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Acute effect of sildenafil on inflammatory markers/mediators in patients with vasculogenic erectile dysfunction

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ABSTRACT

Background: Erectile dysfunction (ED) is associated with an incremental inflammatory activation. Evidence suggests that chronic phosphodiesterase 5 (PDE-5) inhibition may have a favorable effect on inflammatory activation and surrogate markers of ED. The aim of this study is to investigate the acute effect of sildenafil on circulating pro-inflammatory markers/mediators in ED patients.

Methods: The study comprised a randomized, double-blind, crossover trial carried out on two separate arms: one with sildenafil 100 mg, and one with placebo. Twenty-seven subjects participated in the study (seven in the pilot and 20 in the main phase). In the main phase, blood samples were collected at baseline and at 2 and 4 h after sildenafil or placebo administration to determine fibrinogen, high sensitivity C-reactive protein (hsCRP), high sensitivity interleukin-6 (hsIL-6) and tumor necrosis factor α (TNF-α).

Results: Administration of sildenafil produced a significant sustained reduction of fibrinogen, hsCRP and hsIL-6 (maximal absolute response of −44 mg/dl, 0.42 mg/l and 0.68 pg/ml at 4 h). Likewise, TNF-α was acutely decreased after sildenafil (maximal response of −13 pg/ml, 2 h). The effect of sildenafil on fibrinogen, hsCRP and hsIL-6 and TNF-α was independent of the baseline values of these markers/mediators or the baseline testosterone level (all $P < 0.05$). Soluble vascular cell adhesion molecule 1 (sVCAM-1) levels remained unchanged.

Conclusions: The present study shows for the first time the acute effect of sildenafil administration on pro-inflammatory markers/mediators in men with vasculogenic ED. This finding may have important implications in ED patients who are considered to be at increased cardiovascular risk.

1. Introduction

Vasculogenic erectile dysfunction (ED) and cardiovascular disease (CVD) share a common pathophysiological basis of etiology and progression [1–3]. Inflammation plays an important pathophysiological role in both ED and CVD [4]. Through enhanced production of cytokines and expression of cellular adhesion molecules, the dysfunctional endothelium promotes inflammation within the vascular wall and sets the stage for initiation and progression of atherosclerotic lesions in both penile vasculature and in peripheral and coronary blood vessels [4]. It has been shown that patients with vasculogenic ED have increased inflammatory activation compared to subjects without ED [5].

There are numerous studies suggesting that phosphodiesterase-5 (PDE-5) inhibitors, which are the first-line therapy of ED, might be effective in reversing generalized endothelial dysfunction [6]. Acute treatment with PDE-5 inhibitors showed favorable effects on brachial artery flow-mediated dilatation up to 24 h post-dose in men with [7] and without ED [8] and in patients with coronary artery disease [9] and chronic heart failure [10]. Furthermore, chronic treatment restores endothelium-dependent relaxations at various sites of the vascular tree, even up to one week after cessation of the treatment [11]. Beneficial acute (sildenafil, vardenafil) and chronic (sildenafil) effects of PDE-5 inhibitors on aortic stiffness and wave reflections in men with ED are also well-known [6,12–15].

Given the unfavorable influence of inflammation on arterial function [16–18], the aforementioned effects of PDE-5 inhibitors could be partly attributed to a robust anti-inflammatory action. Indeed, previous studies reported a chronic effect of sildenafil and tadalafil on endothelial function and pro-inflammatory markers/mediators including intercellular and vascular cell adhesion molecules-1 (ICAM-1 and VCAM-1, respectively), high sensitivity C-reactive protein (hsCRP), and interleukin-6 (IL-6) [11]. However, whether PDE-5 inhibitors acutely reduce levels of pro-inflammatory compounds has not been investigated. Therefore, the aim of this study is to investigate the acute effect of sildenafil on circulating markers/mediators of subclinical inflammation in men with vasculogenic ED.

