Intracerebral Hemorrhage after Sildenafil Citrate Use: An Incidental Association?

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INTRODUCTION

The most common causes of intracerebral hemorrhage (ICH) are structural vascular anomalies and dysfunctional coagulation. ICH caused by sildenafil is rarely reported in the literature. Sildenafil is a selective phosphodiesterase-5 (PDE-5) enzyme inhibitor, and causes an increase in cyclic guanosine monophosphate (cGMP) in the vascular smooth muscle of the corpus cavernosum, leading to muscle relaxation and vasodilation. Sildenafil has same effects on intracranial vasculature by way of PDE-1 and 2 enzymes. Overdose of sildenafil or use over an extended period of time increases the likelihood of intracerebral hemorrhage.

CASE REPORT

A 35-year-old male was admitted to the emergency department in a disoriented state and with a serious headache. His wife reported that he had noticed a serious headache two hours after taking 50 mg of sildenafil without having sexual activity. He had used the drug for nearly a month, two to three times in a day without supervision of an urologist. He had no hypertension, family history of cerebral arteriovenous malformation, cerebral aneurysms, or ICH. On

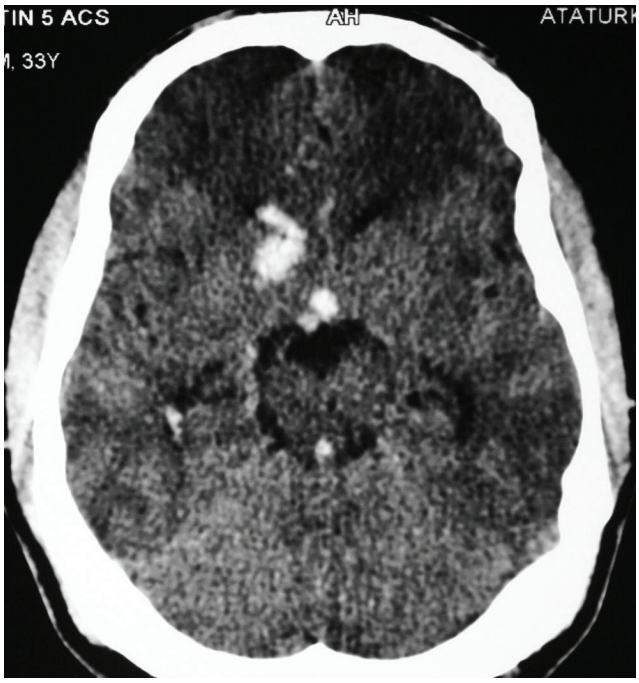

Figure 1. Cranial computed tomography scan demonstrates hemorrhage in the right nucleus caudatus.

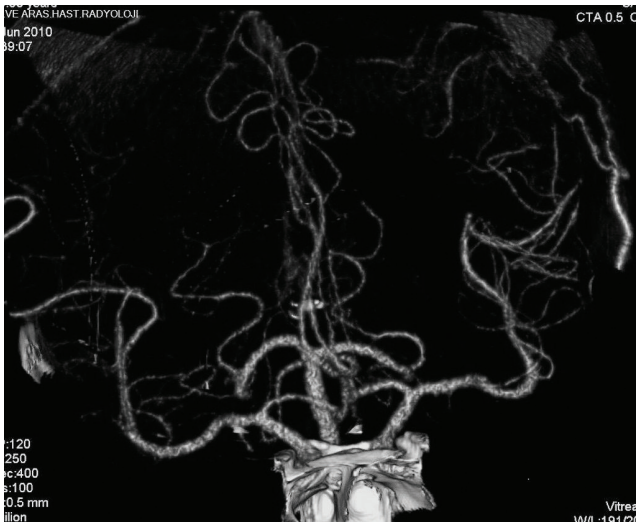

Figure 2. Computed tomography scan angiography and the cerebral digital subtraction angiography show no vascular pathology.

admission, blood pressure was 120/90 mm Hg, and pulse rate was 90 beats/minute. The Glasgow coma score was 12. The neurological examination was normal, with the exception of mild neck stiffness. Routine blood examination, platelet count and coagulation factors were normal. Cranial computed tomography (CT) scan revealed hemorrhage in the right nucleus caudatus, which opened in the lateral and third ventricles (Figure 1). CT scan angiography and the cerebral digital subtraction angiography (DSA) revealed no vascular pathology (Figure 2).The patient was consulted by a cardiology department to rule out cardiac causes, and reported as normal findings. He admitted to the intensive care unit for observation, and discharged after five days with normal neurologic examination.

DISCUSSION

Sildenafil is a PDE-5 enzyme inhibitor, and causes an increase in cGMP in the vascular smooth muscle of the corpus cavernosum. The nitric oxide (NO)-cGMP pathway may be responsible for cerebral vasodilation by similar mechanisms in the brain.[3] It has been suggested that sildenafil also acts on the PDE-1 and PDE-2 enzymes, which are involved in the control of cerebral vasculature.[4] There are many reported side effects of sildenafil in the literature including headache, visual and retinal disturbances, dizziness, and a pupil-sparing third nerve palsy, which explain systemic distribution into the microvasculature.[5] Hypertension and sexual activity are known risk factors for ICH.[6]

The ingestion of sildenafil and onset symptoms after three hours without sexual activity suggests that sildenafil may be related to the ICH in this patient. The cranial CT angiography and DSA did not reveal any vascular anomalies explaining the cause of ICH. The relationship between the ICH and sildenafil ingestion is speculative in the literature.[7] It is known that sildenafil increases the response of cerebral vasculature to $C0^2$ and causes increased cerebral blood flow and cerebral blood volume intracranially.[8] 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.[2] In hypertensive patients, these effects are much more prominent and dose dependent.[9] Increased blood $C0^2$ tension was not considered as a cause of ICH, due to the patient's lack of strenuous activity. It was shown that sildenafil modulates NO-cGMP pathways in the rat brain, and endog-

enous NO releasing is potentiated by sildenafil.[10,4] Modulation of the NO-cGMP pathway may potentiate the effect of sildenafil and cause bleeding in cerebral blood vessels.

CONCLUSION

To conclude, taking sildenafil for an unusually extended period of time, and at a high dose may cause persistent vasodilatation on cerebral vasculature which may increase the probability of ICH. Additionally, it may be an incidental side effect as presented case.

CONFLICT OF INTEREST

None declared.

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