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Cardiovascular Safety of Sildenafil

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Contents

Abstract

Initial reports of myocardial infarction and sudden death in men with erectile dysfunction who had taken sildenafil (sometimes in conjunction with nitrates) raised concerns that sildenafil may increase the risk of cardiovascular events in men with erectile dysfunction and vascular disease. A significant body of evidence now indicates that sildenafil generally has a good safety profile in men with erectile dysfunction and cardiovascular disease.

Sildenafil therapy does not appear to be associated with ischaemic events either at the time of introduction of therapy or during longer-term use. Rates of discontinuation from sildenafil therapy due to adverse events are similar to placebo in men with cardiovascular disease. Sildenafil does not interact in a potentially hazardous way with antihypertensive or antianginal therapy, with the exception of nitrates. Nitrates should not be administered within 24 hours of sildenafil therapy, and care should be taken to determine whether sildenafil may have been used before nitrates are administered to patients.

Sildenafil appears to be generally well tolerated in most patients with chronic, stable cardiovascular disease.

The prevalence of moderate to complete erectile dysfunction in men aged 40–70 years has been reported to be in excess of 30%.[1] Sildenafil is widely used for the treatment of erectile dysfunction of

organic, psychogenic or mixed aetiology in patients with a wide range of co-morbidities.[2] Clinical trials have provided more than 11 000 patient-years of observation of sildenafil therapy, and within the first 3 years of its release few new revelations regarding its efficacy and safety profile have arisen.[3,4]

Extensive research shows sildenafil to be beneficial in treating erectile dysfunction in the majority of patients with cardiovascular disease and cardiovascular risk factors. The effectiveness of sildenafil has been investigated in men with erectile dysfunction associated with ischaemic heart disease,[5] hypertension,[6,7] congestive heart failure,[8] and diabetes mellitus.[9,10] The potential of sildenafil has also been explored in other areas, such as erectile dysfunction associated with prostatectomy, radiotherapy, spinal cord injury and Parkinson's disease.[11-14]

The efficacy and safety of sildenafil in treating erectile dysfunction in men with cardiovascular disease is of particular interest. Men with erectile dysfunction frequently have cardiovascular disease and thus have an increased risk of cardiovascular events, as any condition that compromises blood flow may affect erectile function. Sildenafil is a potent inhibitor of phosphodiesterase type 5 (PDE5) which catabolises cyclic guanosine monophosphate (cGMP) formed in response to nitric oxide (NO). While PDE5 is principally found in the corpus cavernosum, it also occurs in the systemic vasculature where increased cGMP formation produces vasodilation. Potentiation of cGMP in vascular smooth muscle by PDE5 inhibition raises the concern that sildenafil therapy may increase the risk of myocardial ischaemia in patients with both symptomatic and asymptomatic coronary artery disease by producing a rapid reduction in systemic vascular resistance leading to impaired coronary perfusion.[4,5]

This article reviews the safety data on the use of sildenafil for erectile dysfunction in men with cardiovascular disease.

1. Discontinuations Due to Adverse Effects During Sildenafil Therapy

Discontinuation rates for sildenafil therapy due to adverse events in the general male population with erectile dysfunction is comparable to those seen with placebo.[3] Of 2199 subjects participating in open-label extension studies of sildenafil, adverse events accounted for 2% and lack of efficacy for 4% of discontinuations over a 1-year period.[15] The most commonly reported adverse event in 18 placebo-controlled trials was headache (16% of sildenafil recipients, 4% of placebo recipients), with a 1.1% discontinuation rate for sildenafil treatment and 0.4% for patients receiving placebo. Other commonly reported adverse events were flushing (10% sildenafil, 1% placebo), dyspepsia (7% sildenafil, 2% placebo), nasal congestion (4% sildenafil, 2% placebo), urinary tract infection (3% sildenafil, 2% placebo), and abnormal vision (3% sildenafil, 0% placebo).[15]

Most of these adverse events are a result of vasodilation and a direct extension of the inhibition of PDE5 in blood vessels by sildenafil. Thus, while sildenafil therapy is associated with a significantly higher adverse event rate than placebo, these events do not deter men from experiencing the benefits of therapy and are not associated with a high rate of discontinuation of therapy.

