Cerebrovascular Accident Following Unprescribed Use of Sildenafil: Is it Underestimated?

Sildenafil citrate is a commonly used agent in the treatment of erectile dysfunction. Cardiovascular and cerebrovascular complications have been reported associated with sildenafil use. Despite the well-described cardiovascular side effects, little is known about the development of cerebrovascular diseases. We present a 46-year-old patient with stroke and global aphasia due to the combined use of sildenafil and alcohol. Patients may be reluctant to mention sildenafil use, and drugs like sildenafil should be considered as a contributing factor to stroke in cases of other wise unexplained etiology. Turk J Phys Med Rehab 2010;56:204-6.

Key Words: Sildenafil, cerebrovascular accident, alcohol, stroke, sildenafil citrate

Introduction

Sildenafil citrate is a commonly used agent in the treatment of erectile dysfunction. Sildenafil leads to an increase in cyclic guanosine monophosphate (cGMP) levels through selective inhibition of phosphodiesterase-5 expression (1) with subsequent elevation of intracellular calcium inducing the relaxation of the vascular smooth muscles (2), which results in decrease in the blood pressure by 8-10 mmHg (3). The decrease in the blood pressure increases the heart rate by means of the sympathetic reflex arc. The combination of sildenafil with nitrates may have undesirable results due to the hypotensive effects of both agents (4). Despite the well-described cardiovascular side effects (3), little is known about the risk for development of cerebrovascular disease. We report a case of a man presenting with cerebrovascular accident (CVA), which has developed 2.5 hours after sildenafil use.

Case Presentation

A 46-year-old man was admitted to our hospital after presenting with a history of loss of consciousness for 12 hours that had happened 2.5 hours after ingesting 20-25 units of alcohol and 50 mg sildenafil and had been followed by right arm and leg weakness, global aphasia and gait difficulties.
There was a past history of 50-100 units of alcohol intake a week. Family history revealed hypertension and atherosclerotic heart disease. Medical history was obtained from a male friend accompanying the patient when the event occurred. The patient was not a smoker and had no history of hypertension or any other cardiovascular and cerebrovascular risk factors. There was no previous use of sildenafil or any regular medication.

Neurological examination showed right-sided hemiplegia and hyperactive deep tendon reflexes on the hemiplegic side. Plantar responses were abolished bilaterally. Computed tomography (CT) of the brain revealed acute infarction in the territory of the left middle cerebral artery (MCA), thus, the patient was commenced on acetylsalicylic acid (300 mg/day) and nadroparine (0.3 ml/day). Mannitol (400 ml/day) was subsequently started due to mild impairment in the level of consciousness on the 3rd day post-CVA. A repeat CT scan revealed a subacute infarction in the territory of the left MCA (Figure 1).

The patient underwent electrocardiography (ECG), Holter ECG, transthoracic echocardiography (ECHO), magnetic resonance angiography (MRA) of the supra-aortic vessels, cranial magnetic resonance imaging (MRI) (Figure 2), and carotid Doppler ultrasonography, which were normal, except for a mild increase in arterial blood pressure (150/90 mmHg). During the further follow-up, the mean systolic and diastolic blood pressures were 128 mmHg (range: 100-116 mmHg) and 84 mmHg (range: 70-100 mmHg), respectively. The patient had normal hemoglobin, platelet count, protein C and S, p-ANCA, c-ANCA, serum lipid profile (total cholesterol, LDL, HDL and triglycerides), antiphospholipid antibody levels and renal function. Cranial MRA showed a left MCA occlusion. Eleven days after the CVA, a repeat cranial MRA showed recanalized left MCA.

Transesophageal ECHO revealed a bicuspid aortic valve and a small interatrial septal defect interpreted as patent foramen ovale (PFO), which resulted in a shunt from the right atrium to the left one with Valsalva maneuver contrast ECHO. Concurrently, Doppler ultrasonography of the lower extremities was normal.

A month after the CVA, the patient was transferred to the rehabilitation unit. He was conscious, but his cooperation and orientation were limited due to the global aphasia. There was no sign of neglect. There was a slight shoulder subluxation on the hemiplegic side. Upper extremity, hand and lower extremity stages were 1, 2 and 1 respectively according to the Brunnstrom stages of motor recovery. The patient was walking with the assistance of another person. Strengthening, range of motion, balance, coordination, proprioceptive neuromuscular facilitation and mobilization exercises and cognitive rehabilitation were carried out as part of the rehabilitation program. A month later, there was a significant improvement in visual and oral communication of the patient. Muscle strengths, balance and Brunnstrom stages were improved significantly as compared with the initial examination (upper extremity Brunnstrom stage 3, hand 2 and lower extremity 4). At discharge, the patient was able to walk independently with the assistance of a tripod.

**Discussion**

Central nervous system and cardiovascular system events due to sildenafil use have been reported previously (3). A 61-year-old man who had symptoms associated with posterior cerebral circulation ischemia after 50 mg sildenafil on 3 separate occasions has been reported. (5). Morgan et al. (6) have
also reported a 50-year-old patient, who had transient ischemic attacks (TIA) after using 3 individual doses of sildenafil of 50 or 100 mg. The time interval between the drug ingestion and TIAs was 2 hours. Our patient has only used the drug once and the period after the drug intake was also 2.5 hours.

It was reported that the undesirable cardiovascular side effects of sildenafil were much more prominent when combined with organic nitrates (7). The effects of nitrates on nitric oxide are similar to those of alcohol. Our patient had ingested alcohol before taking sildenafil. Due to the similar pathophysiological process, the cardiovascular side effects of sildenafil might have been potentiated by the combination of sildenafil and alcohol.

A paradoxical embolism occurring during a sexual intercourse due to a Valsalva-like maneuver could be a probable mechanism in our case. However, the time interval between the sildenafil use and stroke onset argues against this hypothesis (8).

An important feature of our case was the occurrence of CVA after drug ingestion. As sildenafil is an agent used to treat sexual dysfunction, it is occasionally used without prescription to improve sexual performance. This may cause embarrassment and may not be disclosed during history taking. Therefore, the patient must be assured of complete confidentiality. Unfortunately, the non-prescription purchase of these kinds of drugs is often underestimated. Hence, the clinicians should be aware of the possibility of drug use if a clear etiology is not found to elucidate the cause of the CVA.

Sildenafil is available and easily purchasable via internet without prescription. There are many adverse events and deaths reported, mainly associated with ischemic heart diseases and lately, with cerebrovascular diseases. There is no clear statement of whether sildenafil was commenced by prescription of a physician or was illicitly acquired in most of these cases. We would like to underline the concerns about the potential medical risks, which may develop in future following the illegitimate use of sildenafil or newer similar medications (9). We think that serious actions should be taken against the unmonitored use of sildenafil and further studies are required to determine the overall incidence of unprescribed use of sildenafil and the rate of related serious adverse events and deaths.

**Conclusion**

Since our patient has an existing risk factor for early CVA (i.e., PFO), we believe that the abrupt onset of vascular event in relation to drug use might be relevant. Therefore, we conclude that the use of drugs like sildenafil should be considered as an etiology of otherwise unexplained CVA.

**References**