Evaluation of the Effects of Sildenafil Citrate (Viagra) on Vertebral Artery Blood Flow in Patients with Vertebro-Basilar Insufficiency

Zulkif Bozgeyik, MD[1]
Sait Berilgen, MD[2]
Huseyin Ozdemir, MD[1]
Aslan Tekatas, MD[3]
Erkin Ogur, MD[1]

Objective: To investigate the effects of sildenafil citrate (Viagra) on the vertebral artery blood flow of patients with vertebro-basilar insufficiency (VBI) using color duplex sonography (CDS).

Materials and Methods: The study included 21 patients with VBI (aged 31–76; mean 61.0 ± 10.5 yrs). We administered a 50 mg oral dose of sildenafil citrate to all patients. Next, we measured the peak systolic velocity (Vmax), end diastolic velocity (Vmin), resistive index (RI), pulsatility index (PI), diameter, area, and flow volume (FV) of vertebral arteries using CDS before the administration of sildenafil citrate; 45 minutes after, and 75 minutes after administration. Statistical testing was performed using SPSS for windows version 11.0. The statistical test used to determine the outcome of the analysis was the repeated measures analysis of variance (ANOVA) test.

Results: Compared to the baseline values, the vertebral artery diameter, area, and FV increased significantly following the administration of sildenafil citrate. The diameter, area and FV increased from 3.39 mm at 45 minutes to 3.64 mm at 75 minutes, 9.43 cm^2 to 10.80 cm^2 at 45 minutes and 10.81 cm^2 at 75 minutes, as well as from 0.07 L/min at baseline to 0.09 L/min at 45 minutes and unchanged at 75 minutes, respectively.

Conclusion: Sildenafil citrate elicited a significant effect on vertebral artery diameter, area and FVs.

Index terms:
Sildenafil citrate
Vertebral artery
Color duplex sonography
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[1]Firat University School of Medicine, Department of Radiology, Elazig, Turkey;
[2]Firat University School of Medicine, Department of Neurology, Elazig, Turkey;
[3]Elazig Government Hospital, Department of Neurology, Elazig, Turkey

Address reprint requests to:
Zulkif Bozgeyik, MD, Firat Tip Merkezi, Radyoloji Bolumu, 23119, Elazig, Turkey.
Tel. 90 424 233 35 55-1396
Fax. 90 424 237 67 73
e-mail: bozgeyik4@hotmail.com

Vertebro-basilar insufficiency (VBI) is a clinical syndrome, which is related to blood flow insufficiency in the vertebral, basilar and posterior cerebral artery feeding territories. Frequent symptoms of hemodynamic insufficiency in the vertebrobasilar artery system may result from altered blood flow rates to the vestibulocochlear system, producing peripheral receptive hearing loss, tinnitus, vertigo and dizziness (1). The examination of vertebral artery (VA) blood flow by color duplex sonography (CDS) is demonstrated to be a safe and noninvasive method. Usually, flow volume (FV) or velocity of VAs is used for the evaluation of VBI. These properties enabled us to utilize this technique in the diagnosis of VBI (1, 2).

Sildenafil citrate (Viagra) is a highly selective inhibitor of the cGMP-degrading intracellular enzyme phosphodiesterase 5 (PDE5) (3). Inhibition of PDE5 induces cGMP accumulation in the penile tissue and this process causes an erection. This drug has emerged as the safest oral vasoactive drug in the treatment of erectile dysfunction (ED). The success rate of sildenafil citrate in ED is varies between 60% and 85%, which is comparable with other vasoactive injectable agents used to treat ED (4). This high success rate and easy use are the major reasons for the worldwide popularity of this drug in the treatment of ED.

Several studies investigated the effect of sildenafil citrate on cerebral, cavernous and coronal arteries (3, 5, 6). In addition, beneficial effects of sildenafil were reported in the treatment of primary pulmonary hypertension (7). The effects of this drug on VAs have not been studied before.

The aim of this study was to investigate the early phase effects of this agent on VA blood flow in patients with VBI by using CDS.