Priapism rarely occurs, with most clinical trials reporting a zero incidence rate.[16] Some reports of priapism have occurred in circumstances where other factors were likely to have contributed, such as sickle-cell disease and cyclosporin therapy (which may delay the metabolism of sildenafil).[17,18]

A Swedish study[8] in men with cardiovascular disease and erectile dysfunction reported a discontinuation rate of 7% for men in the sildenafil treatment group compared with 9% in the placebo group. None of the discontinuations were due to adverse events in patients taking sildenafil. The evaluation concluded that sildenafil is an effective and well

tolerated treatment for erectile dysfunction in patients with multiple cardiovascular disorders.

2. Myocardial Infarction and All-Cause Mortality During Sildenafil Therapy

An abstract presentation of a review of reported clinical trials of sildenafil reported no difference in the rate of serious cardiovascular events or deaths between placebo- and sildenafil-treated patients.[19]

After a total observation time of 6884 patient-years of sildenafil therapy (including double-blind and open-label studies) and 543 patient-years of placebo therapy, an analysis by Mittleman et al.[20] (also only available as an abstract) found that the incidence of myocardial infarction during sildenafil therapy was 0.8 (95% CI 0.60–1.04) per 100 patient-years compared with 1.11 (0.41–2.40) per 100 patient-years with placebo. The incidence of all-cause mortality was 0.42 (0.28–0.61) per 100 patient-years for patients receiving sildenafil compared with 0.74 (0.20–1.84) for patients receiving placebo. There has been no further published information from this study and it is uncertain whether any of the deaths during sildenafil therapy were related to sexual activity or involved interactions with other drugs.

The Southampton Drug Safety Research Unit prescription event monitoring study[21] surveyed primary-care physicians with respect to all adverse events reported by men receiving sildenafil prescriptions. In the preliminary analysis of 5601 patients (mean age 57 years) receiving their first prescription of sildenafil for erectile dysfunction, morbidity and mortality rates were compared with age-standardised norms. Patients were followed for an average of 4.9 months. No events were recorded during the first month of treatment, and a first-dose effect was not apparent. The standardised morbidity rate for fatal or non-fatal myocardial infarction (including other deaths related to ischaemic heart disease) was 0.30 per 100 patients-years (0.16–0.43) in patients taking sildenafil compared with 0.30 in the general community, suggesting that sildenafil therapy was not associated with an obvious increase in the risk of myocardial infarction.

Thus, the evidence currently available suggests that sildenafil therapy does not appear to be associated with an increased risk of myocardial infarction or mortality. The proportion of men who had coronary artery disease in these studies is uncertain, but it is likely to have been appreciable considering the relatively high prevalence of erectile dysfunction in men with cardiovascular disease.

3. Effects of Sildenafil on Haemodynamics and Myocardial Ischaemia in Patients with Ischaemic Heart Disease

Sildenafil produces relatively modest changes in blood pressure and other haemodynamic parameters in patients with cardiovascular disease.[22,23] Importantly, sildenafil does not appear to produce potentially adverse effects on coronary blood flow, coronary vascular resistance or coronary flow reserve.[22,24] Sildenafil 40mg caused statistically significant but relatively minor reductions in pulmonary arterial pressure (27% at rest, 19% during exercise) and cardiac output (7% at rest and 11% during exercise) from baseline in eight men with stable ischaemic heart disease.[25]

The effects of sildenafil 100mg orally on systemic and coronary artery haemodynamics were studied in 14 patients with stable angina (mean age 61 years) with >70% stenosis in at least one coronary artery. The change in systemic and pulmonary arterial pressure and systemic vascular resistance following sildenafil administration was less than 10% of baseline. No change in cardiac output, pulse, or rate pressure product was observed. Coronary blood flow was not reduced following adenosine injection in either the severely stenosed arteries nor the less stenosed arteries. In fact, coronary flow reserve increased by 13%.[22]

