Sildenafil does not improve nitric oxide-mediated endothelium-dependent vascular responses in smokers

Víctor Dishy,¹ Paul A. Harris,² Rosanna Pierce,³ Harish C. Prasad,¹ Gbenga Sofowora,¹ Holly L. Bonar,² Alastair J. J. Wood¹ & C. Michael Stein¹

Division of Clinical Pharmacology¹, General Clinical Research Center, Department of Biomedical Engineering² and The Vascular Surgery department³, Vanderbilt University Medical Center, Nashville, TN, USA

Correspondence

Dr C. Michael Stein, Division of Clinical Pharmacology, Room 562 PRB, Vanderbilt University Medical Center, Nashville TN 37232-6602, USA.

Tel: +1 (615) 343-2575

Fax: (615) 343 2551

E-mail:

michael.stein@vanderbilt.edu

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Aims

To examine the hypothesis that sildenafil, a phosphodiesterase type 5 inhibitor that inhibits cGMP breakdown, could enhance nitric oxide-mediated vasodilation and reverse endothelial dysfunction in chronic smokers.

Methods

Flow-mediated dilation of the brachial artery and forearm postischemic reactive hyperemia (both nitric oxide-mediated responses) were measured before and after sildenafil 50 mg and placebo in a double-blind, randomized, crossover study in 9 men who were chronic smokers (21 ± 3 pack years).

Results

There was no significant change in flow-mediated dilation after either sildenafil (0.18%, 95%CI -1.7–2%) or placebo (0.24%, 95%CI -2.8–3.3%) ($P = 0.88$ and 0.8 , respectively). Sildenafil had no significant effect on resting forearm blood flow or postischemic reactive hyperemia ($P = 0.39$ and 0.7 , respectively). Resting heart rate and blood pressure were unaffected by sildenafil.

Conclusions

Acute sildenafil administration did not improve endothelial function in chronic smoking men.

Introduction

Endothelial dysfunction is characterised by impaired endothelium-dependent, nitric oxide (NO)-mediated vasodilation and may play a role in atherogenesis [1]. It is present in several conditions associated with increased cardiovascular risk [2] and has been successfully reversed by risk factor modification or drugs.

A novel approach to improve endothelial function would be to enhance the effects of cyclic GMP, the

mediator of the vascular effects of NO, by inhibiting its breakdown by phosphodiesterase type 5 (PDE 5). Sildenafil is a specific PDE 5 inhibitor that facilitates erection by the inhibition of cyclic GMP breakdown in the corpus cavernosum [3]. However, since PDE 5 is widely expressed in other vascular beds [4], sildenafil may enhance NO-mediated responses elsewhere. In young healthy men with normal endothelial function we have shown that sildenafil had no effect on NO-

mediated vasodilation [5]. However, an improvement may only be manifest in individuals with preexisting endothelial dysfunction. Thus, we examined the hypothesis that sildenafil would enhance NO-mediated vascular responses in chronic smokers, a group known to have endothelial dysfunction [10–12].

Methods

Subjects

We studied nine, otherwise healthy, men (age 39 ± 0.5 3 years, BMI 27.7 ± 1.5 kg m⁻², 21 ± 3 pack years, 10–40 cigarettes/day, who were current and chronic smokers. All subjects gave written informed consent and the study was approved by the Vanderbilt University Institutional Review Board.

Study design

Brachial artery flow-mediated dilation and postischemic reactive hyperemia were measured by ultrasound and strain gauge plethysmography, respectively, as we have described previously [5] to assess nitric oxide-mediated vascular responses in a conduit artery [9] and in forearm resistance vessels [10]. Subjects fasted for at least 4 h before the study and abstained from alcohol, caffeine and grapefruit juice for a minimum of 12 h before the study. Each subject continued to smoke his usual number of cigarettes throughout the study and smoked a cigarette immediately before the beginning of each study session. Subjects were studied on two separate

days. After 30 min of lying supine, resting and postischemic measurements of heart rate, blood pressure, brachial artery diameter, brachial artery flow and forearm blood flow were obtained. On each day subjects received capsules containing either placebo or sildenafil citrate 50 mg (Viagra, Pfizer Inc. NY) in a double blind, randomized, crossover design. One hour after drug administration, to coincide with the time of expected peak serum levels of sildenafil [3], measurements were repeated.

Statistical analysis

Flow-mediated dilation was expressed as the percent change in diameter of the brachial artery comparing resting and peak postocclusion measurements. The Area Under the time/flow Curve (AUC) of the reactive hyperemia response was calculated and used to compare responses before and after subjects received placebo and sildenafil. All data are expressed as mean $\pm$ SEM. Resting and postischemic measurements before and after subjects received placebo and sildenafil were compared by a two tailed, paired *t*-test, with *p* < 0.05 as the level of statistical significance.

