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The effect of sildenafil citrate (Viagra) on cerebral blood flow in patients with cerebrovascular risk factors

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Objectives – Sildenafil citrate is widely used for erectile dysfunction. The present study examined the short-term effects of sildenafil administration in individuals with cerebrovascular risk factors, including patients with a history of stroke. *Materials and Methods* – Twenty-five consecutive male patients with erectile dysfunction and vascular risk factors were included in the study. A perfusion brain SPECT study was performed at baseline and 1 h after the oral administration of sildenafil. *Results* – Associations between any of the risk factors and the perfusion scores were not detected, with the exception of stroke. Stroke patients showed significantly more areas with diminished perfusion after sildenafil administration compared to baseline. *Conclusions* – In patients with diabetes or hypertension, a dose of 50 mg sildenafil does not appear to produce detrimental effects on cerebral blood flow. However, patients with a history of stroke may be at increased risk of hemodynamic impairment after the use of sildenafil.

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Introduction

Sildenafil citrate (sildenafil, Viagra™) is a highly selective inhibitor of the cGMP-degrading intracellular enzyme phosphodiesterase 5 (PDE5) widely used as treatment for erectile dysfunction. Sildenafil potentiates the actions of endogenous nitric oxide released during sexual stimulation from the endothelial cells or parasympathetic nerves (1) leading to relaxation of the smooth muscle cells. PDE 5 is present in penile tissue, platelets, skeletal muscle, and vascular and visceral smooth muscle (2). It is also present in brain tissue, mostly cerebellum and hippocampus and in the superior cervical ganglion (3, 4). PDE5 has also been shown to be present and active in the guinea pig basilar artery (5).

Sildenafil appears to have a therapeutic effect for disorders related to the pulmonary system and the central nervous system (6). PDE 5 inhibition in the lungs leads to a reduction of pulmonary vascular resistance, decreased right ventricular afterload, and improved overall circulation. In the central nervous system, it may have neuroprotective effects in multiple sclerosis as well as a significant memory enhancing action (7). In rat models, sildenafil increases brain levels of cGMP, synaptogenesis, angiogenesis, and neurogenesis, all of which could contribute to enhancement of functional recovery (8). Administration of sildenafil to rats with embolic stroke enhances angiogenesis and selectively increases the cerebral blood flow (CBF) level in the ischemic boundary, and improves neurological functional recovery compared to saline-treated rats. In non-ischemic rats, a transient increase in CBF has been observed (9).

In humans, studies investigating the effect of sildenafil on CBF and oxygenation are rare (10, 11). Neurological side effects have been described with Sildenafil, including migraine, transient global

amnesia, and transient ischemic attacks (TIA) or stroke (12, 13). It has been suggested that adverse events associated with sildenafil may be attributed to its vasodilatory properties. However, in a study of 10 healthy subjects given placebo or sildenafil 100 mg on two separate days (10), inhibition of cGMP degradation by sildenafil had no significant effects on CBF or cerebral and extracerebral artery diameter.

Sildenafil is widely used by men aged 40–70 years, a population with multiple cerebrovascular risk factors. The present study was therefore designed to determine the short term effect of sildenafil administration in individuals with cerebrovascular risk factors, including patients with history of stroke.

Materials and methods

Twenty-five consecutive male patients (mean age 62, range 43–73 years) with erectile dysfunction were included in the study. Twenty-one of these patients had vascular risk factors. Of these, 12 patients had a history of stroke (Table 1). The vascular risk factors were defined as: (1) hypertension (2) diabetes mellitus (3) hyperlipidemia (4) heavy smoker (5) obesity (6) stroke or documented TIA in the past; and (7) peripheral vascular disease (14–16).

The inclusion criteria were as follows: (1) older than 18 years of age; (2) males with erectile dysfunction using or not using sildenafil; and (3) two vascular risk factors as described above. The exclusion criteria were as follows: (1) evidence of brain tumor; (2) evidence of craniotomy in the past; (3) data of coexistence of neurodegenerative disease of the brain (neurodegenerative dementia or neurodegenerative extrapyramidal); (4) inflammatory diseases of the central nervous system; (5) carotid artery stenosis of more than 25% or any evidence of intracranial artery stenosis (All patients underwent CTA (CT angiography) as well as transcranial Doppler (TCD) and carotid duplex examinations); (6) history of cluster headache type migraine; (7) usage of nitroglycerine derivative type drug; (8) well known allergic reaction to one of the PPDE 5 inhibitors; and (9) patients unable to sign a consent form. In addition, patients with cardiac failure, arrhythmia and ischemic heart disease (IHD) were not included in the study.