The effects of sildenafil on myocardial ischaemia were studied in 14 patients with chronic stable angina who were receiving β-adrenoceptor antagonist (β-blocker) therapy. The patients underwent an exercise test at baseline, at the end of a run-in phase, and 2 hours after an oral dose of sildenafil 50mg.[26] Sildenafil had no effect on exercise-induced ischaemia. Sildenafil did not reverse the beneficial effect of β-blocker therapy on exercise-induced myocardial ischaemia in patients who were symptomatically controlled on atenolol. Sildenafil did not adversely or beneficially affect stress test results for patients who had not responded completely to atenolol treatment.

Results of treadmill stress testing in 32 male patients with ischaemic heart disease (mean age 49.3 years) also found no deleterious cardiovascular effects of sildenafil.[23] No ischaemic changes occurred after sildenafil intake, and no significant differences in blood pressure or heart rate were found during treadmill testing 1 hour after the administration of sildenafil 100mg compared with baseline treadmill testing.

The effect of sildenafil on the ischaemic threshold in men with exercise-induced angina was examined in a double-blind, parallel-group study in men with erectile dysfunction and chronic stable angina.[25] The study assessed the effect of sildenafil on the time to onset of exercise-limiting angina during incremental treadmill exercise testing. Patients received sildenafil 100mg or placebo 1 hour prior to treadmill exercise. In 56 patients receiving sildenafil the time to onset of any angina and exercise-limiting angina were significantly increased from baseline by 17.3 and 9.8%, respectively, compared with 52 patients given placebo. Exercise duration was significantly increased in the sildenafil treatment group. Blood pressure was similar after exercise in the two treatment groups, while the rate pressure product was lower in the sildenafil group at rest, during exercise and throughout the recovery period.[25]

The maximum exercise equivalent of peak sexual activity (during orgasm) is reported to be around 6 metabolic equivalents of oxygen consumption (METS). This is substantially lower to that usually achieved during exercise stress testing.[27]

Although the available information is limited, these results suggest that sildenafil is well tolerated by men with stable ischaemic heart disease.

4. Use of Sildenafil in Heart Failure

There is limited information about the safety of sildenafil in men with heart failure.

The effects of sildenafil on haemodynamics and exercise tolerance has been studied in 24 men with chronic, stable heart failure. Sildenafil, following both single-dose (50mg) and long-term (50–150mg) administration, significantly improved the results of maximal exercise testing and increased oxygen consumption at maximal exercise and during a 6-minute walk test.[28]

These results are encouraging with respect to the potential safety of sildenafil in patients with chronic stable heart failure but more information is needed before firm recommendations can be made about the safety of sildenafil in this patient group.

5. Drug Interactions

5.1 Antihypertensive Agents

Erectile dysfunction commonly occurs in association with hypertension or the use of antihypertensive medication.[1,29] Currently there are five major classes of commonly used antihypertensive agents (β-blockers, α_1-adrenoceptor antagonists, diuretics, ACE inhibitors and calcium channel antagonists). Sildenafil is associated with small additive decreases rather than large synergistic decreases in blood pressure when given to patients taking anti-

hypertensive medicines.[30] Clinical trials have indicated that sildenafil administration is well tolerated when administered in conjunction with any antihypertensive agent belonging to the classes listed above.[31,32] The frequency and severity of adverse events (including serious adverse events) when sildenafil is added to antihypertensive therapy is comparable to the addition of placebo.[4]

The results of a study of 16 men with hypertension demonstrated that the co-administration of sildenafil with amlodipine produced an additive effect on blood pressure reduction rather than a synergistic effect.[31] The lack of synergy is presumably because of the absence of an effect of amlodipine on the NO-cGMP pathway. A similar effect may be expected between sildenafil and other calcium channel antagonists.[32]

