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Clinical safety of oral sildenafil citrate (VIAGRA™) in the treatment of erectile dysfunction

A Morales[1], C Gingell[2], M Collins[3], PA Wicker[4] and IH Osterloh[3]

[1]*Department of Urology, Queen's University, Kingston General Hospital, Kingston, Ontario, Canada;* [2]*Urology Department, Southmead Hospital, Bristol, UK;* [3]*Pfizer Central Research, Sandwich, UK; and* [4]*Pfizer Central Research, Groton, Connecticut, USA*

Sildenafil citrate has been shown to be effective in a wide range of patients with erectile dysfunction and has been approved in the United States for this indication. The overall clinical safety of oral sildenafil, a potent inhibitor of phosphodiesterase type 5, in the treatment of erectile dysfunction was evaluated in more than 3700 patients (with a total of 1631 years of exposure worldwide). Safety and tolerability data were analysed from a series of double-blind, placebo-controlled studies and from 10 open-label extension studies of sildenafil in the treatment of erectile dysfunction. A total of 4274 patients (2722 sildenafil, 1552 placebo; age range 19–87 y) received double-blind treatment over a period of up to six months' duration, and 2199 received long-term, open-label sildenafil for up to 1 y. The most commonly reported adverse events (all causes) were headache (16% sildenafil, 4% placebo), flushing (10% sildenafil, 1% placebo), and dyspepsia (7% sildenafil, 2% placebo) and they were predominantly transient and mild or moderate in nature. These adverse events reflect the pharmacology of sildenafil as a phosphodiesterase type 5 inhibitor. No cases of priapism were reported. The rate of discontinuation due to adverse events (all causes) was comparable for patients treated with sildenafil (2.5%) and placebo (2.3%). In open-label extension studies, 90% of patients completed long-term sildenafil treatment, with only 2% withdrawing due to adverse events. Sildenafil is a well-tolerated oral treatment for erectile dysfunction.

Keywords: erectile dysfunction; sildenafil; phosphodiesterase type 5 inhibitor; safety

Introduction

Sildenafil, an oral agent which has proven effective for the treatment of erectile dysfunction (ED), enables a natural erectile response to sexual stimulation by enhancing the relaxant effect of nitric oxide (NO) on the corpus cavernosum.[1,2] Normal penile erection involves the release of NO from nonadrenergic-noncholinergic nerves and endothelial cells of the cavernosal bodies.[3–5] NO activates guanylate cyclase, resulting in increased synthesis of cyclic guanosine monophosphate (cGMP), which induces corpus cavernosal smooth muscle relaxation, increased blood flow to the penis, increased intracavernosal pressure, and penile erection.[4–6] Sildenafil is a potent inhibitor of cGMP-specific phosphodiesterase (PDE) type 5, which is the predominant PDE isozyme responsible for the degradation of cGMP in the corpus cavernosum.[3,7] When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE type 5 by sildenafil causes increased concentrations of cGMP in the corpus cavernosum. Sexual stimulation is required for sildenafil to produce its beneficial pharmacological effects on erectile function.

For most patients, the recommended dosing regimen for sildenafil is 50 mg taken, as needed, approximately 1 h before sexual activity. However, sildenafil may be taken from 0.5 h–4 h before sexual activity. Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg. The maximum recommended dosing frequency is once per day. Sildenafil is rapidly absorbed, with maximum observed plasma concentrations reached within 30–120 min (median 60 min) in the fasted state. The terminal phase half-life of sildenafil is 3–5 h.[7]

Sildenafil has been shown to be efficacious in the treatment of ED of various aetiologies.[8] A series of 21 double-blind, placebo-controlled studies evaluated the overall safety and tolerability of sildenafil. Three

Correspondence: Dr A Morales, Department of Urology, Kingston General Hospital, Victory 4, Kingston, Ontario K7L2V7, Canada.
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others, thereby preventing their inclusion in the pooling of the safety data. This article describes the data from the remaining 18 double-blind, placebo-controlled studies and 10 long-term, open-label studies in which sildenafil was administered to more than 3700 patients (with a total of 1631 years of exposure worldwide).