Table 1 Clinical and imaging variables in patients with risk factors

No	Age	DM	HTN	Lipids	Smoking	Obesity	PVD	Stroke	SPECT	P1	P2	P3	P4
1	63	+	–	+	–	–	–	–	Diffuse	9	0	3	0
2	69	+	+	+	–	–	–	+	Diffuse	0	46	0	52
3	60	+	+	+	–	–	–	+	Focal	0	0	0	0
4	62	+	–	+	+	–	+	–	Focal	9	0	3	1
5	57	+	+	–	–	–	–	+	Focal	7	4	3	16
6	64	+	+	+	+	–	–	–	Focal	2	14	1	15
7	59	+	+	+	–	–	–	–	Diffuse	52	0	20	0
8	67	–	–	–	–	–	–	–	Focal	6	3	0	14
9	59	+	–			–	–	–	Focal	28	0	12	0
10	67	–	–	–	–	–	–	–	Focal	13	0	4	0
11	61	–	+	+	+	–	–	–	Focal	21	0	20	0
12	72	–	–	–	–	–	–	+	Focal	4	0	1	3
13	60	–	–			–	–	+	Focal	1	1	1	3
14	69	–	+	+	–	–	–	–	Diffuse	9	1	1	3
15	73	–	–			–	–	–	Diffuse	6	12	1	12
16	45	–	–	–	–	–	–	+	Focal	9	9	3	4
17	62	–	+	–	+	–	–	–	Focal	4	3	0	0
18	69	–	+	–	–	–	–	+	Focal	11	9	0	15
19	64	–	–	+	+	–	–	+	Focal	3	2	0	2
20	63	–	+	+	+	–	–	–	Focal	19	0	13	0
21	43	–	+	+	+	–	–	+	Focal	2	1	1	1
22	60	–	+	–	–	–	–	+	Focal	8	0	3	2
23	65	+	+	–	–	–	+	–	Focal	16	0	7	0
24	54	–	+	–	+	–	–	+	Focal	14	7	8	4
25	62	+	–	–	–	–	–	+	Diffuse	1	0	0	3

P1 > 15% increase in perfusion max per voxel in Brodmann area values.

P2 > 15% decrease in perfusion max per voxel in Brodmann area values.

P3 > 15% increase in perfusion mean per voxel in Brodmann area values.

P4 > 15% decrease in perfusion mean per voxel in Brodmann area values.

DM, diabetes mellitus type 2; HTN, hypertension; PVD, peripheral vascular disease; SPECT, pattern of perfusion abnormalities.

All patients who were included in the study had a physical examination and the most recent CT scan (less than 1 year) was reviewed. Demographic data, medical history and medications taken were recorded.

The study was approved by the ethics committee of our institution, and all subjects gave their written informed consent for the study.

HMPAO SPECT imaging

A perfusion brain SPECT study was performed twice in each patient. The baseline study was performed 10–15 min after i.v. injection of 444 MBq Tc-99m-HMPAO and the second study was performed 1 h after the oral administration of 50 mg sildenafil citrate, using 1110 MBq Tc-99m-HMPAO. One hundred and twenty frames of 15 s were acquired using a circular rotation mode into a 128 × 128 image matrix.

NeuroSPECT image processing

The reconstructed tridimensional raw images were transferred in an Interfile format to a PC computer in order to reprocess, quantify and normalize their volume.

Normalization of HMPAO brain uptake – Neurogam Software from Segami Corp. (MD, USA) was used to perform an analysis of voxel by voxel brain uptake of HMPAO. Results were normalized and expressed as percentage of maximal uptake observed in the brain.

Volume normalization – The technique of Talairach was employed in the present study. The tridimensional volume of the brain was reoriented by defining a line that fits the inferior pole of the occipital lobe and the inferior edge of the frontal lobe. This line is automatically rendered horizontally. A correction is made for lateral deviations defining a line above the interhemispheric fissure and automatically orienting this line in the vertical plane. In this reoriented image, the intermediate level of the pons and anterior plane of the temporal lobes are defined. The volume of analysis is then limited in the lateral planes, superior and inferior planes of the brain. With this information, the Talairach technique renders the brain volume into a normalized volume and allows a voxel by voxel comparison of the HMPAO uptake in the brain cortex with a normal data base, corrected also volumetrically, for normal individuals at the age of 18–45 or at the age of 45–80 years.

