Clinical research

Sildenafil citrate does not reduce exercise tolerance in men with erectile dysfunction and chronic stable angina

Kim M. Foxa*, Udho Thadanib, Patrick T. S. Ma, Stephen D. Nashd, Zoe Keatinge, Michael A. Czorniakf, Hunter Gilliesg, Mátyás Keltai, on behalf of the CAESAR I (Clinical American and European Studies of Angina and Revascularization) investigators

Royal Brompton and Harefield NHS Trust, London, UK
University of Oklahoma Health Sciences Center and VA Medical Center, Oklahoma City, OK, USA
Heart Health Institute, Calgary, Canada
Syracuse Preventive Cardiology, Syracuse, NY, USA
Pfizer Global Research and Development, Sandwich, UK
Pfizer Global Research and Development, New London, CT, USA
Hungarian Institute of Cardiology, Budapest, Hungary

Received 27 March 2003; received in revised form 11 September 2003; accepted 19 September 2003

Aims The aim of this study was to evaluate whether sildenafil, used for treatment of erectile dysfunction (ED), affects the exercise tolerance and ischaemic threshold in men with exercise-induced angina not taking nitrates.

Methods This was a double-blind placebo-controlled study in men with ED and chronic stable angina, assessing the effect of sildenafil on time to limiting angina during incremental treadmill exercise. Patients remained on their antianginal therapy and received a 100-mg dose of sildenafil or placebo 1 h prior to treadmill exercise. Other measurements included times to onset of angina, 1-mm ST-segment depression, and total exercise time.

Results Adjusted treatment differences for the time to limiting angina, time to onset of angina, total exercise time, and time to 1-mm ST-segment depression were (mean±SE) 20±10 s (95% CI, 1–39; P=0.040), 32±11 s (95% CI, 11–53; P=0.004), 20±10 s (95% CI, 0–39; P=0.049), and 12±17 s (95% CI, −21 to 45, P=0.48), respectively, in favour of sildenafil. There were no serious treatment-related adverse events.

Conclusion Sildenafil was well tolerated and did not adversely affect any exercise parameter in men with coronary artery disease and ED. Favourable trends in total exercise duration and times to onset of angina and limiting angina were recorded with sildenafil use.

© 2003 The European Society of Cardiology. Published by Elsevier Ltd. All rights reserved.

KEYWORDS
Angina; Erectile dysfunction; Exercise tolerance; Ischaemia; Sildenafil citrate; ST-segment depression

* Corresponding author: Kim M. Fox, MD, Royal Brompton and Harefield Trust, Sydney Street, London, SW3 6NP, UK. Tel.: +44-20-7351-8626; fax: +44-20-7351-8629

Kim Fox is a paid consultant and advisor for Pfizer Inc. Udho Thadani is a study investigator and consultant and works with several pharmaceutical companies on trial design and speakers bureaus. Patrick Ma is a study investigator for Pfizer Inc. Stephen Nash has served as primary investigator on multiple clinical trials and is a consultant for Merck, Pfizer Inc., Wyeth-Ayerst, Sankyo, and Boehringer Ingelheim. Zoe Keating is an employee of Pfizer Inc. Michael Czorniak is an employee of Pfizer Inc. Hunter Gillies is an employee of Pfizer Inc. Mátyás Keltai is a study investigator and consultant for Pfizer Inc.

E-mail address: k.fox@rbh.nthames.nhs.uk (K.M. Fox).