Methods

Safety and toleration data were analysed from 18 out of 21 randomised, double-blind, placebo-controlled (Phase II/III) studies of sildenafil (with 2355 patients receiving doses of 25 mg–100 mg) and 10 long-term, open-label studies of sildenafil in the treatment of ED of a variety of aetiologies (namely, organic, psychogenic, or mixed organic/psychogenic). In the 18 placebo-controlled studies, a total of 4274 patients (2722 sildenafil, 1552 placebo; age range 18–87 y) with ED (mean duration 5 y) received double-blind treatment of up to six months' duration. The 18 placebo-controlled studies had various designs (Table 1), and included fixed-dose and flexible-dose regimens. The fixed-dose studies assessed efficacy, safety, and tolerability by dose, and the flexible-dose studies assessed these endpoints in dosing situations that most closely resemble those used in clinical practice. Patients were aged 18 y or older with broad-spectrum ED of more than six months' duration, including those with concomitant disease, such as diabetes, hypertension, and depression, and those who had previous prostate surgery. The main exclusion criteria were penile anatomical deformities, treatment with nitrates or anticoagulants, and any significant concomitant medical condition that would impair the patient's ability to participate. Eighty-six percent (2340 out of 2722) of the patients treated with sildenafil took the drug on an as needed basis (PRN). However, patients were instructed not to take more than one dose daily. A total of 2199 patients received long-term, open-label sildenafil treatment for up to 1 y, including 1430 who had received double-blind sildenafil and 769 who had received double-blind placebo. Nitrate therapy was excluded in all of these studies since sildenafil potentiates the hypotensive effects of nitrates. The safety database for these 28 studies totalled 1631 y of sildenafil exposure.

In all studies evaluated for this analysis, investigators recorded the occurrence of observed and patient-reported adverse events throughout the course of treatment. The nature of the adverse events (mild, moderate, or severe) and their outcome were also recorded. Investigators were asked to classify the relationship of the adverse event to the study drug as definitely related, uncertain, or not related. In all studies, a treatment-related adverse event was defined as any event classified as definitely related or of uncertain relation to the study drug. This classification was also used when relationship data were missing. Serious adverse events included any event that suggested a significant hazard, such as those that were fatal, life-threatening, permanently disabling, requiring hospitalisation, or that involved cancer, a congenital anomaly, or a drug overdose. Laboratory tests and blood pressure measurements were conducted at the screening visit, at regular intervals during study drug administration, and at the end of each study (final visit). In two of the placebo-controlled studies, electrocardiogram (ECG) recordings were obtained within 24 h of dosing.

Results

Adverse events

In PRN flexible-dose, placebo-controlled studies, which reflect drug usage in clinical practice, the most commonly recorded adverse events of all causes reported by patients receiving sildenafil were headache (16%), flushing (10%), and dyspepsia (7%) (Table 2). Nasal congestion, abnormal vision, diarrhoea, dizziness, and rash were also reported. The incidences of the most commonly recorded adverse events of all causes were higher in patients receiving sildenafil than in those receiving placebo.

Table 1 Number of patients treated in Phase II/III studies

	Number of patients	
Studies (*number*)	*Sildenafil*	*Placebo*
Phase II/III placebo-controlled (18 of 21)[a]	2722	1552
PRN dosing[b] (11)	2340	1332
Flexible dosing (6)	734	725
Fixed dosing (5)	1606	607
Phase II/III open-label extension (10)	2199	—

[a]Three studies are of different designs and are not included in the analysis.

