Endothelial Antioxidant Administration Ameliorates the Erectile Response to PDE5 Regardless of the Extension of the Atherosclerotic Process

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ABSTRACT

Introduction. The lack of phosphodiesterase type 5 inhibitor effects in patients with erectile dysfunction (ED) of arterial origin may be caused by an endothelial dysfunction that causes a series of biochemical alterations leading to a reduced nitric oxide (NO) bioavailability and increased oxidative stress.

Aim. The aim of this study was to evaluate the effects of the treatment with endothelial antioxidant compounds (EAC) on the erectile response to sildenafil in patients with arterial ED already treated with sildenafil (100 mg twice a week for 8 weeks).

Mean Outcome Measures. A patient was considered responsive when the 5-item International Index of Erectile Function questionnaire score increased by >5 points.

Methods. Fifty-three patients with arterial ED, hypertension, and diabetes mellitus were randomly given, for 8 weeks, EAC (1 dose/day) and, after a wash out of 8 weeks, sildenafil (100 mg) plus EAC. The patients were divided into the following four groups: A (N = 12): patients with ED alone; B (N = 14): patients with ED plus atheromasic plaques and/or increased intima-media thickness of common carotid arteries; C (N = 14): patients with ED plus lower limb artery abnormalities; and D (N = 13): patients with ED plus carotid and lower limb artery abnormalities.

Results. The administration of EAC plus sildenafil resulted in a significantly higher number of responsive patients (N = 36, 68%) compared with sildenafil alone (N = 24, 45%) or EAC alone (N = 17, 32%). The percentage of patients who successfully responded to the combined treatment increased in the various groups. It was 83%, 64%, 71%, and 54%, respectively, for groups A, B, C, and D. Furthermore, patients treated with EAC and sildenafil reached a successful response in a shorter length of time (3 weeks) compared with patients responsive to sildenafil (5.2 weeks) or EAC (5.7 weeks) alone.

Conclusion. EAC administration to patients with arterial ED improved the success rate to sildenafil. These data suggest that, in such patients, a combined treatment may be considered to increase bioavailable NO and to neutralize radical oxygen species, which in turn inactive NO. **Vicari E, La Vignera S, Condorelli R, and Calogero AE. Endothelial antioxidant administration ameliorates the erectile response to PDE5 regardless of the extension of the atherosclerotic process. J Sex Med 2010;7:1247–1253.**

Key Words. Erectile Dysfunction; Sildenafil; Antioxidant; IIEF; Endothelium

Introduction

Erectile dysfunction (ED) of organic origin mainly appears after the age of 50 years, in presence of arterial treatable abnormalities [1]. This type of ED has been interpreted as an initial sign of local penile atherosclerosis without the presence of a significant hemodynamic vascular stenosis. However, it is likely to progress toward a more generalized arterial involvement in the future [2,3]. Therefore, arterial ED may appear before an ischemic cardiopathy in ~70% of the cases [4] or atherosclerotic involvement of other organs with definitive arterial stenosis [5]. We have

previously reported that, at the moment of the diagnosis, ED of arterial origin is associated with poly-district atherosclerosis in the vast majority of the cases. Indeed, ED, as a clinical sign of isolated penile artery abnormality, was found in 25% of the patients, whereas penile artery atherosclerosis was found in association with carotid (intima-media thickening and/or plaque) and/or lower limb artery atherosclerosis in the remaining 75% of the cases [6]. In a subsequent study, we reported that patients with arterial ED and generalized atherosclerosis had a lower peak-systolic velocity (PSV) compared with patients with isolated arterial ED or with ED and carotids or lower limb atherosclerosis [7].

Although the advent of phosphodiesterase type 5 inhibitors (PDE5) has revolutionized the treatment of men with ED, the highest efficacy, both in terms of number of responsive patients and quality of erection, has been observed in patients with ED and a normal vascular component and/or presumably psychogenic ED (80%). In contrast, the success rate is much lower in patients with altered arterial and/or venous components [8–10]. Thus, it is difficult to envisage the patients with ED who will be poor responders to PDE5 treatment [11,12]. To reduce the number of "false" poor responders, some pre-treatment key points should be considered during the andrological counseling [13]. As the effect of PDE5 relates to nitric oxide (NO) production and to cavernous nerve integrity, a low responsiveness may be justified by the presence of clinical conditions or comorbidities [5], which cause a severe endothelial disorder by reducing NO bioavailability and increasing oxidative stress [14–16]. In this regard, de Tejada stated that "the limitation in the efficacy of PDE5i is that a minimum or 'critical amount' of NO is necessary for these drugs to work." Thus, the Author suggests that therapeutic strategies for optimizing PDE5 treatment success rate or in resistant patients should be oriented in the following three directions: (i) facilitate NO release by α_2-antagonist administration; (ii) enhance NO synthesis by administering more substrate (L-arginine; hydroxyarginine) for the reaction; and (iii) reduce radical oxygen species-mediated NO inactivation by antioxidant administration [15].

Propionyl-L-carnitine was initially available as the only active compound having an endothelial antioxidant activity. Recently, at the dose of 250 mg, it has become available on the market as an "integrating" drug, in association with vitamin B_3 (20 mg) and L-arginine (2,500 mg), hence with an amino acid physiological precursor of NO (Ezerex®, Sigma Tau, Pomezia, Rome, Italy). The efficacy of the treatment with propionyl-L-carnitine plus sildenafil ("salvage therapy") in diabetic patients with ED, who are poor responders to the administration of sildenafil alone [17], has recently found preliminary support [18]. This study showed that propionyl-L-carnitine plus sildenafil improves penile arterial hemodynamics and the clinical response (increased 5-item International Index of Erectile Function questionnaire [IIEF5] score) in patients with ED, suggesting that such a therapeutic strategy more efficaciously improves the "endothelial metabolism" (decreased monocyte oxidative response) in these patients. Therefore, the purpose of this study was to evaluate the effects of the administration of endothelial antioxidant compounds (EAC) plus sildenafil in patients with ED of arterial origin associated with atherosclerotic signs in other arterial districts (generalized atherosclerosis) who were low responders to PDE5 [19]. A group of patients with arterial ED alone (a clinical model of atherosclerosis still in its initial phase, limited to the penile district) who had the best erectile response to sildenafil served as a control group.

Subjects and Methods

Patient Selection

We evaluated the erectile response in 53 consecutively selected patients (average age 56.0 years, range 52–77 years) with both controlled hypertension (pharmacologically treated but without β-blockers and thiazide diuretics that may cause ED and/or with values < 160/95 mm Hg) and diabetes mellitus (fasting plasma glucose < 115 mg/dL and/or hemoglobin A1c < 7.5%). All patients also fulfilled the following criteria:

1. Arterial ED diagnosed by dynamic duplex Doppler ultrasound of the penile arteries with pulsed Doppler analysis following intracavernous administration of 20 μg of alprostadil (Caverject, Pfizer, New York, NY, USA). After injection, PSV was measured every 10 minutes for 20–30 minutes. A PSV <30 cm/sec and a non-temporal peak-systolic progression suggested the presence of an arterial disease [20].
2. Penile arterial dysfunction observed alone or in combination with peripheral atherosclerosis diagnosed by duplex flussimetry of the carotid and lower limb arteries. In particular, carotid