Effect of sildenafil citrate upon myocardial ischemia in patients with chronic stable angina in therapy with beta-blockers

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Background. **It has been suggested that phosphodiesterase 5 (PDE5) inhibition is potentially hazardous and that it increases the risk of cardiac events in patients with coronary artery disease. This study sought to evaluate whether PDE5 inhibition with sildenafil exerts any effect on exercise-induced myocardial ischemia in patients on beta-blockers.**

Methods. **Fourteen patients underwent a baseline exercise test off-therapy and were then started on atenolol (100 mg once daily). After a run-in phase of 1 week, patients underwent a second exercise test and were randomized to receive either sildenafil (50 mg) or placebo given in a random order on two different occasions, 2 days apart. Exercise test was repeated 2 hours after the administration of sildenafil or placebo.**

Results. **All patients had a > 1 mm ST-segment depression while off-therapy. Eight patients had a negative exercise test response after atenolol, which was unaltered by the adjunct of either sildenafil or placebo. In the remaining subjects, atenolol significantly prolonged the time to 1 mm ST-segment depression and the exercise time. Sildenafil and placebo did not reverse the beneficial effect of atenolol upon exercise-induced myocardial ischemia.**

Conclusions. **PDE5 inhibition does not worsen exercise capacity and exercise-induced myocardial ischemia in patients with chronic stable angina whose symptoms and exercise test response are well controlled by beta-blocker therapy.**

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Erectile dysfunction – the persistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual activity[1] – is a frequent condition in men. Its prevalence increases with age reaching rates which range from 39 to 67% for males aged 40 to 70 years. Erectile dysfunction is a particularly frequent condition in patients with coronary artery disease because risk factors for coronary artery disease also exert an effect on erectile function and because atherosclerosis may influence the arterial blood supply to the pudendum plexus[2].

Treatment of erectile dysfunction includes a wide range of locally acting substances and/or prostheses. Sildenafil citrate has recently been introduced as an orally active pharmacological treatment for erectile dysfunction. This drug, initially developed for cardiac use, acts as a highly selective inhibitor of phosphodiesterase 5 (PDE5), which is involved in the mechanisms of penile erection since it induces relaxation of smooth muscle in the corpora cavernosa and penile arterial vessels thus leading to an increased arterial inflow and a reduced venous outflow[3,4]. Because of its high specificity for PDE5, cardiovascular side effects in the normal healthy population are minimal and related to mild systemic vasodilation (i.e., headache, flushing, small decrease in blood pressure). Although their incidence is small, serious cardiovascular events, including significant hypotension, may occur in a minority of patients at risk.

The wide overlap of patients with risk factors for erectile dysfunction and for ischemic heart disease suggests the need of evaluating the possible relationship between sildenafil treatment, coronary artery disease and cardiovascular drug interaction for a safe prescription of sildenafil in patients with ischemic heart disease.

Sildenafil acts as a selective inhibitor of PDE5, the predominant phosphodiesterase isoenzyme metabolizing cyclic guanosine monophosphate (cGMP) and thus increases the intracellular levels of cGMP and leads to either corpora cavernosa relaxation or peripheral vasodilation. Nitric oxide, an en-

dothelium-derived relaxing factor, on the other hand, stimulates the production of cGMP by the guanylate cyclase enzyme[5,6]. Therefore, on the basis of its mechanism of action via the nitric oxide-cGMP pathway, the American College of Cardiology and the American Heart Association have recommended that sildenafil be absolutely contraindicated in patients who are on chronic nitrate drug therapy or in those using nitric oxide donors in any form (such as phenobarbitol), due to the risk of developing potentially life-threatening hypotension. Chronic therapy with nitrates does not modify cardiovascular morbidity and mortality and, therefore, it can be safely discontinued during sildenafil use. However, it still remains to be determined whether the use of beta-blocking agents may protect patients with coronary artery disease during sildenafil citrate (Viagra™, Pfizer Italiana, Rome, Italy) treatment. Furthermore, because of the vasodilator effect of sildenafil citrate, an increase in the anti-ischemic effect of beta-blockers may be hypothesized. The purpose of the present study was to evaluate the effects of sildenafil citrate (Viagra™) upon exercise-induced myocardial ischemia in patients with coronary artery disease and on chronic treatment with a beta-blocker.