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2. Methods

2.1. Study population

From October 2012 to May 31 2013 we enrolled 27 consecutive patients who had been diagnosed at the Cardiovascular and Sexual Health Clinic of the 1st Department of Cardiology of Athens Medical School for vasculogenic ED for more than 6 months. All patients were evaluated by comprehensive medical history and physical examination. Subjects with a history of diabetes, coronary artery disease (CAD), stroke or peripheral artery disease, acute inflammatory diseases, collagen diseases, or malignant neoplasms were excluded. The study complies with the Declaration of Helsinki. The protocol was approved by our Institutional Research Ethics Committee. All subjects gave written informed consent.

2.2. Evaluation of ED

ED of vasculogenic origin was diagnosed according to comprehensive medical and sexual history, score of the five-item form of the International Index of Erectile Function, the Sexual Health Inventory for Men (SHIM score 21 and below indicates ED), [19] hormonal testing (total testosterone and prolactin), and penile Doppler ultrasonography. Doppler studies were performed using 20 μg intracavernous prostaglandin E1 and audiovisual stimulation. Through these baseline evaluations, patients were excluded if their ED was clearly secondary to hormonal, neurologic or anatomic abnormalities. Special emphasis was put upon the onset of ED and medications, including β-adrenergic antagonists and diuretics.

All men were considered competent to have a safe sexual activity and take PDE-5 inhibitor therapy.

2.3. Study design

The study comprised a randomized double-blind, crossover trial with sildenafil or placebo administration. The study was carried out on two separate arms: one with sildenafil, 100 mg and one with placebo. Thereafter, following a 1-week washout period, patients were switched to treatment period with the other drug.

Blood samples have been collected from seven ED patients consenting to participate in the pilot study at baseline and at 1, 2, 4 and 8 h after sildenafil or placebo administration to determine the two points in time with the greater influence of sildenafil or placebo on levels of inflammatory markers/mediators. In the main part of the protocol, blood samples were drawn from 20 patients in two time points chosen according to results of the pilot study.

Patients were studied while on regular medications and on each study day they had taken their morning dose of medication. No changes in type of medication or dose occurred in any patient during the study period. No patient had received PDE-5 inhibitors in the last 6 months so as to avoid the confounding effect of a possible decrease in levels of pro-inflammatory markers/mediators that previous studies have shown [11]. During the entire period of the study, patients were instructed to avoid other PDE-5 drugs or testosterone therapy.

No participant in the pilot or in the main study reported adverse events or discontinued the study due to adverse events.

2.4. Measurement of inflammatory markers/mediators

Immediately after acquisition of venous blood, plasma or serum were separated by centrifugation (3000 *g* at 48 °C for 15 min), then placed in aliquots and stored at −70 °C for the measurement of inflammatory markers/mediators.

High sensitivity IL-6 (hsIL-6), TNF-a and soluble VCAM-1 were measured using ELISA (R&D Systems, Minneapolis, MN, USA). Fibrinogen and hsCRP were measured by immunonephelometry (Siemens BCS, BCSXP and Abbott, Architect 8000, CRP vario High sensitive).

The measurements of inflammatory markers/mediators were made by researchers unaware of the study hypothesis.

2.5. Statistical analysis

Baseline levels of fibrinogen, hs-CRP, IL-6, TNF-a and VCAM-1 were compared between the Drug 1 and Drug 2 sessions using the paired *t*-test.

The effect of each drug was evaluated with two-way repeated-measures analysis of variance (ANOVA) as follows: two study arms (Drug 1 versus Drug 2) × five time points (*pilot study*, baseline, 1, 2, 4 and 8 h) or × three time points (*main study*, baseline, 2 and 4 h).

Analysis of covariance (ANCOVA) was performed to evaluate whether the changes of inflammatory markers/mediators induced by the sildenafil or placebo were dependent on the baseline values of these markers/mediators, or total testosterone levels.