0195-668X/03/$ - see front matter © 2003 The European Society of Cardiology. Published by Elsevier Ltd. All rights reserved.
**Introduction**

Sildenafil citrate, an oral treatment for erectile dysfunction (ED), is a potent and selective inhibitor of cyclic guanosine monophosphate (cGMP)–specific phosphodiesterase type 5 (PDE5). The enzyme is expressed in the smooth muscle of the corpus cavernosum of the penis and is also located in the systemic vasculature. Based on its moderate vasodilatory properties, sildenafil was originally studied as an antianginal agent but was subsequently shown to potentiate the nitric oxide–cGMP pathway that mediates corpus cavernosum smooth muscle relaxation. Although abundant in vascular smooth muscle, PDE5 has not been found in human cardiac myocytes. Moreover, sildenafil is approximately 4000-fold more selective for PDE5 than PDE3, the cyclic adenosine monophosphate (cAMP)-dependent PDE involved in control of cardiac contractility, and approximately 80-fold more selective for PDE5 than PDE1, the main isozyme in human ventricle. Sildenafil is a weak vasodilator, resulting in small, transient decreases in systolic (10 mmHg) and diastolic (7 mmHg) blood pressure (BP) when administered orally; no clinically significant effects on heart rate (HR) have been reported.

Men with cardiovascular disease are more likely to have ED than the general population because both conditions share a number of risk factors, such as diabetes, smoking, obesity, hypertension, hyperlipidaemia, and lack of physical activity. In addition, some drugs used to treat cardiovascular disease or comorbidities may induce ED. After experiencing a cardiovascular event, such as a myocardial infarction (MI) or coronary bypass surgery, patients may be apprehensive about re-engaging in sexual activity. In general, the energy expenditure during sexual activity for most people equates to two to three metabolic equivalents (METS) before orgasm and three to four METS during orgasm, comparable to common daily activities, such as light housework and gardening. However, the relative and absolute cardiovascular risk of sexual activity is extremely low. With the introduction of sildenafil, many patients with cardiovascular disease and ED have been able to resume sexual activity.

Studies have shown that sexual activity does not lead to exaggerated HR or BP responses and that stable angina patients are not at greater relative cardiovascular risk during sexual intercourse. An earlier study assessing the occurrence of ischaemia during an exercise stress test and sexual activity demonstrated that all patients who developed ischaemia during sexual activity also had ischaemia during exercise, and patients without ischaemia during exercise did not develop ischaemia during sexual activity. These findings support the treadmill exercise test as a reliable surrogate for determining the toleration of sexual activity in patients with ischaemic heart disease. Therefore, the purpose of this study was 2-fold: We investigated the safety and tolerability of sildenafil in patients with ED and stable angina not requiring nitrates using treadmill exercise as a surrogate for sexual activity. Second, the mechanism of action of sildenafil, suggestive of its potential as an antianginal agent, prompted an investigation into the effect of sildenafil on the time to limiting angina. The data obtained will provide cardiologists with important information in determining the effects of sildenafil on the anginal and ischaemic threshold during sexual activity in men with ED and coronary artery disease (CAD) who do not require nitrates.

**Methods and patient population**

This was a randomized, double-blind, placebo-controlled, parallel-group, multicentre study examining the effect of sildenafil (single dose of 100 mg) on the time to onset of limiting angina during incremental treadmill exercise in patients with ED and chronic stable angina. Patients were required to have a score of <26 on the International Index of Erectile Function (IIEF) Erectile Function domain, or to have received treatment for ED. Patients were maintained on their usual antianginal therapy; however, because the use of sildenafil with organic nitrates is contraindicated, subjects receiving nitrate therapy were not studied.

**Inclusion criteria**

Male patients aged 18 years or older were included if they had evidence of CAD (≥60% occlusion of at least one coronary artery) documented by a coronary angiography, positive radionuclide scan, or positive echocardiographic stress test or if they had a previous MI, coronary artery bypass surgery, or percutaneous transluminal coronary angioplasty. Patients remained on their usual antianginal medications throughout the study and were required to demonstrate reproducible exercise-induced angina during two screening exercise tests, 5 to 10 days apart, in which limiting angina, associated with ≥1-mm ST-segment depression (measured 80 ms after the J point), had to occur within 3 to 9 min after start of the exercise, with a variability between the two visits of ≤20%. A 12-lead electrocardiogram (ECG) was monitored continuously; patients discontinued exercise when limiting angina developed or, in the absence of angina, when the ST-segment depression reached 3 mm, whichever occurred first. Other limiting end-points leading to termination of exercise were a significant decrease (>80 mmHg) or increase (>240 mmHg) in systolic BP; ataxia, vertigo, dizziness, cyanosis, pallor, or any other symptoms suggestive of distress; clinical evidence of acute cardiac decompensation; clinically serious atrial or ventricular arrhythmias; and heart block.