In this tridimensional image, a color scale is used that represents values above the normal mean in red, values two standard deviations above the normal mean in silver, all values below the normal mean in green color and all values below two standard deviations below the normal mean in blue. Thus, areas of abnormal hypoperfusion are defined as those with 95% probability of being hypoperfused and are displayed in blue, while areas of hyperperfusion defined as those with 95% probability of being effectively hyperperfused in comparison with the normal database are displayed in silver (Segami Corp., MD, USA).

In order to define, with high reproducibility, the exact localization of areas of hypoperfusion observed in these patients, 58 regions of interest corresponding to Brodmann Areas were analyzed and the mean values of HMPAO uptake were displayed together with the maximum and minimum values defined as the upper 2.5% and lower 2.5% of uptake in the region of interest. Only the mean and maximum values were used in this report.

Data analysis

Analysis of data was carried out using SPSS 9.0 statistical analysis software (SPSS Inc., Chicago, IL, USA, 1999). Risk factors, including comorbidities and smoking, were defined as dichotomous variables (yes/no) and were described using frequency counts and are reported as n (%). Perfusion scores were assessed for normality using the Kolmogorov–Smirnov test (cut-off at $P < 0.01$) and all had distributions significantly deviating from normal. Perfusion scores were therefore described as median (min-max) in addition to mean and standard deviation and were compared by risk factors using the Mann–Whitney U-test. All tests are two-sided and considered significant at $P < 0.05$.

Results

Twelve of 25 patients with cerebrovascular risk factors had a history of stroke, ranging from 1 to 5 years prior to the study (Table 1). Ten of the 12 patients had a territorial lesion on the SPECT study, in the distribution of the middle cerebral artery (MCA). Eight of the 13 patients without prior stroke had also non-territorial focal areas of diminished CBF. The remaining patients had diffuse CBF abnormalities. None of the patients developed brain-related symptoms.

No associations between any of the risk factors/co-morbidities and any of the perfusion scores variables were detected, with the exception of

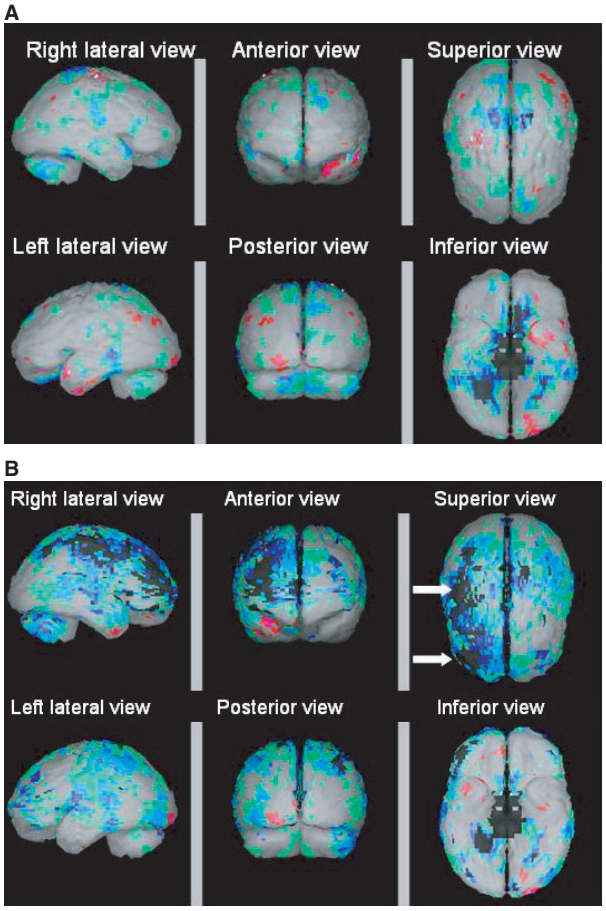

Figure 1. Three dimensional representation of brain perfusion in a patient after stroke showing mild perfusion abnormalities at baseline (A) and severe hypoperfusion of the right MCA territory 1 h after oral administration of sildenafil (B, white arrows).

