Sildenafil: Study of a Novel Oral Treatment for Erectile Dysfunction in Diabetic Men

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The efficacy and safety of oral sildenafil, a potent inhibitor of phosphodiesterase type 5, were evaluated in men with diabetes mellitus and erectile dysfunction (ED). Twenty-one men (aged 42–65 years) were enrolled in a double-blind, placebo-controlled, three-way crossover study conducted in two parts. In part I, the effect of a single dose (25 mg or 50 mg) of sildenafil or placebo on penile rigidity was assessed by penile plethysmography during visual sexual stimulation. In part II, daily diary records of erectile activity and a global efficacy question were used to evaluate once-daily dosing with 25 mg or 50 mg of sildenafil or placebo for 10 days. After a single 50 mg dose of sildenafil, the adjusted geometric mean duration (min) of penile rigidity >60 % at the base of the penis during visual sexual stimulation was significantly increased (10.1 min) compared with placebo (2.8 min; $p = 0.0053$). In part II, sildenafil significantly increased the number of erections considered sufficiently hard for vaginal penetration compared with placebo ($p = 0.0005$). Improved erections were reported by 50 % and 52 % of patients treated with 25 mg and 50 mg of sildenafil, respectively, compared with 10 % of those receiving placebo (p values < 0.05). Adverse events were mostly mild or moderate in nature and included muscular pains, headache, and dyspepsia. Sildenafil is a well-tolerated and potentially efficacious oral treatment for ED in men with diabetes mellitus. © 1998 John Wiley & Sons, Ltd.

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Introduction

Erectile dysfunction (ED) is a common complication of diabetes mellitus, with an estimated prevalence of greater than 30 %,[1] ranging from 15 % at age 30 to 34 years to 55 % at age 60 years.[2] The onset of ED occurs earlier in diabetic men than in men in the general population.[3,4] Various treatment options are available, most notably the use of external vacuum devices,[5] intracavernous self-injection of vasoactive agents,[6] and transurethral insertion of prostaglandin E_1;[7] while these treatments can be effective, they are not ideal.[8] An efficacious oral agent would extend patient options in the treatment of ED associated with diabetes.

Normal penile erection is a haemodynamic event involving relaxation of smooth muscles of the corpus cavernosum and associated arterioles that is mediated by a nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) mechanism.[9] In response to sexual stimulation, locally released NO stimulates the production of cGMP by guanylate cyclase. In turn, cGMP stimulates smooth muscle relaxation and penile erection. Sildenafil (VIAGRA™) is a potent inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5), the predominant PDE degrading cGMP in the corpus cavernosum.[10] By its inhibition of PDE5, sildenafil has the potential to enhance erectile activity under conditions of sexual stimulation. Indeed, sildenafil has been demonstrated to be an effective oral therapy in men with ED of no established organic cause[11] and in those with ED of organic, psychogenic, or mixed aetiology.[12]

In the present study, we assessed the efficacy and safety of 25 mg or 50 mg of sildenafil taken as a single dose, followed by once daily dosing for 10 days in diabetic men with ED.

Patients and Methods

Men aged 18 to 70 years with a history of diabetes mellitus Type 1 or 2 of 5 years or more and with ED (defined as the inability to achieve and/or maintain erections for satisfactory sexual activity) of at least 6 months' duration were eligible for the study. A diagnosis of ED was made based on the medical history, a

Abbreviations: cGMP cyclic guanosine monophosphate, ED erectile dysfunction, NO nitric oxide.

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physical examination, standard laboratory tests, and other diagnostic procedures performed prior to the study, including nocturnal penile tumescence testing, an intracavernosal injection test, penile duplex ultrasonography, and endocrine testing. Not all diagnostic procedures were conducted in each patient. Exclusion criteria included: clinically significant ischaemic heart disease or peripheral vascular disease; treatment with antidepressants/tranquillizers, nitrates, anticoagulants, or salicylates in the 2 weeks prior to the study; history of a bleeding disorder; severe untreated proliferative diabetic retinopathy. No additional treatments for ED were allowed 2 weeks prior to dosing or throughout the course of the study. Twenty-one diabetic men (Type 1: $n = 7$; Type 2: $n = 14$) were enrolled in the study after giving written informed consent. The mean age of the men was 51 (range 42–65) years. The mean duration of diabetes was 11 (range 3–32) years, and the median duration of ED was 3 (range 1–14) years. Six men had evidence of peripheral or autonomic (abnormal cardiovascular function tests) neuropathy.