Routine BP and HR measurements were taken at the end of each workload. Patients who either failed to demonstrate a progressive increase in systolic BP during the exercise stress test or developed a clinically significant arrhythmia were excluded.

**Main exclusion criteria**

Patients were excluded if they presented with one of the following: comitant use of chronic long-lasting nitrates or nitric oxide donors or inability to discontinue long-lasting nitrates 1 week prior to and throughout the study; unstable angina; use of digoxin or β-blockers; a contraindication to β-blockers or calcium channel blockers; a resting systolic BP of <90 mmHg or >170 mmHg and a resting diastolic BP of <60 mmHg or >105 mmHg; a history of MI within the last 6 months; any ECG...
abnormalities preventing the interpretation of ischaemia; or clinically important valvular or congenital heart disease. Patients who were unwilling or unable to discontinue sublingual nitroglycerin for relief of angina prior to and for 24 h following the exercise test were also excluded. Subjects had blood drawn for the measurement of sildenafil prior to the screening exercise tests and prior to study drug administration at visit 3; those with detectable levels of sildenafil were excluded from the analysis.

Study protocol

All exercise stress tests used a standard Bruce multistage exercise test protocol consisting of up to seven 3-min stages. The workload was constant within each stage, but it gradually and continually increased between stages from a treadmill speed of 1.7 mph and a slope of 10% (stage 1) to a speed of 6 mph and a 22% slope (stage 7).

Electrocardiographic parameters, such as ST-segment depression, were analysed by a cardiologist using hand-held digital calipers and entered into an electronic database. A minimum of three to five consecutive QRS complexes were measured individually and averaged by the software program to produce a mean value for each interval. The resting 12-lead ECG was used as a baseline reference, and HR was always measured from the one with the qualifying 1-mm-ST segment depression. The baseline ECG ST-segment deviation was then measured from the same lead as existing baseline ST segment depression. The baseline ECG ST-segment deviation was then measured from the same lead as the one with the qualifying 1-mm-ST segment depression.

If the two screening tests were within the above specifications, a final test was conducted 5 to 10 days later, 1 h after administration of sildenafil (100 mg) or matching placebo. The primary end-point was the time to limiting angina, defined as the level of angina symptoms that would normally make the patient want to terminate the exercise. If no angina occurred, exercise duration was used to equate the time to limiting angina. Secondary end-points included time to onset of angina, time to 1-mm ST-segment depression, total exercise time, BP, HR, and rate pressure product (RPP). In those men who experienced unresolved angina post exercise stress testing, and if the treatment blind did not have to be broken, treatment could include any non-nitrate-based therapy to alleviate symptoms.

Overall, 144 patients who completed the two screening exercise tests were randomized to sildenafil (n=74) or matching placebo (n=70). However, during a central blinded review of data, a total of 36 patients were excluded for not meeting the definition of reproducible stable angina (n=26), for exhibiting significant plasma levels of sildenafil or its metabolite prior to exercise testing (n=8), for unknown plasma levels of sildenafil prior to exercise testing (n=1), and for carrying out the treadmill exercise 4 h postdose (n=1). This left 108 patients with evaluable data (n=56, sildenafil; n=52, placebo). A stratified randomization was applied to this study to ensure that a balance of treatment was achieved among those patients taking different classes of antianginal medication (β-blockers, calcium channel blockers, both, or neither).

Statistical analysis

The primary efficacy end-point for this study was the time to limiting angina. The objective was to demonstrate 1-sided equivalence (noninferiority) of sildenafil against placebo in a number of key end-points, including the primary end-point. Following consultation with clinical experts, changes within 20% were not considered to be clinically meaningful. If 250 s is the expected exercise time in this population, this translates to a tolerance region of ±50 s.