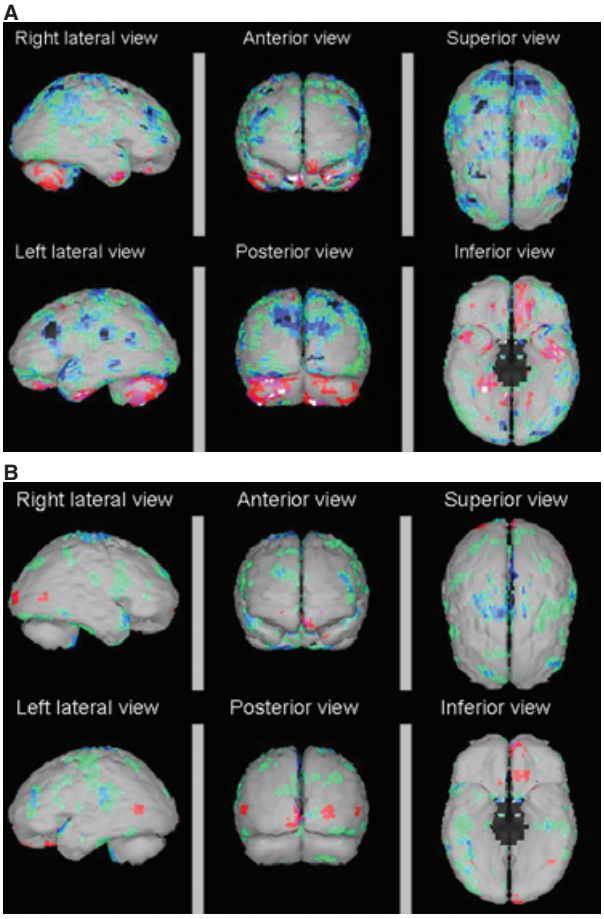

Figure 2. Another patient with vascular risk factors but no stroke, showing scattered perfusion abnormalities (A), with significant improvement 1 h after oral administration of sildenafil (B).

stroke. Stroke patients showed significantly more areas with diminished perfusion after sildenafil administration compared to baseline ($<15\%$ of normal men in similar age group, mean and max Brodmann area values, Fig. 1) and significantly fewer areas with increased perfusion after sildenafil administration ($>15\%$ of normal men in similar age group, mean and max Brodmann area values) compared to non-stroke patients (Fig. 2). The statistically significant value of 15% reduction was chosen as a referent value for perfusion deficit. It is an average value between 10% used in different SPECT studies (17) and 20% used for SPECT studies in occlusive carotid artery disease and after carotid endarterectomy (18, 19). Specifically, in subjects with stroke history, Brodmann areas with significantly diminished post-sildenafil scores were areas 1,2,3 on the left ($P = 0.035$), areas 5 and 7 on the right ($P = 0.03$ and $P = 0.002$, respectively) and area 20 on the left ($P = 0.002$).

Discussion

Sildenafil citrate selectively inhibits PDE5 and increases the level of cGMP, leading to beneficial effects in target organs. For example, sildenafil inhibits phosphodiesterase-5 (PDE5) in the corpus cavernosum, which contains most of the blood in the penis during erection (20). PDE5 is also found in other parts of the body such as the lungs, platelets, various forms of smooth muscle and several brain regions (21). There are 11 different types of phosphodiesterases which are distributed throughout the body (22), of which only three selectively hydrolyze cGMP relative to cAMP.

The present study was performed to analyze the effect of short term sildenafil administration on the pattern of CBF in subjects with vascular risk factors. The pattern of perfusion changes was different among patients with all risk factors compared to patients who had a stroke. Patients with vascular risk factors but no stroke had

increased perfusion after sildenafil administration. Among the stroke patients, all subjects demonstrated a regional decrease of blood perfusion at baseline, followed by two different patterns of perfusion changes after administration of sildenafil: (1) a local or regional perfusion decrease in one or more areas of the brain compared to baseline not associated with the location of previous stroke and (2) a local decrease in one or more regions combined with increased perfusion in other locations, also unrelated to the area of stroke.

The post-sildenafil perfusion decrease observed in stroke patients in the present study may be related to an abnormal reaction of dynamic cerebral autoregulation. Dynamic cerebral autoregulation is defined as the ability to restore CBF in situations of sudden changes in perfusion pressure. The impairment is well documented unilaterally or bilaterally in acute stroke (23) including patients with lacunar infarcts and in the presence of intracranial or extracranial artery stenosis (24, 25). This autoregulation is not impaired in elderly persons or in previously treated hypertensive patients (26). These perfusion changes are similar to the 'steal phenomenon' noted after acetazolamide administration (27). However, the mechanism of acetazolamide effect is different from that of sildenafil. Acetazolamide is associated with changes in CO_2 concentration and a direct effect on cerebral vessels, while sildenafil acts via the nitric oxide mechanism. Perfusion abnormalities in our study were not accompanied by acute clinical abnormalities; however, dramatic changes in blood pressure can occur during the coital act which may augment the alterations in perfusion.