MATERIALS AND METHODS

A total of 26 patients were screened for this study. Five patients were excluded due to congestive heart disease, acute ischemic heart disease, stroke or myocardial infarction, concomitant treatment with nitrates or presence of hypotension, previously described migraine attack, stenosis of the VA, which was diagnosed by angiography, and comorbid conditions. Finally, 21 patients (15 females, 6 males) with VBI (aged 31–74, mean 61.0 ± 10.5 years) volunteered to participate in this study. An experienced neurologist examined patients for symptoms like vertigo, gait disturbance, drop attack and positional vertigo, which were clinical diagnostic criteria of VBI. The radiologic criterion for VBI was accepted as lower than 200 mL/min FV of VAs (2). All of the patients' bilateral VAs were examined in the supine position with the head slightly turned on the opposite side using a linear transducer (6–13 MHz broadband transducer). VA measurements were executed between 3th and 4th cervical vertebra. The research protocol was approved by the Local Ethics Committee and all patients signed a written informed consent form.

All the Doppler sonographic measurements were performed by the same operator using a Toshiba Aplio SSA-770A/80 scanner (Tokyo, Japan). The basal values of the peak systolic velocity (Vmax), end diastolic velocity (Vmin), resistive index (RI), pulsatility index (PI), bilateral VA diameter, area and FV were measured by a radiologist experienced in longitudinal plane images using automatic measurement settings. All parameters measured from the right and left VAs were averaged to calculate the mean values. The basal measurements of VA were taken at operating room. Following a 15 minutes rest time in supine position, 50 mg of sildenafil citrate was administered orally to each patient. Because of maximum plasma concentration of sildenafil is achieved within 30–120 minutes (average 60 minute), the CDS evaluation for all of the above mentioned parameters were repeated at 45 minutes and 75 minutes after the administration of the drug. The Doppler angle was constantly sustained between 45 and 60 degrees in the evaluated arteries. The intravascular FV was calculated as the product of the angle-corrected time averaged flow velocity (TAFV) and the cross-sectional area (A) of the circular vessel using the formula: FV= TAFV x A. The cross-sectional areas of the VA were determined as the distance between in the internal layers of the parallel walls (2).

All statistical analyses were performed using SPSS for windows version 11.0 (SPSS, Chicago, IL). Statistical analyses of data collected before the initial drug administration, and at 45 minutes and 75 minutes after drug administration, were performed using the repeated measures variance analysis (ANOVA) test. Statistical significance was set at $p < 0.05$.

RESULTS

Significant changes were observed in six of the 14 measured parameters. Compared to baseline values, diameter, area, and FV of the VAs increased following the administration of sildenafil citrate. The diameter increased from 3.39 mm at baseline to 3.64 mm at 45 minutes and 75 minutes, the area increased from 9.43 cm^2 at baseline to 10.80 cm^2 at 45 minutes and 10.81 cm^2 at 75 minutes, and the FV increased from baseline 0.07 L/min to 0.09 L/min at 45 minutes and was unchanged at 75 minutes. Between 45 minutes and 75 minutes, the values were not significantly different for the diameter, area and FV. The values

Table 1. Peak Systolic Velocity (Vmax), End Diastolic Velocity (Vmin), Resistive Index (RI), Pulsatility Index (PI), Diameter, Area and Flow Volume of Vertebral Arteries

Parameters	Baseline	Post Dosage (45 minutes)	Post Dosage (75 minutes)
Vmax (cm/sec)	41.25 ± 17.50	43.50 ± 20.00	41.54 ± 25.73
Vmin (cm/sec)	12.01 ± 5.66	12.74 ± 6.03	12.41 ± 9.69
RI	0.57 ± 0.11	0.60 ± 0.11	0.57 ± 0.13
PI	1.36 ± 0.30	1.40 ± 0.49	1.37 ± 0.39
Diameter (mm)	3.39 ± 0.69	3.64 ± 0.69*	3.64 ± 0.73†
Area (mm^2)	9.43 ± 3.75	10.80 ± 3.83*	10.81 ± 4.37†
Volume (L/min)	0.07 ± 0.04	0.09 ± 0.06*	0.09 ± 0.08†

Note.— *Baseline versus post dosage 45 minutes, †Baseline versus post dosage 75 minutes, $p < 0.05$

of Vmax, Vmin, RI and PI were not different between baseline and 45 minutes and 75 minutes (Table 1).