The study was a two-centre, randomized, double-blind, three-way crossover trial and was approved by the local ethics committees. Each of the three treatment periods consisted of two parts. In part I, the effect of a single dose of sildenafil or placebo on penile rigidity during visual sexual stimulation was assessed in the clinic using penile plethysmography (RigiScan®, Dacomed Corporation, Minneapolis, Minnesota, USA). Patients were evaluated in a quiet, private room on an unoccupied hospital ward. After a physical examination was performed, penile plethysmography was used to measure rigidity at the base of the penis and at the tip of the penis below the glans. After 15 min of continuous recording, a single dose of sildenafil (25 mg or 50 mg) or placebo was administered. Using videos and magazines, visual sexual stimulation commenced 30 min after dosing and continued for 90 min. The duration (min) of penile rigidity >60 % was monitored; this level of rigidity is sufficient for sexual intercourse.[13] In part II, which started the day after completion of part I, daily diary records and a patient global efficacy question were used to evaluate the effect of once-daily dosing with 25 mg or 50 mg of sildenafil or placebo in the home setting over a period of 10 days. In part II, study drug was taken each day approximately 30 to 6 min prior to the usual time for sexual activity, regardless of whether sexual activity was planned. The patients self-administered sildenafil (25 mg or 50 mg) or placebo once daily for 10 days. There was a washout period of 3–10 days at each crossover stage in part II. Patients maintained a daily diary of erectile activity, evaluating the quality of their erections on a grading scale of 1–4 (Table 1). At the end of each treatment period, each patient answered a global efficacy question: did the quality of your erections improve during the 10 days you took the treatment? Laboratory safety tests and physical examinations, including measurements of blood pressure and heart rate, were performed prior and subsequent to dosing in each treatment period and at the follow-up visit. All adverse events that occurred during the study or within 7 days of the end of treatment were recorded and classified by severity (mild, moderate, or severe). In addition, any adverse event that the investigator considered to be serious (defined as any event that is fatal or life-threatening, results in permanent disability, requires hospitalization, or involves cancer, a congenital anomaly, or drug overdose) was reported immediately.

Table 1. Classification system for self-grading erections

Grade 1	Increase in size but not hard
Grade 2	Hard, but not hard enough for vaginal penetration
Grade 3	Hard enough for vaginal penetration (but not completely hard)
Grade 4	Completely hard

From RigiScan recordings in part I, only erections that started after dosing were included in calculations of duration. The duration of erections with >60 % rigidity was calculated by summing the number of minutes that a patient had an erection of >60 % rigidity for all post-dose erections for that treatment period. These data were transformed logarithmically since they were not normally distributed. The transformed variables were analysed using analysis of variance (ANOVA), which included terms for centre, patient, type of RigiScan machine, and treatment. The mean values, adjusted for the terms of the ANOVA model, and 95 % confidence intervals (CI) were back transformed to give geometric means and corresponding 95 % CI. Comparisons were made between each dose of sildenafil and placebo. For part II of the study, the number of grade 3 or 4 erections per week was calculated using the data from patient diaries. The total number of grade 3 or 4 erections occurring within 24 h post-dose was multiplied by 7 and divided by the number of doses taken. The association between each dose of sildenafil and placebo was analysed using ANOVA. The responses to the global efficacy question were analysed using the non-parametric Mainland–Gart method.[14]

Results

Of the 21 men randomized in this two-centre study, all completed treatment with placebo and 50 mg of sildenafil and 20 completed treatment with 25 mg sildenafil. One man was hospitalized with pneumococcal pneumonia and withdrew before completing the study. Safety data were analysed for all 21 men following all three treatments.

As shown in Figure 1, after a single dose of sildenafil, the adjusted geometric mean (95 % CI) duration (min) of penile rigidity >60 % at the base of the penis during visual sexual stimulation was significantly increased with 50 mg of sildenafil compared with placebo (25 mg

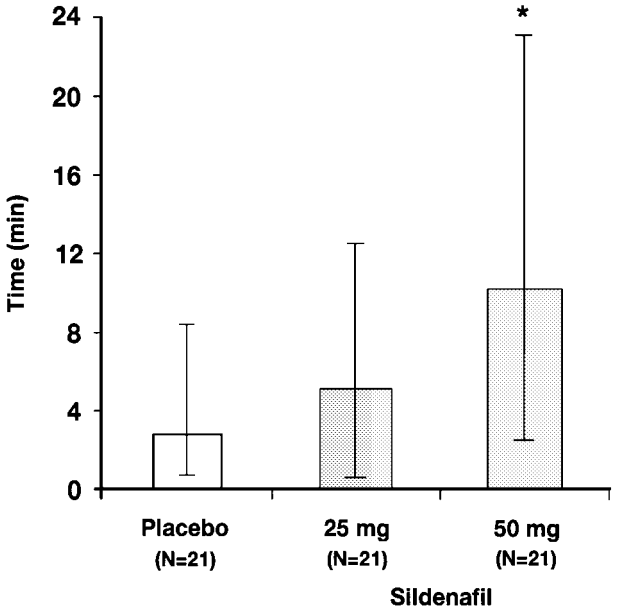

Figure 1. Duration (min) of penile rigidity >60 % at the base of the penis during visual sexual stimulation. Bars and vertical lines represent the adjusted geometric mean and 95 % CI. *Denotes $p = 0.0053$ for the comparison with placebo