Eighteen placebo-controlled trials involving 1685 men administered one or more antihypertensive agents concluded that sildenafil was well tolerated in combination with antihypertensive therapy and was equally effective in the treatment of erectile dysfunction regardless of antihypertensive treatment.[32] The incidence of adverse events reported during sildenafil therapy was similar for patients receiving antihypertensive therapy and those receiving placebo, including events possibly related to blood pressure reduction (hypotension, dizziness, syncope) and events typically associated with the use of sildenafil (headache, flushing, dyspepsia). Sildenafil produced a small additive effect with antihypertensive drug therapy in reducing blood pressure that was similar in magnitude to the effect on blood pressure in patients not receiving antihypertensive therapy. Interesting, the greatest additive effect of sildenafil appeared to be with β-blocker therapy (figure 1). There was no increase in adverse events when sildenafil was used in patients receiving multiple antihypertensive drugs. Sildenafil administration was associated with adverse events in 38% of patients receiving placebo therapy compared with 31–36% for the five classes of antihypertensive drugs alone or in combination.[32]

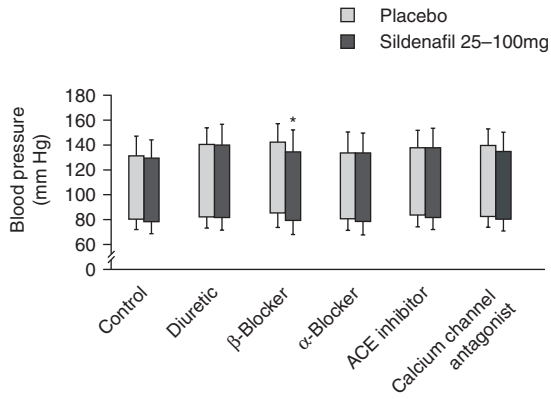

Fig. 1. The effects of sildenafil 25–100mg compared with placebo on blood pressure (BP) in men receiving antihypertensive therapy or no antihypertensive therapy (control) [n = 1685]. Columns represent mean BP after treatment, with diastolic represented by the bottom of the bar and systolic represented by the top of the column. Error bars indicate their respective standard deviations. Additive BP falls were small and only statistically significant for coadministration with β-adrenoceptor antagonists (β-blockers).[32]

5.2 Nitrates

Sildenafil interacts in a well documented, potentially life-threatening way with nitrates by producing marked hypotension.[3,33] Nitrates act as NO donors leading to increased NO availability. The combination of an increase in NO-mediated cGMP formation and a partial inhibition of cGMP catabolism by sildenafil-mediated PDE5 inhibition in vascular smooth muscle leads to marked vasodilation. The combination of sildenafil and NO-donor drugs of any form synergistically potentiates vasodilatory effects causing excessive reductions in blood pressure.[33]

In patients with chronic stable angina, a study of the effects of sildenafil administration in conjunction with either isosorbide mononitrate or sublingual nitroglycerin (glyceryl trinitrate) demonstrated mean blood pressure falls of −52/−29 and −36/−21mm Hg, respectively compared with −25/−15 and −26/−12mm Hg in patients receiving nitrates

alone.[34] An evaluation of the additive effects of sildenafil and nitrates on blood pressure in healthy male volunteers found a significantly greater occurrence of systolic blood pressure falls of greater than −25mm Hg and symptoms of hypotension with the combination compared with nitrates alone.[30]

For this reason the use of nitrates is contraindicated within 24 hours of sildenafil administration and vice versa. However, it remains uncertain precisely how soon after receiving sildenafil it is safe to permit the administration of nitrates.