Table 2 Adverse events of all causes reported by ≥2% of patients treated with sildenafil or placebo in PRN flexible-dose, placebo-controlled studies

	Percentage of patients reporting event[a]	
Adverse event	*Sildenafil (n = 734)* %	*Placebo (n = 725)* %
Headache	16	4
Flushing	10	1
Dyspepsia	7	2
Nasal congestion	4	2
Urinary tract infection	3	2
Abnormal vision[b]	3	0
Diarrhoea	3	1
Dizziness	2	1
Rash	2	1

[a]Other adverse events (respiratory tract infection, back pain, flu syndrome, and arthralgia) occurred at a rate of ≥2%, but were equally common with placebo.
[b]Abnormal vision: mild and transient, predominantly colour tinge to vision, but also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision.

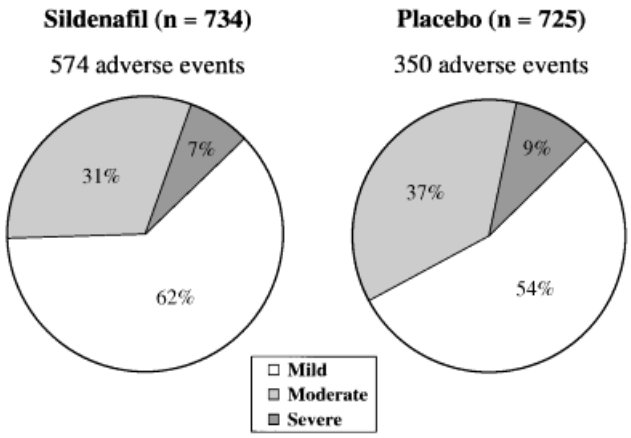

Figure 1 Severity of adverse events of all causes for patients treated with sildenafil or placebo in PRN flexible-dose, placebo-controlled studies.

Adverse events were predominantly transient and mild or moderate in nature (Figure 1), with approximately two-thirds of all reports classified as mild.

The overall rate of discontinuation from treatment due to adverse events of all causes in PRN flexible-dose, placebo-controlled studies was comparable for patients in the sildenafil (2.5%) and placebo (2.3%) treatment groups. Headache (1.1%), flushing (0.4%), and nausea (0.4%) were the most common adverse events of all causes leading to discontinuation for patients receiving sildenafil. Only one patient in 2722 subjects treated with sildenafil discontinued treatment due to abnormal vision. Headache (0.4%) was the most common adverse event (all causes) leading to discontinuation

In PRN fixed-dose, placebo-controlled studies, the majority of the adverse events were also mild or moderate and self-limiting in nature for both patients receiving sildenafil and those receiving placebo. In PRN fixed-dose studies, the overall incidence of treatment-related adverse events and the incidences of the most commonly reported treatment-related adverse events (headache, flushing, dyspepsia, nasal congestion, abnormal vision, and dizziness) increased as the dose of sildenafil increased. The incidences of dyspepsia (17%) and abnormal vision (11%) were higher at 100 mg than at the lower doses of sildenafil in fixed-dose studies. The most common description of abnormal vision was a mild and transient colour tinge to vision. The overall nature of adverse events was similar to that observed in the PRN flexible-dose studies. The rates of discontinuation from treatment due to treatment-related adverse events were comparable at 25 mg (0.6%) and 50 mg (0.4%) of sildenafil and then increased at the 100 mg dose (1.2%); the corresponding rate for the placebo group was 1.0%. The most frequent adverse event causing discontinuation was headache in the fixed-dose studies (0.6% in the 100 mg sildenafil group).

In the 10 long-term, open-label studies, 2199 patients received sildenafil. The majority of adverse events of all causes reported during these open-label studies were mild or moderate in nature, with the most common being headache (10%), flushing (9%), dyspepsia (6%), and respiratory tract infection (6%). The overall incidence of abnormal vision in open-label extension studies was low (2%), with no long-term visual sequelae reported. The incidence and nature of the visual adverse events were similar in diabetic and nondiabetic patients. Only 10% of patients enrolled discontinued treatment prior to the end of the study for reasons that included loss to follow up, protocol violation, lack of efficacy, and adverse events. Adverse events of all causes accounted for 2% of the withdrawals over a 1 y period and lack of efficacy 4%. Headache was the most common adverse event (all causes) leading to discontinuation of treatment.

