

Acute and Prolonged Effects of Sildenafil on Brachial Artery Flow-Mediated Dilatation in Type 2 Diabetes

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OBJECTIVE — Flow-mediated dilatation (FMD), induced by occlusion of the brachial artery, is an index of nitric oxide-dependent endothelial function that is impaired in patients with type 2 diabetes. Sildenafil (Viagra) is an inhibitor of phosphodiesterase 5 (PDE-5), which is used for management of erectile dysfunction in a broad range of patients, including those with type 2 diabetes. Its effects on endothelial function in these patients have not been previously assessed.

RESEARCH DESIGN AND METHODS — We assessed the acute and prolonged effects of a low dose of sildenafil (25 mg) on FMD in patients with type 2 diabetes. We performed a double-blind, placebo-controlled cross-over trial in 16 patients (14 of whom completed the study) with type 2 diabetes who had erectile dysfunction without overt clinical heart disease.

RESULTS — In these patients, the mean \pm SD brachial artery diameter (BAD) measured by ultrasound was 4.33 ± 0.6 mm. After inducing FMD, the BAD increased 8% to 4.66 ± 0.6 mm ($P = 0.2$). One hour after oral administration of sildenafil 25 mg, FMD increased the BAD significantly by $15\% \pm 4.99 \pm 0.5$ mm ($P \leq 0.01$), whereas it did not change with placebo (4.6 ± 0.6 mm, $P = 0.1$). After treatment with sildenafil 25 mg daily for 2 weeks and testing 24 h after the last dose, the mean FMD was 14% ($P = 0.01$). In contrast, the mean FMD with placebo was 9% ($P = 0.45$).

CONCLUSIONS — We conclude that acute and prolonged sildenafil treatment has a favorable effect on brachial artery flow-mediated dilatation that persists for at least 24 h after the last dose. Further investigation is needed to determine whether this prolonged effect has clinical implications in patients with type 2 diabetes.

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Erectile dysfunction is common in men with diabetes and is often associated with vascular disease. Endothelial dysfunction is an important abnormality that contributes to erectile dysfunction and vascular disease in diabetes (1,2) and is associated with insulin resistance (3).

Nitric oxide released by vascular endothelial cells induces smooth muscle cell

relaxation and inhibits vascular smooth muscle proliferation. Nitric oxide exerts many of its effects by activation of soluble guanylate cyclase, resulting in increased production of cyclic guanosine monophosphate (cGMP), which results in lower intracellular calcium levels and, therefore, vasodilatation (4). Nitric oxide production and action is abnormal in patients with type 2 diabetes (5,6).

Phosphodiesterases (PDEs) are a family of enzymes present in a variety of tissues, including vascular smooth muscle, that are responsible for the breakdown of cyclic nucleotides, cAMP and cGMP. PDE-5 is the most important form of PDE in cavernosal smooth muscle. Inhibition of this enzyme by a PDE-5 inhibitor such as sildenafil enhances nitric oxide-induced vasorelaxation by increasing vascular smooth muscle cGMP concentration (7).

Sildenafil has been shown to be an effective oral treatment for erectile dysfunction in men with diabetes (8). The effect of sildenafil on endothelial function in patients with diabetes has not been previously investigated. Therefore, we conducted a study to determine the acute and prolonged effects of sildenafil on brachial artery FMD in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Patients

Patients were recruited into the study after informed consent, and the study was approved by the Institutional Review Board. A total of 16 patients (14 of whom completed the study) were enrolled to participate in this investigation. Patients enrolled in this study had a mean \pm SEM age of 44 ± 7 years, erectile dysfunction, and type 2 diabetes. Patients had mean systolic and diastolic blood pressure of 128 ± 8 and 84 ± 6 mmHg, respectively. The mean fasting triglyceride, HDL cholesterol, and LDL cholesterol levels were 232 ± 42 , 35 ± 6 , and 124 ± 18 mg/dl, respectively. In these patients, mean HbA_{1c} and fasting glucose levels were 8.4 ± 1.1 g% and 168 ± 21 mg/dl, respectively. Patients taking nitrates, patients treated with sildenafil in the last 3 months, and patients with hepatic failure or renal failure were excluded from the study.

Study design

This was a prospective, double-blind, placebo-controlled cross-over study. Pa-

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Abbreviations: BAD, brachial artery diameter; cGMP, cyclic guanosine monophosphate; FMD, flow-mediated dilatation; PDE, phosphodiesterase.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

tients were randomly assigned to one of two treatment groups. One group received sildenafil 25 mg and the other received placebo (with appearance identical to sildenafil). Both patients and investigators were blinded to the assigned treatment. After baseline measurement of FMD, the first 25-mg dose of sildenafil or placebo was administered, and exactly 1 h later, FMD measurement was repeated as described below.