Results

Flow-mediated brachial artery dilation, reactive hyperemia and haemodynamic measurements, for placebo and sildenafil study days are shown in Table 1. The changes in flow-mediated dilation [mean (95% confidence intervals)] after placebo 0.24% (–2.8%, 3.3%)

Table 1

Ultrasound, plethysmographic and haemodynamic measurements before and after treatment with placebo and sildenafil

	Placebo		Sildenafil	
	Before	After	Before	After
<i>Ultrasound measurements</i>				
Resting brachial artery diameter (cm)	0.54 $\pm$ 0.02	0.53 $\pm$ 0.02	0.51 $\pm$ 0.02	0.52 $\pm$ 0.02
Flow-mediated dilation (%)	3.5 $\pm$ 1.7	3.8 $\pm$ 1.3	4.25 $\pm$ 1.5	4.4 $\pm$ 1.3
<i>Plethysmographic measurements</i>				
Resting forearm blood flow (ml min ⁻¹ 100 ⁻¹ ml)	4.20 $\pm$ 0.35	3.90 $\pm$ 0.37	3.8 $\pm$ 0.4	4.4 $\pm$ 0.5
Area Under the Curve of postischemic forearm blood flow (ml·s min ⁻¹ 100 ⁻¹ ml)	1872 $\pm$ 254	1572 $\pm$ 188	1357 $\pm$ 161	1441 $\pm$ 234
<i>Hemodynamic measurements</i>				
Heart rate (beats min ⁻¹)	74 $\pm$ 4	71 $\pm$ 2	73 $\pm$ 1	72 $\pm$ 2
Systolic blood pressure (mmHg)	127 $\pm$ 4	124 $\pm$ 4	125 $\pm$ 4	127 $\pm$ 5
Diastolic blood pressure (mmHg)	79 $\pm$ 4	79 $\pm$ 4	82 $\pm$ 4	82 $\pm$ 4

Data are mean $\pm$ s.e.mean. *p* > 0.05 for all comparisons.

Figure 1

Reactive hyperemia before (Δ) and after (▲) treatment with sildenafil

and sildenafil 0.18% (−1.7%, 2%) did not differ ($p = 0.88$ and 0.8 , respectively) and there was no interaction between treatment assignment and changes in flow-mediated dilation before vs after treatment, ($p = 0.97$ repeated measures ANOVA). Neither sildenafil nor placebo had a statistically significant effect on resting brachial artery diameter (0.54 ± 0.02 cm before and 0.53 ± 0.02 cm after placebo, $p = 0.5$ Table 1 0.51 ± 0.02 cm before and 0.52 ± 0.02 cm after sildenafil, $p = 0.5$, Table 1).

Sildenafil administration had no significant effect on the AUC of the postischemic reactive hyperemia (1357 ± 161 ml·s min^{−1} 100^{−1}ml before vs 1441 ± 234 ml·s min^{−1} 100^{−1}ml after sildenafil, $p = 0.7$, Table 1 and Figure 1). Resting blood pressure, heart rate and forearm blood flow were also not affected by either placebo or sildenafil (Table 1).

Discussion

We examined the hypothesis that sildenafil, a PDE 5 inhibitor, would improve endothelial function in a group of chronic smokers by inhibiting cGMP breakdown and enhancing NO-mediated vascular responses. Sildenafil did not improve endothelial function, nor did it alter heart rate or blood pressure.

Several mechanisms may explain why sildenafil markedly enhances the effects of endogenous NO in the corpus cavernosum but not the forearm. Vascular beds vary in their sensitivity to sildenafil. Thus, sildenafil can decrease pulmonary arterial pressure significantly with minor or no changes in systemic blood pressure [11]. On the other hand, direct injection of high concentrations of sildenafil into the brachial

artery causes only a mild increase in forearm blood flow [12].

Variability among vascular beds may be caused by differences in the local expression of phosphodiesterases or sensitivity to the effects of NO. In different vascular beds the levels of PDE 5 vary, as do those of PDE 1 and PDE 2 [4], which are not inhibited by sildenafil at concentrations achieved therapeutically. In the forearm vasculature, NO is produced tonically and contributes to vascular tone, but in the corpus cavernosum it is only released episodically during sexual stimulation [13]. Since NO can down-regulate eNOS expression [14], a vascular bed that is constantly exposed to NO, such as occurs in the forearm, may be less sensitive to the effects of PDE5 inhibition.

In contrast to our previous findings in healthy men [5], and now also in smokers, studies in patients with heart failure [15] and diabetes [16] found that sildenafil improved endothelial function significantly. In patients with heart failure [15], sildenafil increased flow-mediated dilation approximately 4-fold and in patients with diabetes it almost doubled flow-mediated dilation [16]. Our study had approximately 75% power to detect a doubling of flow-mediated dilation, a response within the range observed in those studies. The causes of endothelial dysfunction are multifactorial and include decreased expression and activity of endothelial nitric oxide synthase, increased destruction of NO by free radicals, decreased sensitivity to NO, increased levels of endogenous NO antagonists such as asymmetric dimethylarginine and increased endogenous vasoconstrictors such as endothelin. This diversity of mechanisms may explain the improvement of endothelial dysfunction by sildenafil in some conditions but not others.

In conclusion, sildenafil did not potentiate endogenous NO-mediated vascular responses in forearm conduit or resistance vessels in chronic smokers. Differential vascular responses to sildenafil may localize its enhancement of endogenous NO-mediated vasodilation to vascular beds such as the corpus cavernosum. The relative contribution of different mechanisms underlying endothelial dysfunction may affect the ability of sildenafil to reverse endothelial dysfunction of different aetiologies

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