Methods

Patient population. The study population included 14 patients (all males; mean age 52 ± 11 years, range 42-66 years) with proven coronary artery disease, a positive exercise test and erectile dysfunction.

Coronary artery disease was defined as stenosis > 70% in one of the major epicardial coronary arteries as assessed at quantitative coronary angiography.

None of the patients had recently (< 6 months) undergone a revascularization procedure and, at the time of the study, all had significant coronary artery disease.

Patients with unstable angina, or a recent (< 3 months) acute myocardial infarction, as well as those with congestive heart failure (NYHA functional class > II), primary valvular disease, congenital heart disease, and myocardial or pericardial disease were excluded from the study. Patients with severe organic insufficiency, left ventricular hypertrophy, conduction disorders that could invalidate the interpretation of the ST segment, uncorrected hypokalemia or those receiving digitalis and antidepressant drugs were also excluded.

Study protocol. Patients entered the study after a baseline exercise test performed in complete pharmacological washout and at least showing 1 mm ST-segment depression. After the baseline test, patients received atenolol 100 mg once daily and, after 1 week, were randomized to receive a single 50 mg dose of sildenafil or placebo in a double-blind single cross-over study. A symptom-limited exercise test was performed at baseline, after 1 week of atenolol therapy (100 mg once daily), and, on two occasions 2 days apart, 2 hours after the administration of sildenafil or placebo. Treatment was allocated according to a computer-generated random list prepared before the beginning of the study.

All patients gave their informed consent to the study which had been approved by the local ethics committee.

Exercise testing. All patients underwent repeated symptom-limited exercise tests on different days and at the same hour of the day (± 1 hour) according to the modified Bruce protocol. The baseline test was performed in complete pharmacological washout. Nitrates other than sublingual nitroglycerin were withdrawn 1 day before the test; calcium channel blocking and beta-adrenergic blocking agents were withdrawn 4 and 5 days before the study respectively. Up to 6 hours before each exercise test, sublingual nitrates were allowed for the treatment of anginal episodes.

A 12-lead ECG was obtained at rest, every minute during the test, at the onset of 1 mm ST-segment depression, at peak exercise, and every minute during recovery. The V_1 to V_6 and the I and II leads were continuously monitored. The systolic and diastolic blood pressures were measured at rest and monitored every 3 min during exercise and recovery.

A positive response in the ECG was defined as a horizontal or downsloping > 1 mm ST-segment depression at 60 ms after the J point and occurring in ≥ 6 consecutive complexes. The exercise test was concluded at the point of physical exhaustion or in the presence of a > 3 mm ST-segment depression, severe angina, severe dyspnea, complex ventricular arrhythmias or a > 20 mmHg decline in systolic blood pressure. The total exercise time, the time to myocardial ischemia, the duration of ECG ischemic changes, heart rates, the blood pressure at the onset of 1 mm ST-segment depression, the maximal ST-segment depression, and the time to the development of angina during exercise were recorded. The ST segment 60 ms after the J point was evaluated after signal averaging by a computer-assisted system in all 12 leads. The lead showing the greatest ST-segment depression during pre-treatment exercise was selected for analysis. The supervision and analysis of the exercise tests were performed by experienced investigators who were unaware of treatment and of its sequence.

Statistical analysis. Data are expressed as mean ± SD or as percentages where appropriate. The two-tailed paired nonparametric test (Wilcoxon) was performed to evaluate statistical significance. A p value of < 0.05 was considered statistically significant.

Results

The clinical characteristics of the study population are shown in table I. All patients had chronic stable angina and proven coronary artery disease as assessed at selective coronary angiography: 7 patients had one-

Table I. Clinical characteristics of the study population.

