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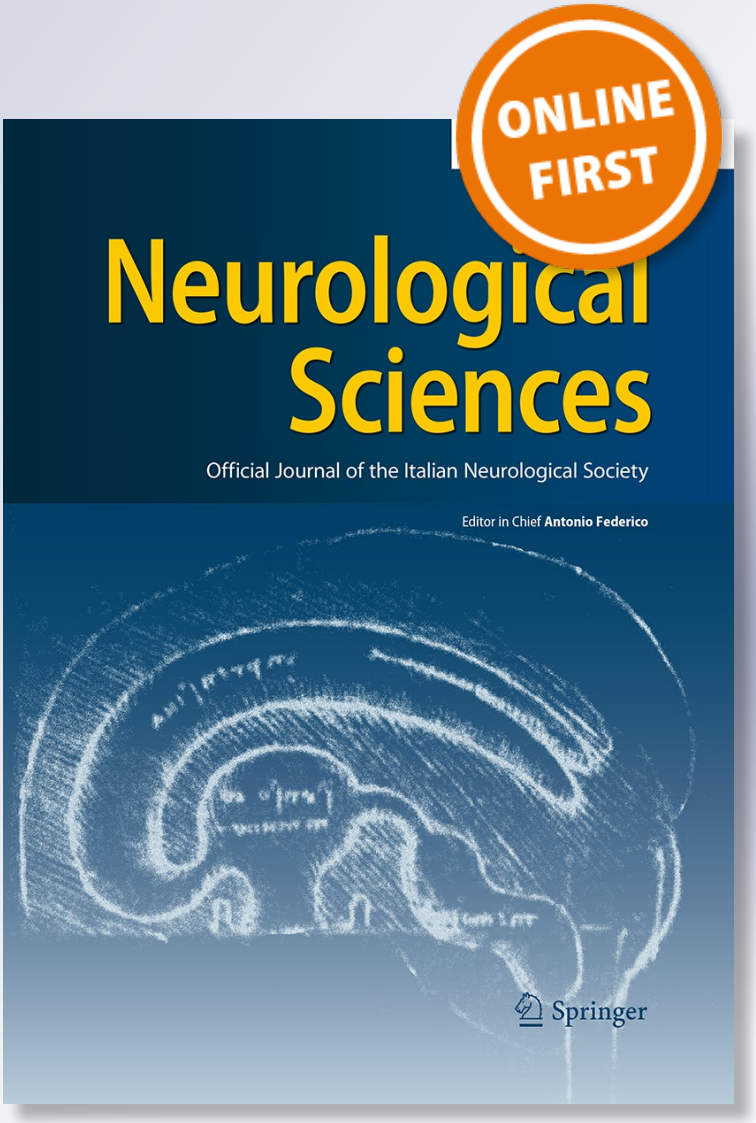

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LETTER TO THE EDITOR

Stroke after tadalafil use

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Tadalafil, a phosphodiesterase type 5 (PDE5) inhibitor, which augments cyclic guanine monophosphate in the central nervous system, has been shown to increase neurogenesis, angiogenesis, and synaptogenesis, and to improve functional outcomes compared with placebo in a rat model of ischemic stroke [1].

Sildenafil, another PDE5 inhibitor, also showed similar effects in preclinical studies of stroke models in the rat [1]. Although infrequently, sildenafil has been also associated with serious cardiovascular events such as ischemic stroke, intracerebral hemorrhage, and anterior ischemic optic neuropathy [2–6]. There is only one study reporting an association between tadalafil usage and stroke [7]. Here, we describe a patient who sustained a subcortical infarction after tadalafil use.

A 52-year-old man was admitted to our institution because of right facial weakness, slurred speech, and right hemiparesis developed about 2 h after taking 10 mg of tadalafil without participating in sexual intercourse. Four months before the beginning of the present complaints, after he had ingested the first and only other dose of 10 mg of tadalafil, he experienced the same neurologic symptoms, again without achieving an erection or participating in sexual intercourse. In that occasion, however, his symptoms slowly returned to baseline over 1 h.

On admission to our hospital, the neurologic examination showed that the patient was mildly dysarthric, had right lower facial weakness, 3/5 strength (Medical Research Council Scale) in his right upper extremity, and 4/5 strength in his right lower extremity. Sensory examination and coordination tests were normal. His medical history was normal, and he was taking no medications. He was a non-smoker and did not drink alcohol. His blood pressure and the cardiovascular examination were normal. Brain MRI performed the day after admission demonstrated an acute/subacute infarction of the posterior limb of the left internal capsule (Fig. 1). On magnetic resonance angiography there were no significant stenoses of extracranial or intracranial vessels. Cardiac evaluation including heart ultrasound was normal. Immunologic tests and screening for thrombophilias were also normal. A therapy with 300 mg of aspirin per day was started for 1 week, and was then reduced to 150 mg per day.