sildenafil: 5.0 (1.9–12.4); 50 mg sildenafil: 10.1 (4.2–23.1, $p = 0.0053$ versus placebo) and placebo: 2.8 (0.7–8.4)). At the tip of the penis (Figure 2), the adjusted geometric mean (95 % CI) duration (min) of rigidity >60 % was 1.2 (0.2–3.8) for 25 mg of sildenafil, 2.2 (0.7–6.0) for 50 mg of sildenafil ($p = 0.0126$ versus placebo), and 0.4 (–0.2–2.1) for placebo.

In the home setting (part II), both 25 mg and 50 mg doses of sildenafil significantly increased the total number of erections hard enough for sexual intercourse (i.e. grade 3 or 4) compared with placebo. The greatest number of grade 3 or 4 erections occurred within 1 h of dosing (data not shown). The individual responses to treatment over 10 days, together with the mean number of grade 3 or grade 4 erections per week, are shown in Figure 3. The mean numbers of erections (95 % CI) sufficiently rigid for sexual intercourse (i.e. grade 3 or 4) per week were 1.3 (0.9–1.8, $p = 0.0025$) for patients taking 25 mg of sildenafil and 1.6 (1.1–2.1, $p = 0.0002$) for patients taking 50 mg of sildenafil compared with 0.6 (0.4–0.9) for placebo-treated patients. Seven men had no discernible erectile activity with daily administration of 25 mg or 50 mg of sildenafil. Four patients had erections in response to one dose but not the other dose of sildenafil.

At the end of 10 days of treatment, a significantly greater percentage of patients reported improvement in their erections with daily administration of sildenafil. Of the 20 patients who completed treatment with both placebo and 25 mg of sildenafil, 10 patients (50 %) reported that their erections were improved on 25 mg of sildenafil compared with two patients (10 %) on placebo ($p = 0.048$). Of these 20 patients, nine reported improvement on sildenafil but not placebo, one on placebo but not sildenafil, and one on both sildenafil and placebo. After treatment with placebo and 50 mg of sildenafil, 11 of 21 patients (52 %) recorded improvement in the quality of their erections on 50 mg of sildenafil compared with two patients (10%) on placebo ($p = 0.028$). Of these 21 patients, nine reported improvement on sildenafil but not placebo and two on both sildenafil and placebo.

Treatment with sildenafil was well tolerated. The most frequent adverse events were headache, diarrhoea, nausea, and myalgia, with the majority of these considered to be related to the study drug. The number of

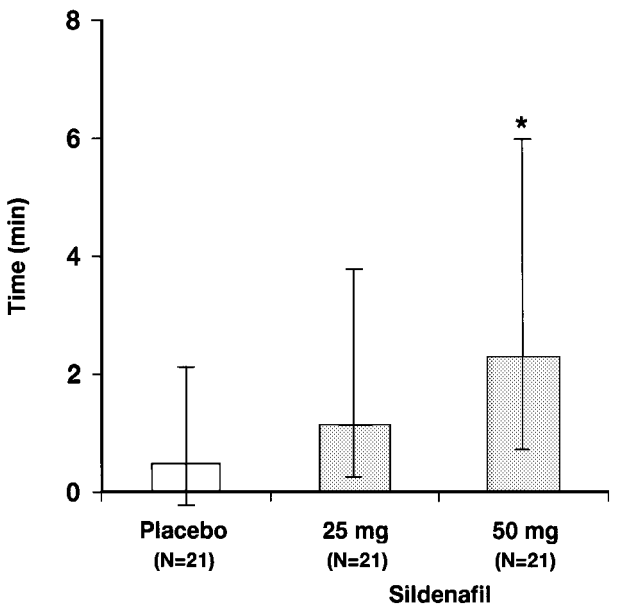

Figure 2. Duration (min) of penile rigidity >60 % at the tip of the penis during visual sexual stimulation. Bars and vertical lines represent the adjusted geometric mean and 95 % CI. *Denotes $p = 0.0126$ for the comparison with placebo