No cases of priapism were reported in any of the sildenafil studies.

Additional topics

PDE type 5 occurs in the systemic vasculature and as such the incidence of cardiovascular events following sildenafil therapy was of interest. In the 18 placebo-controlled studies, the incidence of cardiovascular adverse events other than flushing (described above) was 3.0% with sildenafil and 3.5% with placebo. Overall, 79% of all cardiovascular adverse events were mild, 16% were moderate, and

Table 3 Incidence of serious cardiovascular adverse events and myocardial infarction in patients treated with sildenafil or placebo in Phase II/III studies

	Incidence (95% *CI*) [a]	
Studies	*Sildenafil*	*Placebo*
Phase II/III placebo-controlled		
Serious cardiovascular events[b]	4.1 (2.7–5.5)	5.7 (3.3–8.2)
Myocardial infarction	1.7 (0.8–2.6)	1.4 (0.2–2.6)
Phase II/III open-label extension		
Serious cardiovascular events[b]	3.5 (2.3–4.7)	—
Myocardial infarction	1.0 (0.3–1.6)	—

[a]Incidence is expressed as rate per 100 man-years of treatment. CI denotes confidence interval.
[b]Serious cardiovascular events include myocardial infarction, angina, and coronary artery disorder.

similar pattern for placebo. The rate of discontinuation of treatment due to cardiovascular adverse events was low and comparable for patients receiving sildenafil (0.9%) and those receiving placebo (0.9%) in the 18 placebo-controlled studies.

Of the 2722 patients receiving sildenafil in the 18 placebo-controlled studies, 885 (33%) were also taking antihypertensive medications. The tolerability of sildenafil treatment was comparable for patients taking antihypertensive medications and those not taking these medications.

The incidence rate (per 100 man-years of treatment) of serious cardiovascular adverse events was comparable for patients who received sildenafil in placebo-controlled studies (4.1; 95% CI 2.6–5.5), patients who received sildenafil in open-label extension studies (3.5; 95% CI 2.3–4.7), and patients who received placebo (5.7; 95% CI 3.3–8.2) (Table 3). The rate of myocardial infarction was 1.7 per 100 man-years of treatment (95% CI 0.8–2.6) for patients treated with sildenafil in placebo-controlled studies compared with 1.4 per 100 man-years (95% CI 0.2–2.6) for those receiving placebo, and 1.0 per 100 man-years (95% CI 0.3–1.6) for patients taking sildenafil in open-label extension studies. There were no serious adverse events of any type judged to be related to sildenafil treatment.

Pooled data from the 18 placebo-controlled studies indicated no change from baseline in the median value for systolic blood pressure, diastolic blood pressure, or heart rate for either the sildenafil group ($n = 2146$) or the placebo group ($n = 1133$).

There was no evidence of sildenafil-induced abnormalities in either ECG parameters or laboratory test measurements.

Discussion

Treatment with oral sildenafil was well tolerated, with no serious safety concerns identified. Consistent with its known effects on the NO/cGMP pathway, sildenafil potentiates the hypotensive effects of nitrates. Patients taking organic nitrates were excluded from all 28 studies of sildenafil reported in this article. In man, basal NO plays an important role in the regulation of blood pressure via its arterial vasodilator effect.[9,10] Sildenafil was well tolerated when administered alone or in combination with conventional antihypertensive agents. However, in Phase I studies in the presence of exogenously administered NO (namely, nitrates or NO donors), sildenafil administration was associated with clinically significant decreases in blood pressure. Therefore, administration of sildenafil in patients who are concurrently using organic nitrates in any form is contraindicated.