After usage of sildenafil citrate, we observed some changes on VBI symptoms. In our patients, the most prominent symptoms included vertigo and dizziness. Five patients reported reduced vertigo and dizziness as well as partial recovery of gait disturbance for one patient in the clinical examination. We did not observe any changes in other VBI symptoms during the CDS examination. The most important complaint from the usage of sildenafil citrate was headaches in 17 of 21 patients. We did not observe significant discomfort in the patients evaluated except for minor side effects (*i.e,* nausea, flushing etc.) in a small portion of the study population.

DISCUSSION

Vertebro-basilar insufficiency is a common cause of vestibular disorder, which seen in middle aged and elderly patients. Arteriosclerosis, embolic incidents and compressive effects of cervical spondylosis play the most important roles in the etiology of VBI (1, 2). There are many invasive and noninvasive procedures such as the traditional angiography, magnetic resonance angiography (MRA) and CDS, which provide helpful information about abnormalities in the vertebrobasilar system (8). Evaluation of VAs using CDS is noninvasive, quick and easily applicable, and provides valuable information on the vertebrobasilar system. There are many studies related to VBI in the literature. In a recent study, Acar et al. (2) compared the VA velocity and FV measurements in the diagnosis of VBI using CDS. The authors concluded that for the diagnosis of VBI, the measurement of volume in addition to velocity is more valuable in the detection of moderately damped VA FVs (2).

Sildenafil citrate is rapidly absorbed, reaching maximum plasma concentrations within one hour after oral usage, and has a mean terminal half-life is 3 to 5 hours (9). Herrmann et al. (6) showed minimal reductions in systemic and pulmonary artery pressure without any serious cardiovascular effects after sildenafil usage. Kocakoc et al. (10) reported that sildenafil had no significant effect on aortic and superior mesenteric artery blood flow in ED patients. They did however observe mild blood flow alteration in the carotid arteries (10). In a recent study performed in dogs, significant increases were observed for the Vmax and RI of the aorta as well as decreases in the right carotid and left segmental renal artery Vmax (11).

PDE type 5 is present in vascular smooth muscle and platelets. A recent animal study showed that PDE5 is present in the brain tissue, cerebellum and hippocampus (12). In this study, PDE inhibitors caused cerebral artery dilatation, whereas; Kruuse et al. (3) found that sildenafil usage had no significant effects on cerebral blood flow and the diameter of cerebral and extracerebral arteries. Arnavaz et al. (9) investigated the effects of sildenafil citrate on the middle cerebral arteries. As in the previous studies, the researchers observed no significant effects; rather they found an insignificant decreasing trend in blood flow rates.

In our study, diameter, area and FV of VA significantly increased after sildenafil usage. This alteration might be related to the amount of PDE5 receptor on VAs. According to the aforementioned studies, sildenafil may have different roles in human arteries, which potentially depend on PDE5 receptor levels of each artery.

Sastry et al. (7) investigated the effect of sildenafil on the pulmonary artery in primary pulmonary hypertension. They showed vasodilatation in the pulmonary artery and a decrease in pulmonary vascular resistance. They claimed that this drug may represent the first line of therapy in these patients (7). In another report, milrinone, a PDE3 inhibitor, improved clinical outcome in patients with subarachnoidal hemorrhage by a mechanism of reverse vasospasm (13).

In a recent animal study, administration of sildenafil to rats with embolic stroke enhanced angiogenesis and selectively increased cerebral blood flow in the ischemic boundary, improved the neurological functional recovery compared to the control group (14). In another study, Atalay et al. (15) analysed the effects of sildenafil citrate on the cerebral vasospasm. The vasodilatory effect of sildenafil citrate was observed to be significant on normal cerebral vessels and following subarachnoid hemorrhage-induced vasospasm. According to these results, sildenafil citrate may useful in the treatment of cerebrovascular disease.

In conclusion, values of diameter, area and FV of VAs increased after administration of sildenafil citrate compared to baseline values. Due to its vasodilatatory effects, sildenafil might be useful to improve symptoms of VBI. These findings should be further confirmed by prospective studies in large patient groups.

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