No. patients	14
Sex	All males
Age (years)	52 ± 11
Hypertension	7
Diabetes	2
Prior myocardial infarction	2
One-vessel disease	7
Two-vessel disease	6
Three-vessel disease	1

vessel disease, 6 two-vessel and 1 three-vessel disease; all had a positive exercise stress test. Seven patients were hypertensive and 2 had diabetes mellitus.

All patients had a positive exercise test while off-therapy. Eight patients had a negative exercise test response after atenolol (57%) which was unaltered by the adjunct of either sildenafil or placebo. In the remaining patients, atenolol significantly prolonged the time to 1 mm ST-segment depression from 412 ± 45 to 584 ± 42 s ($p < 0.01$). Atenolol treatment was associated with an increased exercise time in all patients (from 523 ± 54 to 754 ± 42 s, $p < 0.01$). Of note was the observation that neither sildenafil nor placebo reversed the beneficial effect of atenolol upon exercise-induced myocardial ischemia (time to 1 mm ST-segment depression 592 ± 35 and 579 ± 52 s, respectively, $p = 0.1$) and upon the exercise time (762 ± 53 and 748 ± 39 s, $p = 0.1$).

No difference regarding the effect of sildenafil citrate on heart rate and blood pressure either at rest or during exercise was noted in patients with or without arterial hypertension.

The baseline blood pressure and heart rate were not significantly influenced by sildenafil citrate. The heart rate and the rate pressure product at 1 mm ST-segment depression and at peak exercise were also not influenced by sildenafil (Table II).

Six patients had angina during the baseline exercise test while only 2 complained of angina after beta-blockade. The number of patients complaining of chest pain remained unaltered whether sildenafil or placebo was administered.

No side effects such as headache or flushes were noted in any patient after either sildenafil citrate or placebo administration.

Discussion

Cardiovascular diseases are epidemiologically associated with erectile dysfunction because the two diseases often have similar risk factors (i.e., age, atherosclerosis, diabetes, hypertension, cigarette smoking) and share in common the pathogenic involvement of the nitric oxide pathway with an impairment of endothelium-dependent vasodilation: therefore, a large proportion of patients possibly taking sildenafil for erectile dysfunction may also have underlying ischemic heart disease[2].

In spite of the high prevalence of ischemic heart disease in this population, sudden death and myocardial infarction are uncommon events during sexual activity (respectively 0.6 and 0.9% of all events[7]). The relative risk of myocardial infarction is higher in patients with a prior history of ischemic heart disease compared with

Table II. Exercise test response at baseline and after the administration of study drugs in patients with chronic stable angina.

	Baseline	A	A + S	A + P
Resting	14	14	14	14
HR (b/min)	74 ± 8	54 ± 6	56 ± 5	54 ± 6
SBP (mmHg)	146 ± 12	130 ± 14	126 ± 18	132 ± 10
1 mm ST-segment depression	6	6	6	6
HR (b/min)	123 ± 21	115 ± 12	116 ± 10	114 ± 16
SBP (mmHg)	178 ± 24	182 ± 22	178 ± 24	184 ± 28
Rate-pressure product (10^3)	21.9 ± 5.1	23.9 ± 7.6	20.6 ± 7.1	20.9 ± 6.3
Time (s)	412 ± 45	584 ± 42	592 ± 35	579 ± 52
Not attained	8	8/14 (57%)	8/14 (57%)	8/14 (57%)
HR (b/min)	125 ± 25	–	–	–
SBP (mmHg)	172 ± 32	–	–	–
Rate-pressure product (10^3)	22.3 ± 4.6	–	–	–
Time (s)	401 ± 56	–	–	–
Peak exercise				
HR (b/min)	131 ± 24	130 ± 18	132 ± 16	128 ± 22
SBP (mmHg)	186 ± 26	184 ± 32	182 ± 28	186 ± 26
Rate-pressure product (10^3)	24.4 ± 8.1	23.9 ± 7.6	24.0 ± 6.7	23.8 ± 6.9
Time (s)	523 ± 54	754 ± 42	762 ± 53	748 ± 39