The 28 studies reported included more than 3700 patients who received sildenafil and 1631 total years of sildenafil exposure worldwide. The PRN flexible-dose studies provide safety information in a situation resembling dosing patterns in clinical practice, the PRN fixed-dose studies provide insights on the safety of sildenafil by dose, and the open-label extension studies provide data on the long-term safety of sildenafil. Overall, the adverse events reported were transient, mild-to-moderate in nature, and rarely resulted in discontinuation of treatment. Safety data from the three double-blind, placebo-controlled studies not included in this analysis because of design differences were consistent with those reported here. No case of priapism was reported in any of the sildenafil studies.

The overall rate of discontinuation of treatment due to adverse events was low and comparable for patients receiving sildenafil at the recommended doses (25 mg–100 mg) and those receiving placebo in double-blind studies. In open-label extension studies, 90% of the patients enrolled completed long-term sildenafil therapy and only 2% withdrew due to adverse events of any cause. Sildenafil did not result in increased rates of myocardial infarction or other serious cardiovascular events during either short-term or long-term treatment. In fact, there were no serious adverse events related to sildenafil in the studies reported here. Furthermore, a study in which sildenafil was administered as needed for 16 weeks and then withdrawn demonstrated that there are no adverse effects associated with treatment withdrawal.[11]

The majority of the adverse events associated with sildenafil treatment are related to vasodilation (including headache, flushing, and nasal congestion), gastrointestinal events (dyspepsia), and visual effects (abnormal vision). All of these adverse events reflect the known pharmacological properties of sildenafil and, as would be expected, increase in incidence with increasing dose. Phase I studies showed that sildenafil has modest peripheral vasodilator properties, which can account for the occurrence of headache and flushing in some

hyperemia of the nasal mucosa, since PDE type 5 is located in the blood vessels of this tissue. The adverse events associated with vasodilation were generally mild or moderate in nature and rarely were a reason for discontinuation of treatment. In preclinical studies, sildenafil was shown to relax the isolated lower esophageal sphincter of dogs, indicating that PDE type 5 may have a role in maintaining the integrity of the gastro-esophageal junction. When characterised in clinical trials, the dyspepsia reported with sildenafil treatment was usually described as an occasional burning sensation in the epigastrium, suggesting that esophageal reflux may be the cause, as would be anticipated from the preclinical pharmacology. Although dose-related, the dyspepsia associated with sildenafil treatment was predominantly mild or moderate in nature. Preclinical studies also indicated that PDE type 6 of the retina plays an important role in the visual transduction pathway. Sildenafil demonstrates a 10-fold selectivity for human PDE type 5 over PDE type 6.[2] In studies in dogs, sildenafil produces a dose-related reversible effect on hyperpolarization of retinal tissue in response to light, consistent with the inhibition of retinal PDE type 6. Long-term safety studies with a specific emphasis on ocular safety conducted in rats, dogs, and mice have not revealed any functional or morphological changes in the retina and optical pathways. Clinical pharmacology studies demonstrated that the only acute effect of sildenafil was a mild, transient change in colour discrimination in the blue-green range in some subjects. Sildenafil had no effect on other objective measures of visual function, including visual acuity, contrast sensitivity, intraocular pressure, Amsler Grid, visual fields, and recovery from a photostress test. For patients in the placebo-controlled and open-label extension studies, abnormal vision (usually described as a transient colour tinge to vision) was generally mild-to-moderate in nature and resulted in only one case of treatment discontinuation at doses within the recommended range. In one study in which visual effects were studied intensively in a small number of patients over a 1 y period, no significant change in any visual parameter was noted.

Conclusions

Sildenafil is a well-tolerated oral treatment for ED; its efficacy, excellent safety profile, lack of significant adverse events, convenient oral administration, and low rates of discontinuation from treatment suggest that sildenafil may be a valuable agent for the management of patients with ED.

Acknowledgment

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Editorial comment

Clinical safety of oral sildenafil citrate (VIAGRA™) in the treatment of erectile dysfunction—by Morales *et al*

This study clearly demonstrates that sildenafil is a safe drug and that it will probably gain wide acceptance in the population of male patients

I think that in the near future every physician (from the family doctor to the specialist) must be ready to face a potentially over-

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