

Subarachnoid Haemorrhage : Possibly Caused by the Illegitimate Use of Sildenafil Citrate

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Abstract

Sildenafil (Viagra) has been developed as a drug to treat male impotence. It has also been used to reduce symptoms (e.g. improved exercise capacity) in patients with pulmonary arterial hypertension. A case of subarachnoid haemorrhage (SAH) following the illicit use of sildenafil is reported. ©

INTRODUCTION

Sildenafil is used orally as a vasoactive agent to facilitate attainment of a sexually functional erection in males with erectile dysfunction.¹ It has been associated with headache, flushing, dizziness, visual disturbance and hypotension (especially in cardiac patients who are on nitrates).¹ There are a few anecdotal reports of patients suffering from myocardial infarction with the use of sildenafil.¹ Product information also mentions Subarachnoid haemorrhage (SAH) and intracerebral haemorrhage (ICH) in the adverse effects, but these are seen in less than 2% of patients.¹ Besides, these serious adverse effects are usually seen in patients with cardiac disease and other comorbid illnesses.¹ We report a healthy male who presented with subarachnoid haemorrhage after the illicit usage of sildenafil.

CASE REPORT

A 48 year old male patient presented with h/o sudden onset severe generalized headache on waking up one morning. There was no h/o fever, vomiting, convulsions, photophobia or focal neurological deficit. He described it as the worst headache of his life. There was no similar past history or h/s/o migraine. There was no h/o hypertension (HT), diabetes mellitus (DM) or ischaemic heart disease (IHD) and this was his first hospital admission. The patient was a labourer by occupation and was a non-addict. He was married and had two grown-up sons. On examination, he was agitated and in severe discomfort due to the headache. He was conscious, oriented with a blood pressure (BP) of 140/80 mm of Hg. There was no focal neurological deficit, neck rigidity and plantars were bilaterally flexors. All other

systems were unremarkable on examination. Fundoscopy showed no papilloedema or changes s/o HT. An urgent noncontrast CT Brain was done which showed diffuse subarachnoid haemorrhage in the cisterns, sylvian fissures and parieto-occipital sulci (Fig. 1). Mild hydrocephalus was noted. Biochemical parameters were normal except for serum cholesterol (221 mg%) and serum triglyceride (181 mg%), which were on the higher side. Electrocardiogram and Chest radiograph were normal. 2D Echocardiography was within normal limits. A four vessel digital subtraction angiography (DSA) and a CT Angiography were within normal limits (Figs. 2 and 3).

The patient was started on cerebral dehydrants and oral Nimodipine every 4th hourly. His BP was monitored and maintained > 100 systolic and < 140 diastolic. The

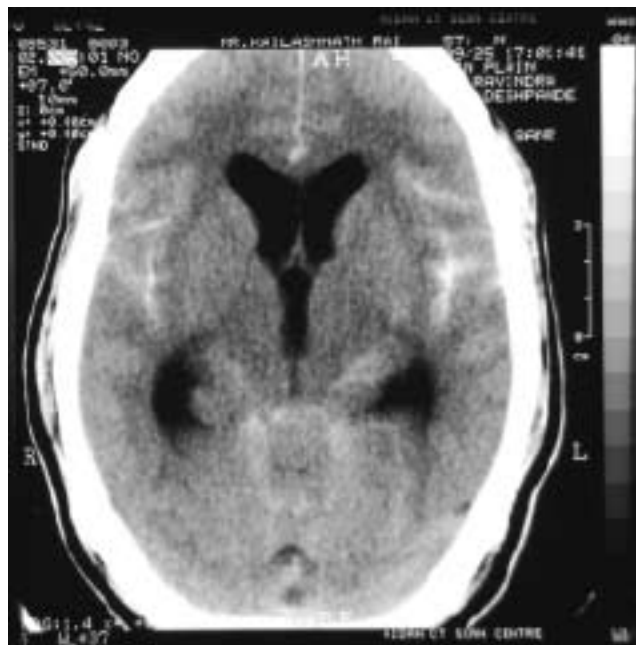


Fig. 1 : Non contrast CT Brain showing diffuse subarachnoid haemorrhage in the cisterns, sylvian fissures and parieto-occipital sulci.

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Fig. 2 : Normal Digital Subtraction Angiography.

electrolytes were monitored to detect hyponatremia. Tab Naproxen was given for his persistent headache which was finally relieved on day 6. On recovering, the patient volunteered information that he had taken tablets of sildenafil citrate (Viagra) in a dose of 1 bid for 4 days (total 8 tablets of 50 mg each) just prior to the episode, with the last dose being approximately 6-8 hours prior to the episode. He had purchased these from a local chemist without a prescription. There was no h/o sexual intercourse during this period as his spouse was not willing. He firmly denied a history of erectile dysfunction. The patient recovered completely and he was discharged on day 15. His BP was always within normal limits in the wards and he was asked to continue Nimodipine for 2 weeks more and get a repeat DSA done at the end of 2 weeks which was normal.