A = atenolol; HR = heart rate; S = sildenafil; SBP = systolic blood pressure; P = placebo.

patients who have no such history and regular exercise appears to prevent triggering of the event[8]. In men, during sexual activity oxygen consumption is moderate and varies from 2.5 METS in passive positions to 3.5 METS in active ones[9]; the heart rate values during intercourse are similar to those observed for other daily life activities[10-12]. In the study by Drory et al.[13], all patients with Holter ECG monitoring-detected ischemia during intercourse also had ischemia during exercise, while patients without ischemia during exercise did not have ischemia during sexual activity. In sum, patients with ischemic heart disease who have an ischemic threshold > 3.5 METS are able to achieve a satisfactory sexual activity, are not exposed to the risk of performing an inappropriate effort and do not significantly increase their baseline cardiovascular risk even if they are currently being treated.

It has been shown, at Holter monitoring studies, that by lowering the oxygen consumption, beta-blocker therapy reduces ischemic episodes during sexual activity. In our study, as expected, beta-blockers normalized the exercise test in 8 out of 14 patients and significantly prolonged the time to 1 mm ST-segment depression and the exercise time. Acute sildenafil administration did not reverse the beneficial effect of beta-blockers upon exercise-induced myocardial ischemia and no collateral effects attributable to drug interaction were observed.

The safety of the administration of sildenafil to a population with erectile dysfunction and ischemic heart disease does not depend on a negative pharmacodynamic property of the PDE5 inhibitor, because sildenafil has no effects on myocardial contractility, does not modify the heart rate and only causes a mild reduction in diastolic and systolic arterial pressure. Furthermore, sildenafil does not alter platelet aggregation and the prothrombin time in patients on anticoagulant or antiplatelet therapy and does not enhance the antihypertensive effect of ACE-inhibitors, calcium antagonists, diuretics, beta-blockers, and alpha-blockers. Moreover, the endovenous administration of sildenafil in patients with chronic stable angina results only in a decreased arterial pulmonary pressure and, to a lesser extent, peripheral resistance.

The only absolute contraindication to the use of sildenafil is simultaneous therapy with nitric oxide donors or a diagnosis of acute coronary syndromes, heart failure, or effort-induced malignant ventricular tachyarrhythmias. However, these contraindications are not related to the pharmacological properties of the drug, but mainly to the inability to perform the effort required for sexual activity. Therefore, the risk of cardiac events in patients taking sildenafil does not appear to be related to an adverse effect of the drug on cardiac hemodynamics, but may be related to the possibility that the patient may feel enabled to expose himself to a higher level of exertion than is appropriate for his clinical condition. It is strongly recommended that patients with coronary artery disease maintain their therapeutic regimen and perform a treadmill test before taking sildenafil, in order to determine the ischemic threshold.

The indication to a safe use of sildenafil in stable coronary artery disease appears to be an ischemic threshold > 3.5 METS, the maximal burden of sexual activity. In patients with a lower ischemic threshold, beta-blockers are excellent drugs for the achievement of this goal; besides, they improve the prognosis after myocardial infarction, reduce the arrhythmogenic risk and, as our data show, simultaneous therapy with sildenafil does not reduce their pharmacological benefits effect and is not associated with any drug interaction.

The dose of atenolol used in this study (100 mg) may not be tolerated by some patients. Therefore, for patients taking lower doses of this drug, the observations of the present study need to be confirmed.

In conclusion, in patients with chronic stable angina whose symptoms and exercise test response are well controlled by beta-blocker therapy, exercise capacity and exercise-induced myocardial ischemia are not worsened by sildenafil citrate (Viagra™). Further, epidemiological studies including larger populations have to be performed so as to elucidate the safety of long-term repetitive PDE5 inhibitor treatment.

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