Spontaneous Intracerebral Hemorrhage in 28-Year-Old Patient Following the Use of Sildenafil: A Case Report

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Abstract

Introduction: Sildenafil is a potent vasodilating agent treating male erectile dysfunction.

Case report: A 28-year-old, medically-free male presented collapsed to the emergency department with vomiting and mild headache. He took many Sildenafil tablets over a few weeks. His head computed tomogram showed a few peripheral intracerebral hemorrhage and small subarachnoid hemorrhage with mild brain edema. Normal angiography was detected. The patient was managed conservatively and discharged after 10 days.

Conclusion: Sildenafil seems to act by redistributing arterial blood flow with concurrent sympathetic hyperactivity, which lead to such hemorrhagic presentation. It is a highly potent drug, and it needs a urology consultation before use.

INTRODUCTION

Intracerebral hemorrhage (ICH) is a neurological deficit detected by brain computerized tomography (CT) scan or magnetic resonance imaging (MRI) showing an intracranial bleed in the brain parenchyma [1]. Vasculopathies e.g. cerebral amyloid angiopathy, hypertension, aneurysms, and vascular malformations are the main causes of ICH besides alcohol ingestion, coagulopathies, drugs, tumors, and genetics causes. Furthermore, ICH has high mortality and morbidity and is considered a serious cerebrovascular event in adults [2].

Sildenafil is a selective phosphodiesterase-5 (PDE-5) enzyme inhibitor. Moreover, it causes an increase in cyclic guanosine monophosphate (cGMP) in the corpus cavernosum vascular smooth muscle leading to muscle relaxation and vasodilation [3]. Sildenafil, by the way of PDE-1 and 2 enzymes, produces similar effects on intracranial vessels. The nitric oxide (NO)-cGMP pathway may cause cerebral vasodilation by comparable mechanisms in the brain. Sildenafil overdose or its use for long periods initiates the occurrence of intracerebral hemorrhage [4].

Sildenafil is commonly used orally as a vasoactive agent to facilitate attainment of a sexually functional erection in males with erectile dysfunction. It can be easily obtained and is mostly used without medical supervision [5-7]. As sildenafil leads to vasodilatation, a possible effect on bleeding incidents has been reported including epistaxis, hemoptysis, intracocular, variceal and rectal bleeding, as well as ICH [8].

Earlier studies have reported several adverse effects of sildenafil, which explain its systemic distribution into the brain microvasculature. These include headache, dizziness, ocular problems, and a pupil-sparing third nerve palsy [3]. Hypertension and sexual activity are known risk factors for ICH [9]. 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 [7].

Here, we are describing a newly married patient who developed spontaneous intracerebral hemorrhage after heavy taking of sildenafil tablets over honeymoon month as the first reported case in Tabuk region, Saudi Arabia.

CASE REPORT

A 28-year-old Saudi male who is medically free and smoker (one and half pack/day), was presented to the emergency department after being collapsed. After that, he vomited frequently, and he had mild headache without seizures. There was no history of hypertension, head trauma, or prior cerebrovascular disease (stroke/transient ischemic attacks), and no underlying vascular or hemodynamically risk factors. The patient...
mentioned that he took too many tablets of sildenafil over a few weeks, the last dose was around 8 hours before the admission. On admission, his blood pressure was 134/87 mm Hg, and pulse rate was 75 beats/minute. The Glasgow coma score was 15. The neurological examination was normal, and there were no obvious signs of trauma. Routine blood examination, platelet count, and coagulation factors were normal. Brain CT scan without contrast showed a few peripheral parenchymal acute hemorrhages; two at the right temporal lobe and small one at the right frontal lobe. Moreover, CT scan showed hyperdense appearance of the falx cerebi and tentorial leaflet as well as hyperdensity at the right Sylvian fissure likely representing small subarachnoid hemorrhage. Obliteration of the cortical sulci and lateral ventricles gave impression of mild brain edema [Fig.1], while magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) examination of the brain were normal [Figs. 2 & 3].

The patient was managed conservatively by D5 1/2 NS 80 ml/kg/hr; regular oral feeding; paracetamol 1 g, orally; tramadol 50 mg IV, TID; nexium 40 mg IV, once a day; and phenytoin 100 mg IV, TID. He had also two follow up CT Brain, the last one showed remarkable improvement. He was discharged from the hospital after 10 days.