Values of $P < 0.05$ were considered statistically significant. Data analysis was performed using the SPSS statistical package for Windows (Version 16.0, SPSS Inc., and Chicago, Illinois).

3. Results

In the pilot study changes in fibrinogen and hsIL-6 levels were examined 1, 2, 4 and 8 h after sildenafil or placebo intake. The maximum decrease in hsIL-6 and IL-6 levels occurred at 2 h (by 0.40 mg/dl and 0.65 pg /ml, respectively) and at 4 h (by 0.47 mg/dl and 0.56 pg/ml respectively) after sildenafil intake.

According to the findings of the pilot study, blood samples at the main phase of the study were drawn at baseline and at 2 and 4 h after sildenafil or placebo administration.

The clinical characteristics of participants of the study (n = 20) are shown in Table 1. All participants in the study had vasculogenic ED defined when peak systolic velocity is less than 35 cm/s or peak diastolic velocity > 5 cm/s. Of them eight had arterial insufficiency (peak systolic velocity less than 35 cm/s).

Table 2 shows baseline levels of fibrinogen, hsCRP, hsIL-6, TNF-a and sVCAM-1 before sildenafil and placebo administration. There were no statistically significant differences in any baseline levels of inflammatory markers/mediators between sildenafil and placebo sessions.

Fig. 1 illustrates responses of fibrinogen, hsCRP, hsIL-6, TNF-a and sVCAM-1 during the study. Response is defined as net Drug 1 (sildenafil) effect minus Drug 2 (placebo) effect on inflammatory levels at each time point. P values on the graphs refer to repeated-measures ANOVA significance between Drug 1 and Drug 2 sessions throughout the study (drug interaction).

Acute administration of sildenafil produced a significant sustained reduction of fibrinogen, hsCRP and hsIL-6 (maximal absolute response of −44 mg/dl, 0.42 mg/l and 0.68 pg/ml at 4 h). Likewise, TNF-a was acutely decreased after sildenafil (maximal response of −13 pg/ml, 2 h). There was a significant drug interaction for all these inflammatory parameters ($P < 0.05$). ANCOVA showed that the effect of sildenafil on fibrinogen, hsCRP, hsIL-6 and TNF-a was independent of the baseline values of these markers/mediators or the baseline testosterone level. As Fig. 1 shows, sVCAM-1 levels were not significantly altered.

4. Discussion

To the best of our knowledge, this is the first study to demonstrate the acute effect of sildenafil administration on pro-inflammatory markers/mediators in men with vasculogenic ED. Our principal finding is that sildenafil administration led to a significant decrease in fibrinogen, hsCRP, hsIL-6 and TNF-a levels which persisted for at least 4 h after drug intake. This finding elucidates potential mechanisms of selective PDE-5 inhibition and may have important clinical implications.

4.1. Clinical implications

Our study has important clinical implications for the management of men with vasculogenic ED that in its own right is a manifestation of generalized arterial disease [20,21]. Previous studies have pointed towards an important role of low-grade inflammation in the pathogenesis of vasculogenic ED [4,5]. It has been extensively debated that inflammation can exert a detrimental effect on the vasculature and heart via two pathways: chronic, low-grade inflammation and an acute systemic inflammatory response. The former has been implicated in atherosclerotic processes [22], while the latter accounts for adverse cardiovascular

Table 1
Population baseline characteristics (n = 20).

Variable	
Age (years)	56 ± 11
BMI (kg/m^2)	28.5 ± 4.0
Hypertension n, %	8 (40)
Hyperlipidemia n, %	8 (40)
Smoking n, %	9 (45)
Antihypertensive therapy n, %	7 (35)
Statins n, %	5 (25)
Testosterone (ng/ml)	4.0 ± 1.5
SHIM	13 ± 4
Peak systolic velocity (cm/s)	39 ± 10

BMI: body mass index; SHIM: Sexual Health Inventory for Men.