Khoury and Kritharides[35] reported a possible case of an interaction between diltiazem, (a cytochrome P450 [CYP] 3A4 inhibitor), sildenafil and nitrates in a 72-year-old man undergoing coronary angioplasty. The patient was receiving regular therapy with diltiazem 30mg three times daily and was given a sublingual nitrate tablet during the procedure to resolve chest pain. It was not known that the patient had taken an unprescribed dose of sildenafil 50mg 48 hours prior to angioplasty. His blood pressure was 160/90mm Hg prior to nitrate administration and within 2 minutes fell to 90/60mm Hg. It was suggested that the clearance of sildenafil, which is metabolised by CYP3A4, was delayed by the coadministration of diltiazem allowing a significant interaction between sildenafil and nitrates at the time of angioplasty. Sildenafil is known to interact with a range of drugs that inhibit CYP3A4.[36]

Administration of sildenafil in conjunction with antihypertensives does not appear to present a safety problem, but interactions with nitrate-donor drugs remain a major concern. There are little data concerning the safety of sildenafil administration with cardiovascular drugs other than those described above.

6. Discussion

It is not unusual that cases of myocardial infarction and death have occurred in men treated with sildenafil because of the high incidence of cardiovascular disease and risk factors in men with erectile dysfunction. Analysis of the incidence rates of myocardial infarction and death for patients receiving sildenafil in clinical trials has found no evidence to support the proposition that sildenafil is associated with an increased risk of serious cardiovascular events (section 3). The rates of these events have been consistent with those expected from epidemiological data. An analysis of postmarketing data[4,5] found that no myocardial infarctions, strokes or deaths were reported during the first month of sildenafil therapy and there was no evidence of increased cardiac morbidity or mortality during the first 5 months of treatment. PDE5 inhibition with sildenafil has not been shown to adversely affect haemodynamics or worsen angina during exercise in men with severe coronary artery disease, patients with chronic stable angina receiving β-blocker therapy, or men with a history of coronary heart disease (section 4).

No clinically significant interaction between sildenafil and concomitant antihypertensive medications from the five conventionally used classes either singularly or in combination has been noted (section 6). Sildenafil provides effective therapy of erectile dysfunction regardless of coexistent antihypertensive medication without increasing the risk of adverse events or hypotension.

Potential interactions with nitrates or NO-donor drugs are the most clinically important safety issue when sildenafil is used in men with cardiovascular disease. While the interaction between nitrates and sildenafil is well known, emergency medical personnel do not always enquire about sildenafil use before commencing nitrate therapy.[37]

Guidelines for the use of sildenafil for treatment of erectile dysfunction in patients with cardiovascular disease have been prepared by a working party (The Princeton Consensus Panel) and published in the *American Journal of Cardiology*.[38] The guidelines recommend classifying patients as

either at low, intermediate or high risk. Those considered to be low risk are patients with: controlled hypertension; mild, stable angina; successful coronary revascularisation; a history of uncomplicated myocardial infarction; mild valvular disease; or less than three cardiovascular risk factors and no symptoms. Those at intermediate risk are patients with: moderate angina; a myocardial infarct within the preceding 6 weeks; left ventricular dysfunction or New York Heart Association Class II heart failure; non-sustained low-risk arrhythmias; or three or more risk factors for coronary disease. Patients considered to be high risk include those with: unstable refractory angina; uncontrolled hypertension; very recent myocardial infarction (<2 weeks previously); high-risk arrhythmias; obstructive cardiomyopathy; or moderate to severe valvular disease. Patients at low risk are considered to be suitable for sildenafil therapy, while stabilisation and/or improvement of those at high risk is recommended before sildenafil therapy is considered. It is suggested that patients at intermediate risk should have specialised cardiovascular assessment and reclassification as either high or low risk made prior to further decisions concerning the use of sildenafil.

Despite the emerging evidence for a good safety profile for sildenafil in patients with cardiovascular disease, there is no significant experience concerning its safety in patients who have recently had an acute coronary event, arrhythmia or cerebrovascular event or undergone coronary artery revascularisation, or patients with decompensated heart failure or uncontrolled hypertension. Further experience is required in patients at higher risk of cardiovascular events.

As with any new drug with cardiovascular effects, there has been an appropriate emphasis on precautionary measures associated with the use of sildenafil in patients with cardiovascular disease. The evidence now available suggests that sildenafil has a generally good safety profile in these patients provided the usual precautions and advice concerning sexual activity and the use of nitrates is adhered to.

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