**DISCUSSION**

Non-traumatic (or spontaneous) intracranial hemorrhage most commonly involves the brain parenchyma and subarachnoid space. This entity accounts for at least 10% of strokes and is a leading cause of death and disability in adults. Intracerebral hemorrhage mortality is about 40% at 30 days, similar to subarachnoid hemorrhage (SAH) in acute mortality. Important causes of spontaneous intracranial hemorrhage include hypertension, cerebral amyloid angiopathy, aneurysms, vascular malformations, and hemorrhagic infarcts [1, 10]. There are some drugs that cause intracerebral hemorrhage like anticoagulants, thrombolitics, sympathomimetics, methamphetamine, and cocaine [3].

One of the major advances in the treatment of male impotence has been the accidental discovery of sildenafil. Although the drug has a good safety profile, certain caution should be kept in mind while using this medication [11]. Product information also mentions SAH and ICH in the adverse effects, but these are seen in less than 2% of patients. Besides, these serious adverse effects are usually seen in patients with cardiac disease and other comorbid illnesses [7].

The relationship between ICH and PDE-5 inhibitors is explained by increased blood flow to the intracranial vessels during sexual intercourse, which is further enhanced by concurrent use of these drugs [2]. Sexual intercourse is known to produce a hyperdynamic circulatory state in both men and women, manifested by increased heart rate and blood pressure [6]. Following sexual stimulation, penile erection occurs through the release of nitric oxide (NO), which causes dilation of the blood vessels of the corpus cavernosum via an accumulation of cyclic guanosine monophosphate (cGMP). The PDE-5 inhibitors enhance this vasodilatory effect of NO-cGMP pathway by inhibiting PDE-5, the enzyme responsible for breakdown of cGMP [2].

Furthermore, the mechanism by which sildenafil alters coagulation that might cause or intensify e.g. intracranial bleeding is not fully understood. Importantly, sildenafil has been shown to inhibit platelet aggregation, which is clearly associated with a higher risk for e.g. intracranial hemorrhage.
However, transcranial doppler studies have shown that sildenafil significantly increases cerebrovascular reactivity. The fact that flushing, headache, and dizziness are well recognized side effects of sildenafil speaks for a considerable effect on cerebral micro-vasculature as well [8]. Studies have also shown that sildenafil acts on phosphodiesterase-1, -2 and -5 receptors and leads to a secondary increase in intracerebral circulation and vasodilatory effects, leading to sympathetic over activity, which increases the risk for intracranial bleeding. Side effects of sildenafil, including flushing, headache, nasal congestion, and changes in pulmonary blood flow indicate the multisystem vasodilation caused by these drugs [2].

Moreover, it is known that sildenafil increases the response of cerebral vasculature to carbon dioxide and causes increased cerebral blood flow and cerebral blood volume intracranially. Altered cerebrovascular reactivity causes a vasodilatory response and blood flow modifications. The effects of sildenafil on cerebral arterial diameter are not hemodynamically significant at rest, but hypercapnia decreases the mean arterial pressure 5 to 15 mm Hg [4].

All previous case studies that detected ICH after sildenafil use have reported minimal volume bleeding in old-aged patients who have risk factors. So, treatment of these cases was only medical, and surgical evacuation was not required [9, 13-15]. Using sildenafil in an overdose along a prolonged period increased the chance of intracerebral hemorrhage in this patient. The cranial MRA and MRV examination of the brain did not reveal any vascular anomalies explaining the cause of ICH. 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 gave history of taking too many tablets of sildenafil over a few weeks and the last dose was around 8 hours before the admission. In view of this, it is most likely that the ingestion of sildenafil by an individual who lacked a legitimate medical need for PDE-5 inhibition that intracerebral hemorrhage. In summary, sildenafil may act by redistributing arterial blood flow, hence rendering brain tissue perfusion poorer, presenting with collapse, vomiting and headache, as shown in the current case. Ensuing sympathetic hyperactivity through PDE-1 and PDE-2 might lead to rupture of vessels. On the contrary, it was suggested that even in a young adult male patient without known risk, initiating factors for ICH should be warned before prescribing sildenafil [3].

CONCLUSION

Sildenafil is a highly potent drug, which needs a urology consultation before using it. The use of this drug in high doses for recreational causes carries a significant risk for cerebrovascular accidents.

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CONFLICTS OF INTEREST

None to declare.