The primary and secondary end-points were analysed using analysis of covariance, adjusted for the following covariates: baseline (average of two screening visits), smoking status, body mass index, age, duration of angina (years), region, and concomitant medications. The difference between treatment means, a 1-sided 97.5% confidence interval, and a noninferiority P value were calculated using placebo as a central point. A positive difference would therefore imply that the average time was longer for sildenafil users compared with placebo users. Minus fifty (−50) s was the limit for noninferiority. As prespecified in the statistical analysis plan, if sildenafil was shown to be noninferior to placebo, then a 2-sided superiority test (at the 5% level) would be carried out.

Results

Demographic characteristics, medical history, and use of concomitant medications of the patient population are shown in Tables 1 and 2. The number of patients with a
history of MI and hypertension was comparable between both groups, whereas the incidence of diabetes was slightly lower in the sildenafil group compared with placebo. Concomitant drug use at screening was comparable for angiotensin-converting enzyme (ACE) inhibitors and β-blockers, whereas the use of calcium channel blockers and hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors was a little lower in the sildenafil group and the placebo group, respectively.

Sildenafil demonstrated noninferiority to placebo for primary and secondary end-points, as all measured times were increased compared with placebo (Tables 3 and 4).

Sildenafil demonstrated superiority to placebo for the time to onset of angina (P=0.0039), the time to limiting angina (P=0.040), and the total exercise time (P=0.0495). Superiority was not demonstrated for time to 1-mm ST-segment depression (P=0.484), however, there was a greater trend towards improvement in the sildenafil group.

Systolic BP was lower in the sildenafil group than the placebo group 1 h following drug administration and remained lower throughout the duration of the study (Fig. 1). Return of HR and BP to baseline after exercise was similar in the two treatment groups; rate pressure product was lower post drug in the sildenafil group at rest, during exercise, and throughout the recovery period (Fig. 1). Sildenafil and placebo were well tolerated, and there were no serious treatment-related adverse events. The most common treatment-emergent adverse events were facial flushing (sildenafil, 9 subjects; placebo, 1 subject), dizziness (sildenafil, 3; placebo, 2), and headache (sildenafil, 2; placebo, 2).

### Discussion

The prevalence of ED in men with CAD is higher than in the general population because both conditions share many risk factors. Many cardiologists are asked for advice on or to evaluate men with ED for their fitness to resume sexual activity; thus, the goal of this study was to provide useful information for cardiologists on the effect of sildenafil on the anginal and ischaemic thresholds, that would aid them in deciding whether sildenafil can be safely prescribed to CAD patients who do not require nitrates.

### Exercise and angina

The inclusion criteria of the current study of 3 to 9 min to onset of limiting angina, and an observed time to 1-mm ST-segment depression of 281 and 275 s for placebo and sildenafil treated subjects, respectively, places the study participants at the severe end of the CAD spectrum. Because of the contraindication with nitrates, it is important that any oral or systemically active PDE5 inhibitor used to treat ED does not aggravate ischaemia or reduce the anginal threshold. In the current study, men with chronic stable angina fared well on an exercise test irrespective of whether they received sildenafil or matching placebo. The primary and all of the secondary end-points demonstrated 1-sided equivalence between sildenafil and placebo. Interestingly, the time to limiting angina and the time to angina improved by 36 s (9.8%) and 18 s (4.7%), and by 47 s (17.3%) and 18 s (4.7%), respectively, for patients taking sildenafil or placebo. From these clinical data it can be concluded that sildenafil treatment does not worsen ischaemia in this patient group and is likely to improve the anginal threshold. The findings of this study, together with evidence that a patient can achieve a level of treadmill exercise between five and six METS, gives prescribers some level of reassurance that the use of short-acting nitrates to relieve angina provoked by sexual activity will be unlikely in a subject with a stable, predictable pattern of angina. A study with another PDE5 inhibitor (vardenafil) demonstrated no effect on exercise time but an improvement in the ischaemic threshold in men with CAD. Subjects in this study omitted their β-blocker therapy prior to exercise testing, which was not done in the sildenafil study. The clinical significance, if any, of the difference in the findings between these two studies remains to be determined.

