Expert Opinion

Phosphodiesterase-5 Inhibitors and Migraine

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The age of Viagra has been a boon for many, but a new source of drug-induced migraine for others.

CASE

A 45-year-old man has a 10-year history of migraine without aura occurring about once a week relieved by an oral triptan. When he sought treatment for erectile dysfunction from a urologist, the side effect of triggering migraine was brought up. Now the patient and the urologist want my opinion about whether the patient should try an oral phosphodiesterase-5 inhibitor (PDE-5) and, if so, do I have a preference?

Questions.—What is the risk of PDE-5 triggering migraines? Does the risk vary among the three medications, sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis)? Is the risk dose-related? What is the latency from taking the PDE-5 medication until onset of the headache? Would taking a migraine symptomatic medication along with the PDE-5 inhibitor prevent the migraine from occurring? Does the long-duration agent, tadalafil, cause long-duration migraines? Do PDE-5-triggered migraines respond to the patient's usual acute migraine medications? Are preventative medications useful in reducing the risk of PDE-5-triggered migraines? How might PDE-5 inhibitors cause migraine?

EXPERT COMMENTARY

Phosphodiesterases (PDEs) are intracellular enzymes responsible for the degradation of the second messengers cAMP and cGMP. So far 11 different types of PDEs have been characterized with different specificity, mode of regulation, and tissue distribution and there are several isoforms and splice variants of each PDE. Because of the specific role and distribution of each PDE type, specific inhibitors for various diseases have been designed. The most widely known are probably the PDE-5 inhibitors for male impotence, where sildenafil was the first on the marked list and recently vardenafil and tadalafil have followed. They all inhibit the cGMP-degrading PDE-5 and work by increasing the intracellular level of cGMP, thus causing smooth muscle cell relaxation or neuronal stimulation. Sildenafil, however, also affects PDE-6 causing a minor degree of visual side effects and tadalafil inhibits PDE-11, the significance of which is still unknown. Vardenafil is more selective than both tadalafil and sildenafil with IC50 of 0.1-0.8, 1-7, and 1-9 nM, respectively. The t_{max} is almost identical for vardenafil and sildenafil, ~0.8 hours, just as the $T_{1/2}$ is approximately 4 hours, whereas for tadalafil t_{max} is ~2 hours and $T_{1/2}$ is 17.5 hours. The side effect profiles for all of the PDE-5 inhibitors are almost identical, headache being the most common, dose-dependent side effect. Headache is reported in up to 30% of patients after sildenafil,[1] 21% of patients after vardenafil,[2] and 16% of patients after tadalafil.[3] The most frequent reason for discontinuation of the PDE-5 inhibitors is headache causing a discontinuation rate of 1.2% after sildenafil 100 mg.

Recently two studies were performed investigating the effects of sildenafil on headache, cerebral blood flow, and artery dilation since sildenafil is an obvious tool to investigate the role of endogenously produced cGMP as part of the nitric oxide-cGMP cascade

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in headache induction. One study was performed in healthy subjects[5] and the other in patients with migraine without aura.[6] Out of 10 healthy subjects (6 men/4 women), 10 reported headaches and 3 of these fulfilled the criteria for one attack of migraine without aura despite no previous history of migraine and no first degree relatives with migraine. Out of 12 migraine patients (12 women), 10 reported induction of a migraine attack similar to their usual migraine attack after ingestion of sildenafil. To our surprise no dilation of the large intracranial or extracranial arteries was found, indicating that the previously reported large artery dilation of the nitric oxide donors may be an epiphenomenon in migraine induction rather than the actual course of migraine. Thus, sildenafil seems to work through other mechanisms than artery dilation in the migraine induction, most likely the perivascular pain-sensitive nerve-fibers or more centrally located neurons in the pain-pathway.

No similar studies have been performed using vardenafil or tadalafil, however given a similar side effect profile and mechanism of action they are likely to have the same effect.

The risk of inducing migraine seems dose-related just as the headache in healthy patients. Another group reported in an abstract, that sildenafil 20 mg induced a mild transient headache in all, but only migraine in 1 out of 7 patients with migraine without aura, within 6 hours after administration.[7]

In the study on migraine patents using sildenafil 100 mg, the headache was slowly progressing and median time to peak headache score was 4.5 hours with 5 patients fulfilling the criteria for migraine within the first 3 hours. All patients except 1 reported good effects of their usual triptans in treating the induced migraine attack. There are no reports on the effect of "pretreating" the attack with triptans, but, like in usual attacks, an effect of pretreatment would not be expected. Theoretically, tadalafil, which has the longest half-life could induce longer lasting migraine or an increased risk of recurrent migraine.

So far, there are no reports of preventive medication being effective in reducing sildenafil-induced migraine. It must be taken into consideration, however, that some preventive medication may itself induce impotence, and thus these compounds should be avoided in the case of already established impotence.

Considering the lifetime prevalence of migraine in the general population of 16%, and given the migraine-inducing effects of sildenafil and possibly also of the other PDE-5 inhibitors, it must be recommended that the labeling of these drugs include a warning to migraine patients, unless the drug companies provide data proving otherwise. Also, in light of the proposed new indications for the use of sildenafil in other patient groups including women, the migraine potential of the PDE-5 inhibitors should be recognized.

In conclusion, migraine patients should be made aware of the risk of inducing a migraine attack before initiation of treatment with PDE-5 inhibitors. The most short lasting PDE-5 inhibitors, vardenafil or sildenafil, in the lowest doses should be used first.

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