/humandocs/>
3. European SmPC of tadalafil (Cialis[®]). (version date: 13-11-2008) <http://www.emea.europa.eu/humandocs/>
4. European SmPC of vardenafil (Levitra[®]). (version date: 19-8-2008) <http://www.emea.europa.eu/humandocs/>
5. Chen H, Wang C, Chuang S, Wang C. Pulmonary embolism after tadalafil ingestion. *Pharm World Sci* 2008;30(5):610-2.
6. Rufa A, Cerase A, Monti L, Dotti MT, Giorgio A, Sicurelli F, Federico A. Recurrent venous thrombosis including cerebral venous sinus thrombosis in a patient taking sildenafil for erectile dysfunction. *J Neurol Sci* 2007;260(1-2):293-5.

This signal has been raised on April 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).