The mean time to limiting angina, hence workload achieved, equates to approximately eight METS in both groups, which is considerably greater than the energy expended during even vigorous sexual activity (five to six METS). The magnitude of the improvement in exercise duration with sildenafil is similar to that seen in other studies investigating the efficacy of mibefradil, amiodipine, and diltiazem as chronic add-on therapy in angina patients with similar disease severity who were already on β-blockers. This observed effect of sildenafil on the anginal and ischaemic thresholds is

<table>
<thead>
<tr>
<th>Table 2 Medical history and use of concomitant medications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Medical history, n</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Drug treatment at screening, n</td>
</tr>
<tr>
<td>ACE-I</td>
</tr>
<tr>
<td>CCB</td>
</tr>
<tr>
<td>BB</td>
</tr>
<tr>
<td>HMG CoA reductase inhibitors</td>
</tr>
<tr>
<td>Patients receiving &gt;1 drug treatment, n</td>
</tr>
</tbody>
</table>

*ACE-I=angiotensin-converting enzyme inhibitor.

*BB=β-blocker.

*CCB=calcium channel blocker.

*HMG CoA=hydroxymethyl glutaryl coenzyme A.
supported by reports from animal models and clinical studies.

**Animal models**

Sildenafil was shown to selectively increase cGMP levels in vitro in coronary vascular smooth muscle but produced no change in cAMP levels consistent with its selectivity for PDE5. In chronically instrumented dogs, sildenafil caused a small increase in coronary blood flow at rest and during exercise, presumably owing to dilatation of the coronary resistance vessels, resulting in increased blood flow to the ischaemic myocardium during exercise. In two other dog models, no evidence was found that sildenafil would aggravate ischaemia by way of coronary steal, and it was concluded that it might even have a beneficial effect.

**Clinical studies**

In five small clinical studies that included patients with atherosclerosis (n=25), coronary artery stenosis...
sildenafil administration was shown to have no adverse effects on cardiovascular parameters or function. In fact, sildenafil improved endothelial function in the coronary circulation, increased total exercise time in heart failure patients, and did not counteract any beneficial effects of atenolol. Taken together, these studies suggest that sildenafil does not adversely affect cardiovascular parameters and may even improve blood supply to the heart.

Recommendations

Because of the relatively high prevalence of cardiovascular disease amongst patients with ED, recommendations for the clinical management of sexual dysfunction in patients with cardiovascular disease were made by two multidisciplinary panels of physicians and surgeons, one in the United States, the other in the United Kingdom. Patients were stratified into high, low, and intermediate categories of cardiac risk, and the majority of patients fell into the low-risk category, which included patients with controlled hypertension, mild stable angina; successful coronary revascularization; a history of uncomplicated MI; mild valvular disease; or no symptoms and <3 cardiovascular risk factors. These patients can be safely encouraged to resume sexual activity or to receive treatment for sexual dysfunction, with the exception of those patients using nitrates.

The current study provides direct evidence that sildenafil does not cause coronary steal or reflex tachycardia. Moreover, a beneficial trend was seen in all of the end-points measured in this population of men with CAD, supporting data from the clinical trial safety database as well as other studies. These data are helpful when considering the prescription of sildenafil to men with ED and stable angina who do not require nitrate therapy.

Acknowledgements

The authors would like to thank Gracinda Ferreira, PhD, for her valuable contribution to the management of this multicentre study.

Appendix A

CAESAR I investigators


References


7. Wallis RM, Corbin JD, Francis SH et al. Tissue distribution of phosphodiesterase families and the effects of sildenafil on tissue cyclic nucleotides, platelet function, and the contractile responses of trabeculae carnea and aortic rings in vitro. Am J Cardiol 1999;83:3C–12C.