Neurologic effects of sildenafil have been demonstrated; specifically, sildenafil has been shown to enhance memory in animal studies (28). Administration of sildenafil directly into the hippocampus after the first trail in object recognition tasks improved memory in mice (29) and enhanced the processes of object information consolidation. Additionally, sildenafil administration improved cognitive performance in animal models of diabetes and electroconvulsive shock-induced memory loss. In a study using magnetic resonance imaging on male Wistar rats subjected to embolic stroke, sildenafil was administered subcutaneously 24-h after stroke and daily for an additional 6 days (9). The ischemic lesion for each animal was divided into an ischemic boundary and ischemic core. After 1 week of sildenafil treatment, the ischemic lesion exhibited enhanced CBF in the boundary region relative to the core region. Sildenafil treatment did not significantly reduce lesion size, but enhanced angiogenesis. Compared to controls, rats treated with sildenafil exhibited improved functional performance.

Another study in aged rats (30) demonstrates a significant reduction of the number of proliferating cells in the subventricular zone (SVZ) compared to young rats, yet treatment with sildenafil 7 days after focal cerebral ischemia significantly increased the number of proliferating cells, indicating increased neurogenesis. In addition, the treatment substantially enhanced functional recovery.

Recent studies in humans have shown that PDE5 inhibitors can counteract deficits in long-term memory caused by pharmacological agents or aging (28). Event-related brain potentials recorded following sildenafil administration suggest an enhanced ability in young men to focus attention on auditory stimuli (31).

Among adverse events associated with sildenafil treatment is headache, attributable to cerebral vasodilatation induced by the accumulation of cGMP in arterial smooth muscle cells. However, in a double-blind, placebo-controlled crossover study in 12 patients with migraine without aura (32) sildenafil did not dilate the middle cerebral arteries significantly. It was postulated that increased cGMP levels in smooth muscle cells may not have been adequate for a dilatory response. Low baseline cGMP production in the cerebral arteries or rapid elimination by cGMP-degrading phosphodiesterases other than PDE5 may explain these observations.

Other cerebral adverse effects of sildenafil have been reported, including TIA (13). In most cases, patients had other risk factors for TIA and sildenafil appears to have triggered the event. Although a definitive cause has not been determined, TIA is thought to occur through reduced blood pressure. Sildenafil may cause venodilation, brief arrhythmia and cerebral arterial vasculature changes in patients with cereberovascular disease. This leads to lowering of blood pressure across diseased arteries and may result in TIA. Sildenafil may also cause increased sympathetic activity and subsequent stroke.

A small number of patients have reported developing seizures subsequent to sildenafil treatment, primarily among patients with co-morbidities such as hypertension. Because it inhibits PDE5, sildenafil causes cGMP accumulation which triggers the release of glutamate (33). The increased release of glutamate may cause seizures in susceptible individuals. Cases of amnesia have been reported after sildenafil exposure. Susceptible people may develop ischemia in the hippocampal region leading to transient global amnesia (34).

We postulate that the observed 'steal effect' may lower cerebral perfusion below accepted values, although this requires further investigation. It seems that the administration of sildenafil, under specific circumstances, may be unsafe for stroke patients, although this too requires substantiation in larger study populations. Additionally, the effect of long acting PDE5 inhibitors vs sildenafil should be clarified.

Study limitations

After ingestion of sildenafil 100 mg, plasma concentration is 1 mg/ml and is maximal after ~1 h (35). In the present study, a relatively small dose of sildenafil was used considering that the intracellular increase in cGMP and the enhancement of relaxation by NO occurs well below this plasma concentration of sildenafil. Nevertheless, the low dose used in the present study does not permit generalization of findings to the general population. Further investigations with higher sildenafil doses are warranted.

Additionally, sequential testing of patients with stroke history and patients with other risk factors could possibly show a higher variability in the stroke group. This may reveal a possible sildenafil independent factor, which may contribute to the observed significant CBF alterations in stroke patients.

Evidently, the mechanisms associated with sildenafil administration after stroke are complex, and additional studies with a larger cohort of patients are necessary for further evaluation of sildenafil effect on CBF.

Conclusions

A dose of 50 mg sildenafil produces a significant change in cerebrovascular reactivity in patients with risk factors. In patients with diabetes or hypertension, this drug does not appear to be associated with detrimental CBF alterations. However, an altered perfusion pattern observed in patients with stroke history necessitates caution in using the drug in that population. These patients may be at risk of hemodynamic impairment after the use of sildenafil.

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