Patients then entered the chronic phase immediately after completing the acute phase. The assigned treatment (sildenafil 25 mg or placebo, once daily) was given for 14 days. The patient returned for measurement of FMD 24 h after administration of the last dose. There was a 2-week washout period between the treatments with prolonged sildenafil or placebo.

Assessment of FMD

Patients underwent a noninvasive evaluation of brachial artery endothelial function at baseline, using a well-described and reproducible method (9,10). The diameter of the brachial artery was measured from two-dimensional ultrasound images with a 7.0-MHz linear array transducer and a standard 128XP/10 system. Reactive hyperemia was induced by inflation of a pneumatic tourniquet to a pressure of 220 mmHg for 5 min. Scans measuring reactive hyperemia began 30 s before and continued for 90 s after deflation of the cuff. The maximal brachial artery diameter (BAD) during these measurements was recorded. FMD was measured as a percentage change in the BAD. The coefficient of variation of FMD measurements is <2%.

Statistical analysis

Data comparing the placebo FMD to the treatment FMD was analyzed using paired Student's *t* test. Preocclusion and postocclusion data were also compared using the paired *t* test. $P < 0.01$ was considered significant.

RESULTS— A total of 14 patients completed both treatment periods of the study. In these patients, the mean \pm SD resting BAD measured by ultrasound was 4.33 ± 0.6 mm. There was no significant change in resting BAD with sildenafil or placebo, both acutely and after prolonged treatment (Table 1).

Table 1—Effect of sildenafil on BAD

BAD	→	Preocclusion (mm)	Postocclusion (mm)	% Increase
Baseline first visit		4.33 ± 0.6	4.66 ± 0.5	8
1 h after administration of:	Placebo	4.28 ± 0.6	4.61 ± 0.6	8 (NS)
	Sildenafil	4.34 ± 0.5	4.99 ± 0.5	15*
24 h after last dose of 14-day treatment with:	Placebo	4.32 ± 0.5	4.72 ± 0.5	9 (NS)
	Sildenafil	4.31 ± 0.6	4.91 ± 0.5	14*

Data are means \pm SD or %. * $P < 0.01$ vs. preocclusion. NS, not significant versus preocclusion.

After the release of the occlusion, the mean FMD-induced maximum BAD increased 8% to 4.66 ± 0.6 mm ($P = 0.2$). One hour after administration of the placebo, the mean BAD (post FMD) increased 8% to 4.6 ± 0.6 mm ($P = 1.0$). Sildenafil 25 mg administered orally, acutely (after 1 h) increased the BAD (post FMD) significantly by 15% to 4.99 ± 0.5 mm ($P = 0.006$ compared with pretreatment and compared with placebo) (Fig. 1A).

After 14 days of treatment and testing 24 h after the last dose, the mean BAD (post FMD) increased 9% to 4.72 ± 0.5 mm ($P = 0.45$) with placebo. In contrast, the mean BAD (post FMD) increased 14% to 4.95 ± 0.5 mm ($P = 0.003$ compared with preocclusion) with sildenafil 25 mg daily (Fig. 1B).

CONCLUSIONS— This study demonstrates that a low dose of sildenafil increases FMD in the brachial artery in patients with type 2 diabetes, acutely as well as after 2 weeks of treatment. Furthermore, after 2 weeks of therapy, this effect is present up to 24 h after the last dose of sildenafil. The improvement in brachial artery reactivity suggests an improvement in endothelial function that represents a near normalization of this functional parameter in these patients.

There are several implications of our findings. First, the acute effect is not surprising and has been previously demonstrated in patients with congestive heart failure by Katz et al. (11). Nevertheless, it is reassuring to observe this effect in patients with type 2 diabetes who are known to have impairment of endothelial dysfunction, which may contribute to both erectile dysfunction and cardiovascular disease.

Second, improvement in endothelial function after prolonged use of sildenafil may have implications for the way this

drug is used in management of erectile dysfunction. Many patients use the medication occasionally; intercourse success rates in these individuals are reported to be in the range of 50–60% after the first use. For those who are not successful at the first attempt, this may lead to disappointment in the effect of the drug, which has led some men to discontinue the treatment. Data compatible with the recent finding show that after eight attempts at using sildenafil, the success rate increases to 86% (12). However, in that study, the interval between dosage was randomly determined by the patient rather than in a consistent, planned manner as in our study. It is possible that chronic use of low-dose sildenafil will lead to restoration of endothelial function such that spontaneous erectile function may be restored without the anxiety associated with taking a pill and having to wait for its effect. Clinical trials are needed to test this hypothesis.