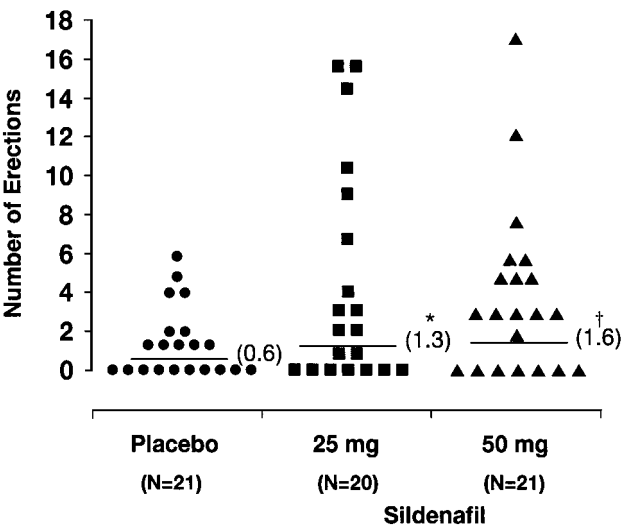

Figure 3. Number of erections sufficiently rigid for sexual intercourse (grade 3 or 4) over 10 days. Values in parentheses represent the adjusted geometric mean number of erections per week. *Denotes $p = 0.0025$ for the comparison with placebo; †denotes $p = 0.0002$ for the comparison with placebo

treatment-related adverse events are listed in Table 2. Adverse events were mostly mild or moderate in nature; nine adverse events of a severe nature were reported (25 mg of sildenafil: three events (diarrhoea, myalgia, and chest pain); 50 mg of sildenafil: five events (back pain, myalgia, diarrhoea, headache, and dyspepsia); and placebo: one event (diarrhoea)), with six of these events considered treatment-related. There were no serious adverse events that were judged to be related to treatment. Treatment with sildenafil did not result in any clinically significant changes in laboratory test results.

Discussion

ED is a common problem in diabetic men of all ages, affecting more than one-third of the population even in the absence of other complications.[1] Diabetes-associated ED is probably multifactorial, with underlying abnormalities of the autonomic nerves and vasculature and psychogenic factors all able to contribute to dysfunction. Diabetes impairs both neurogenic and endothelium-mediated relaxation of penile smooth muscle.[15] Moreover, high levels of advanced glycosylation end-products have been shown to affect NO-mediated relaxation of rabbit and human corporal tissue adversely.[16]

Currently available treatments for ED have a number of disadvantages, including need for needles, rejection of external devices by younger patients and, in the case of available oral remedies, either lack of rigor in establishing effectiveness or limited efficacy.[17] While novel treatments currently being evaluated include topical vasodilators,[18] it is clear that an effective oral treatment for ED that works only during sexual stimulation would represent a convenient and attractive alternative therapy. Recent advances in the understanding of the mechanisms underlying the physiology of penile erection and pathophysiology of ED highlight the role of NO-induced cGMP production in corporal smooth muscle relaxation.[9] Sildenafil, which inhibits the breakdown of the cGMP in the corpus cavernosum, enhances the effect of NO, thereby improving erectile function in patients with ED. Sildenafil at doses of 25–100 mg as needed has been shown significantly to improve erectile function in patients with ED of organic, psychogenic or mixed aetiology.[12] Sildenafil, at the recommended doses of 25–100 mg, as needed, approximately 1 h before sexual activity, but not more than once daily, has received approval for the treatment of ED in the United States; licensing in other countries is pending.

Table 2. Number of treatment-related adverse events

Adverse event	Placebo	Sildenafil	
		25 mg	50 mg
Headache	0	2	2
Myalgia	2	2	1
Nausea	1	2	0
Dyspepsia	0	2	3

The results of the present pilot study demonstrate that daily dosing with 25 mg or 50 mg of sildenafil is an effective oral therapy for ED in many men with diabetes. Sildenafil appears to enhance penile erectile activity only under conditions of sexual stimulation and is not associated with priapism. In this study, seven patients demonstrated no erectile activity with daily administration of 25 mg or 50 mg of sildenafil. It is not immediately clear why these subjects were unresponsive. These patients may require a higher (100 mg) dose of sildenafil. This was not explored in this study; however, 100 mg doses of sildenafil have been used in other studies and are generally well tolerated.[12] Further studies are required to examine whether certain factors (e.g. diabetes type, ED aetiology, diabetes aetiology) may predict which diabetic men will respond to sildenafil.

In general, daily dosing with sildenafil was well tolerated. The side effects of treatment were mostly mild or moderate in nature and included dyspepsia, headache, and muscular pain. No subjects withdrew from the study because of treatment-related adverse events.

In conclusion, sildenafil is a well-tolerated and efficacious oral agent that shows promise in the treatment of ED in men with diabetes.

Acknowledgements

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