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Effect of a Single Oral Dose of Sildenafil on Right-to-Left ShuntFabrizio Sallustio^{a,b}, Silvia Di Legge^{a,b}, Marina Diomedea^{a,b}, Paolo Stanzione^{a,b}^aStroke Unit, Department of Neuroscience, University of Tor Vergata, and ^bFondazione IRCCS Santa Lucia, Rome, Italy*Introduction*

Sildenafil is an inhibitor of phosphodiesterase type 5 (PDE-5), which increases the levels of cyclic guanosine monophosphate (cGMP), thus prolonging the cellular responses to nitric oxide (NO). We have recently demonstrated the beneficial effect of a single oral dose of sildenafil (50 mg) on cerebrovascular reactivity [1]. PDE-5 is abundantly expressed in lung tissue thus representing a target for primary pulmonary hypertension (PAH) treatment with sildenafil which causes specific pulmonary over systemic vasodilation [2]. In this regard, long-term treatment of pulmonary hypertension with sildenafil (25–100 mg) given orally three times a day appears safe and well tolerated.

The presence of a patent foramen ovale (PFO) can explain some cryptogenic ischemic strokes in both younger than 55-year-old and older patients [3], and its closure has been associated with reduced risk of stroke recurrence [4].

We hypothesized that oral administration of sildenafil, through reduction in pulmonary pressure, is able to affect the interatrial pressure gradient by acting on pulmonary resistances thus reducing the right-to-left shunt (RLS). We tested this hypothesis in patients with an acute ischemic stroke, in whom the presence of a PFO was the only demonstrated cause of cerebral embolism.

Methods

Consecutive patients with acute ischemic stroke or transient ischemic attack (TIA) were selected from patients admitted in our stroke unit. Inclusion criteria were: (1) 'undetermined' stroke etiology based on the TOAST criteria; (2) presence of a PFO; (3) able to perform a valid VM, as defined by a reduction of 50% or more in middle cerebral artery (MCA) flow velocity; (4) signed informed consent for the study. The study protocol was approved by the local ethical committee.

All patients underwent standardized TCD monitoring with the bubble test (i.e. injection of 10 ml of agitated saline solution) for detection of RLS at rest and after VM. TCD was recorded according to a standardized protocol [5]: the overall duration of VM was 15 s and the MCA was recorded for 5 min in each phase (at rest, after VM, after contrast agent injection without VM, and af-

ter contrast agent injection followed by VM). A single TCD session was performed after the administration of sildenafil.

The TCD protocol was repeated 1 h after the oral administration of single-dose sildenafil tablets 50 mg. All patients had transesophageal echocardiography (TEE) confirming the presence of a PFO.

A continuous monitoring of heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure was made by means of a beat-to-beat blood pressure monitor (Finometer; FMS, Arnhem, The Netherlands) during the 30 min of the study and 2 h of observation after the study. A 12-lead ECG recording was performed before the baseline TCD study, as well as 15 min before and 90 min after the administration of sildenafil. The median number (IQR) of emboli and RLS severity (i.e. mild or moderate ≤ 10 emboli; severe >10 emboli; shower or curtain) [6] were recorded before and after administration of sildenafil. Changes in shunt severity were recorded as a passage from one category to a lower one or when the study became negative.

All patients underwent to brain magnetic resonance imaging (MRI), chest X-ray, and screening for prothrombotic profile. History review for classic vascular risk factors, as well as chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) was collected. All patients continued taking their medication on the day of the study. Patients fasted for at least 6 h and no patient was medicated with analgesics or sedatives.

Non-parametric data were compared using the Mann-Whitney two-tailed U test. Comparisons of dichotomized data between the index event and follow-up were analyzed using the Fisher's exact test. For the statistical analysis the Statistica Software was used.

Results

Twenty-three consecutive patients were evaluated. They were 11 males and 12 females, mean age ($\pm$ SD) was 66.4 ($\pm$ 14.2) (range 38–92). Median NIHSS at stroke onset was 2 ($\pm$ 3). Patients were on acetylsalicylic acid 100 mg ($n = 14$) or clopidogrel 75 mg ($n = 9$) for secondary stroke prevention. Other concomitant medications were statins ($n = 5$), antihypertensive medications ($n = 11$), antidiabetics ($n = 3$). Thirteen patients (56%) had history of COPD. The median (IQR) number of emboli significantly decreased after sildenafil administration as compared to baseline either at resting condition [32 (23–45) vs. 12 (8–68); $p < 0.001$] or after VM [34 (21–45) vs. 26 (18–54); $p < 0.001$]. During continuous monitoring by a beat-to-beat blood pressure monitor, no significant changes in hemodynamic variables (SBP, DBP, HR) were observed before and after sildenafil administration. No arrhythmias or hypotension were observed. No other adverse effects such as flushing or headache were reported.

RLS severity significantly improved after sildenafil administration: the mild-moderate/severe ratio was 5/18 before vs. 12/11 after sildenafil ($p = 0.02$). There were no statistically significant

differences between patients with change in RLS severity after sildenafil administration and those without change for demographic variables (age, sex), classic vascular risk factors (hypertension, diabetes, hypercholesterolemia, coronary artery disease, smoking, previous TIA/stroke), and diagnosis of COPD.

Conclusions

We observed a significant reduction in the median number of emboli and reduced RLS severity after the administration of a single dose of sildenafil. No adverse events were observed and, in line with previous studies, sildenafil did not affect arterial blood pressure [2]. The emboli reduction was observed 1 h after the oral administration of 50 mg of sildenafil. When administered orally, in capsule form, to adult volunteers, the peak plasma level of sildenafil is seen after 45–60 min, and this time frame coincides with its clinical effects [7]. For this reason, the effect of sildenafil on RLS severity was tested on a single TCD recording. Further, repeated TCD examinations might increase the amount of bubbles in the right atrium thus leading to biased results (i.e. increased shunt severity), and reducing the effects of sildenafil on the number of recorded bubbles.

Despite data on pulmonary arterial pressure were not recorded on TEE, the effect of sildenafil on RLS severity may be attributed to short-term selective decrease in pulmonary arterial pressure. In a recent study from the Mayo Clinic [6], the risk of recurrent stroke in patients treated with PFO closure has been associated to high pulmonary artery and right ventricular pressure, but not residual shunt. Thus, even though not abolished, the reduction in RLS severity obtained after oral administration of sildenafil might reflect the lowering in right intracardiac pressure.

While the role of PFO in patients with cryptogenic stroke remains contradictory and its therapeutic management is still extremely heterogeneous [8], our study showed that a single oral dose of 50 mg sildenafil can safely reduce RLS severity in patients with cryptogenic stroke. Long-term beneficial effects of sildenafil on RLS remains to be determined, as well as its potential as an adjuvant treatment in reducing the risk of paradoxical embolism and stroke recurrence in patients with a PFO.

References

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