Third, in light of the anecdotal reports of cardiovascular events occurring in patients after use of sildenafil, it is reassuring that both acute therapy and prolonged therapy were associated with the beneficial effect on the endothelial FMD. This is particularly important in type 2 diabetes, which is associated with increased risk of cardiovascular disease. Recent data have dispelled initial concerns about an increase in cardiovascular events associated with use of sildenafil (13). Furthermore, other studies have demonstrated the lack of detrimental effect of sildenafil in patients with coronary artery disease (14), and one study has actually demonstrated hemodynamic improvements in such patients, including increase in coronary flow reserve (15). Our results are compatible with these findings.

This study was performed on a small number of patients, and prolonged therapy was given for a relatively short dura-

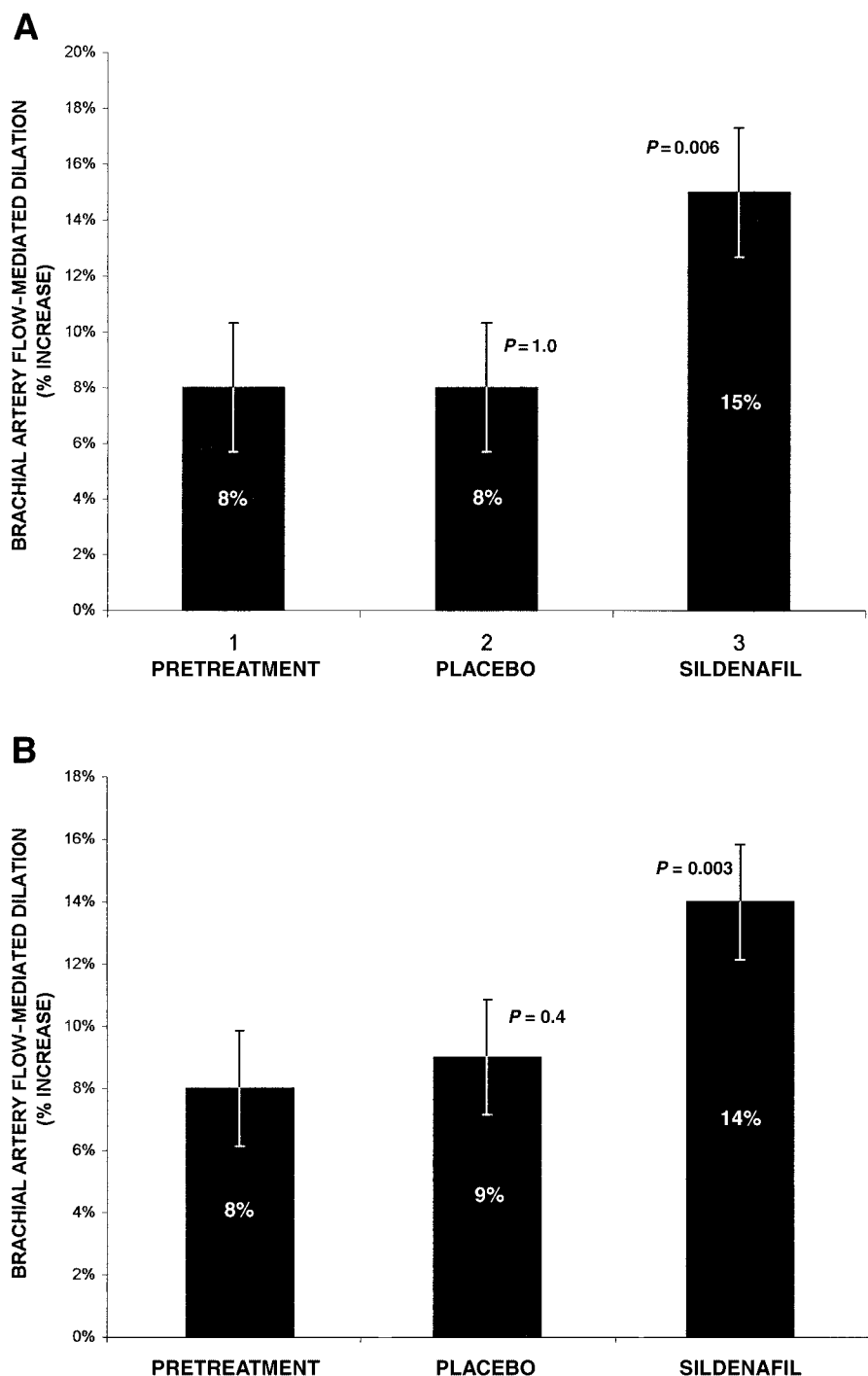


Figure 1—A: Acute effect of sildenafil on FMD. B: Chronic effect of sildenafil on FMD.