After 1- and 2-year follow-up, the patient showed good recovery. He did not take tadalafil or others PDE5 inhibitors and did not suffer more stroke episodes.

Oral PDE5 inhibitors (sildenafil, vardenafil, tadalafil) are the recommended first-line therapy for erectile dysfunction [8]. All three PDE5 inhibitors share a common mechanism of action, preventing cyclic guanosine monophosphate (cGMP) breakdown. Sildenafil and vardenafil have similar molecular structures, but tadalafil is structurally different, which is reflected in its pharmacokinetic profile and its selectivity for PDE isozymes [8]. All three PDE5 inhibitors are rapidly absorbed from the gastrointestinal tract and peak plasma concentrations of tadalafil are reached after approximately 2 h. Sildenafil and

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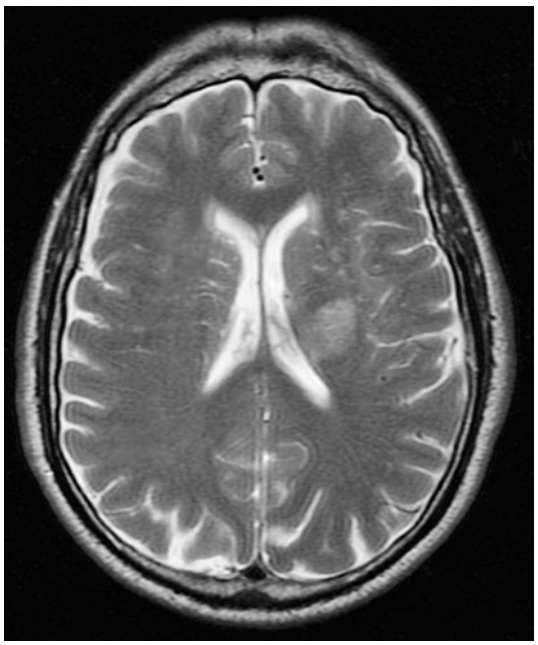

Fig. 1 Brain MRI showing small round lesion, hyperintense in T2-weighted sequences, located in the posterior limb of the left internal capsule and extending to the caudate nucleus, consistent with an acute/subacute infarct

vardenafil both have a terminal half-life of approximately 4 h, and tadalafil has a half-life of 17.5 h [8].

Class-specific side effects include headache, flushing, nasal congestion, dyspepsia and myalgia [8]. PDE5 inhibitors use is not recommended in men who have recent history of stroke or myocardial infarction (within the last 6–8 weeks), or who have significantly low blood pressure, uncontrolled high blood pressure, unstable angina, severe cardiac failure, severe liver impairment or end-stage kidney disease requiring dialysis. Moreover, both sildenafil and tadalafil have been associated with an increased risk of non-arteritic anterior ischemic optic neuropathy [6], but sildenafil has been also recently linked to transient ischemic attack, ischemic stroke and intracerebral hemorrhage [2–5].

This report, describing a patient that developed an ischemic stroke 2 h after ingesting 10 mg of tadalafil, emphasizes that ischemic cerebrovascular events, although rarely, may develop after exposure to multiple PDE5 inhibitors, not only sildenafil [7].

Many findings from our report strongly support a causal relationship between the symptoms of the patient and tadalafil: (1) the time range between the assumption of tadalafil and the occurrence of ischemic stroke is consistent with the pharmacokinetic of the drug; (2) the patient experienced the same symptomatology in both the occasions of tadalafil ingestion; (3) in the two following years of follow-up the patient abstained from PDE5 inhibitors use, and had no clinical cerebrovascular events. However, the lack of transesophageal echocardiography and prolonged cardiac monitoring, prevent the definitive exclusion of an independent cardioembolic source. The mechanism by which tadalafil induced symptomatic cerebrovascular disease in our patient remains not fully understood. As in a previous report, a transient lowering of blood pressure is the most suggestive cause of our patient's symptoms, although a cardioembolic source, provoked by a transient brief atrial fibrillation is also plausible [2, 4].

In conclusion, our case suggests that cerebrovascular ischemic events, even if uncommon adverse effects, should be taken into consideration by the physicians prescribing this drug, especially in the presence of other stroke risk factors. Future studies should deeply investigate this serious and potentially life-threatening association.

Conflict of interest The authors have indicated no financial conflicts of interest.

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