DISCUSSION

The possible association of Subarachnoid haemorrhage (SAH) with sildenafil in a patient with no known cardiac risk factors is a cause of enormous concern. Whilst other drugs, that are known to raise blood pressure, such as amphetamine or cocaine, or reduce clotting capabilities such as warfarin or aspirin, are well established in their association with ICH and SAH, sildenafil is not.²

One of the major advances in the treatment of male impotence has been the serendipitous discovery of sildenafil. Although the drug has a good safety profile, certain admonitions should be kept in mind while using this medication.³

Sildenafil is indicated in the treatment of erectile dysfunction.² It produces a selective vasodilatation of the corpus cavernosum (CC), mediated by the inhibition of phosphodiesterase 5, an enzyme that degrades cyclic guanosine monophosphate (cGMP).² Its therapeutic efficacy has been demonstrated in organic as well as psychogenic



Fig. 3 : Normal CT Angiography.

or mixed erectile dysfunction.²

Although it has many side effects related to its vascular properties (headache, flushing, dizziness, nasal congestion), SAH has not been commonly reported.² Angina pectoris, AV block, myocardial infarction, chest pain, cerebral thrombosis, cerebrovascular haemorrhage (e.g. SAH, ICH), TIA, stroke, coronary artery disease have occurred in less than 2% of patients with erectile dysfunction in controlled clinical trials and in postmarketing surveillance, but have not been directly attributed to the drug.¹ Majority of these patients had preexisting cardiovascular risk factors and many of these adverse effects were reported to occur shortly after taking sildenafil, either with or without sexual activity.¹ Though phosphodiesterase 5 (PDE5) inhibitors are widely used for the treatment of erectile dysfunction, the results on the cerebral vasculature are unknown.⁴ Various studies have indicated a similar nitric oxide-cGMP pathway responsible for cerebral vasodilatation and inhibition of platelet activation and aggregation.² The vascular relaxation effects of sildenafil, whilst designed to only affect the vessels of the corpus cavernosum, may have an effect on cerebral vasculature as flushing, headache and dizziness are well recognized side effects.²

Several cases of intraparenchymal haemorrhage in the setting of PDE5 inhibitors use have been reported.⁴ Spontaneous intracerebral haemorrhage which did not affect the visual function has been reported more commonly.^{2,5-7} McGee et al have reported left homonymous hemianopia secondary to right parietal lobe haemorrhage

after ingestion of 20 mg of vardenafil in a 66 year old healthy male⁸ while Mehdizadeh et al have reported the same due to right occipital lobe haemorrhage after ingestion of 50 mg of sildenafil citrate.⁵ The effect of these agents on the risk of arteriovenous malformation (AVM) is speculative and Steeves et al have reported a case of coital haemorrhage of an AVM after premedication with Tadalafil.⁴

The dose recommended is initially 50 mg, to be subsequently titrated upwards to 100 mg according to the desired response, the maximum single dose being 100 mg in 24 hours.²

There are many recognized adverse health events associated with sexual intercourse.² Whilst the link between sexual intercourse and SAH is well established, that between SAH and sildenafil is not.² At least 39 sildenafil –related deaths have been reported in men who had a history of heart disease, were taking nitrates or who were in poor health. Many of the men who experienced serious adverse effects or death had a variety of concomitant diseases and were taking multiple medications.³

Because of the potential effects on sexual performance, sildenafil has been misused and abused for enhancing erection by men who do not have documented erectile dysfunction.

Our patient was a healthy male with no premorbid illness. He was a non-hypertensive, non-diabetic, non-addict and was not on any prescription medications. He firmly denied sexual intercourse in the week preceding the episode and while he was taking Viagra. He also strongly denied having erectile dysfunction. In view of this, it is most likely that the illegal ingestion of sildenafil by an individual who lacked a legitimate medical need for phosphodiesterase 5 inhibition caused the subarachnoid haemorrhage.

As the safety and efficacy, particularly with frequent and long term use in individuals not suffering from erectile dysfunction has not been established, sildenafil is currently not recommended for simply enhancing erections in such men.

Sildenafil is readily available, not only over the counter (OTC), but also via the internet, wherein there is little or no physician/pharmacist intervention.⁹ This is particularly alarming due to the drug's potential appeal to consumers and its medical risks. It raises concern for the implications of sildenafil acquisition and use without medical monitoring.

CONCLUSION

Sildenafil, whilst filling an apparently huge untapped market, is not without risks. This case illustrates the association of SAH with its use in a healthy patient with no cardiac risk factors. The illicit acquisition of such a potentially dangerous drug is of enormous concern. The potential for the risk of devastating neurovascular complications related to phosphodiesterase inhibitors should be monitored.

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Announcement

VIIIth Annual Conference API Tripura State Branch on 20th and 21st December 2008 (Saturday and Sunday) at Agartala, Tripura.

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