tion. A low dose of sildenafil was used. Further studies using larger doses and longer duration of treatment are needed to elucidate these effects. It is also important to determine whether other indexes of endothelial dysfunction are positively impacted. Several components of endothelial function are impaired in people

with type 2 diabetes (16). Because impairment of nitric oxide production and action (through cGMP) are important mediators of the pathophysiology of erectile dysfunction and cardiovascular disease in diabetes (16), such studies are important.

We conclude that sildenafil improves

FMD (a marker of endothelial function), acutely as well as after prolonged use. The beneficial effect of prolonged sildenafil therapy may have implications for management of erectile dysfunction as well as cardiovascular disease in patients with diabetes.

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References

1. Lue TF: Erectile dysfunction. *N Engl J Med* 342:1802–1813, 2000
2. Sullivan ME, Thompson CS, Dashwood MR, Khan MA, Jeremy JY, Morgan RJ, Mikhailidis DP: Nitric oxide and penile erection: is erectile dysfunction another manifestation of vascular disease? *Cardiovasc Res* 43:658–665, 1999
3. Steinberg HO, Chaker H, Leaming R, Johnson A, Brechtel G, Baron AD: Obesity/insulin resistance is associated with endothelial dysfunction: implications for the syndrome of insulin resistance. *J Clin Invest* 97:2601–2610, 1996
4. Li H, Forstermann U: Nitric oxide in the pathogenesis of vascular disease. *J Pathol* 190:244–254, 2000
5. Johnstone MT, Creager SJ, Scales KM, Cusco JA, Lee BK, Creager MA: Impaired endothelium-dependent vasodilation in patients with insulin-dependent diabetes mellitus. *Circulation* 88:2510–2516, 1993
6. Williams SB, Goldfine AB, Timimi FK, Ting HH, Roddy MA, Simonson DC, Creager MA: Acute hyperglycemia attenuates endothelium-dependent vasodilation in humans in vivo. *Circulation* 97:1695–1701, 1998
7. Ballard SA, Gingell CJ, Tang K, Turner LA, Price ME, Naylor AM: Effects of sildenafil on the relaxation of human corpus cavernosum tissue in vitro and on the activities of cyclic nucleotide phosphodiesterase isozymes. *J Urol* 159:2164–2171, 1998
8. Rendell MS, Rajfer J, Wicker PA, Smith MD: Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial: Sildenafil Diabetes Study Group. *JAMA* 281:421–426, 1999
9. Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, Lloyd JK, Deanfield JE: Non-invasive de-

- tection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* 340:1111–1115, 1992
10. Sorensen KE, Celermajer DS, Spiegelhalter DJ, Georgakopoulos D, Robinson J, Thomas O, Deanfield JE: Non-invasive measurement of human endothelium dependent arterial responses: accuracy and reproducibility. *Br Heart J* 74:247–253, 1995
 11. Katz SD, Balidemaj K, Homma S, Wu H, Wang J, Maybaum S: Acute type 5 phosphodiesterase inhibition with sildenafil enhances flow-mediated vasodilation in patients with chronic heart failure. *J Am Coll Cardiol* 36:845–851, 2000
 12. McCullough AR: SRSA: intercourse success rates with sildenafil citrate (Abstract). *J Urol* 165 (Suppl.):699, 2001
 13. Shakir SA, Wilton LV, Boshier A, Layton D, Heeley E: Cardiovascular events in users of sildenafil: results from first phase of prescription event monitoring in Endogland. *Br Med J* 322:651–652, 2001
 14. Jackson G: Phosphodiesterase 5 inhibition: effects on the coronary vasculature. *Int J Clin Pract* 55:183–188, 2001
 15. Herrmann HC, Chang G, Klugherz BD, Mahoney PD: Hemodynamic effects of sildenafil in men with severe coronary artery disease. *N Engl J Med* 342:1622–1626, 2000
 16. Calles-Escandon J, Cipolla M: Diabetes and endothelial dysfunction: a clinical perspective. *Endocr Rev* 22:36–52, 2001