ORIGINAL RESEARCH—ED PHARMACOTHERAPY

Combination of Alfuzosin and Tadalafil Exerts In Vitro an Additive Relaxant Effect on Human Corpus Cavernosum

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ABSTRACT

Introduction. Phosphodiesterase type 5 (PDE5) inhibitors, such as tadalafil, are a first-line treatment for erectile dysfunction (ED). Nevertheless, some patients do not respond to this treatment. Clinical data suggest that the addition of α1-adrenoceptor blocker, such as alfuzosin, commonly prescribed for lower urinary tract symptoms suggestive of benign prostatic hyperplasia, may be of benefit.

Aim. Evaluation of the effect of alfuzosin, tadalafil or the combination of both on human corpus cavernosum.

Methods. Human cavernosal tissues were obtained from 10 patients undergoing penile surgery. Strips contractility was studied in organ baths. Concentration–response curves to tadalafil were generated on norepinephrine (NE, 1–10 μM)-precontracted strips in the presence of alfuzosin or vehicle. Frequency–response curves (FRC) to electrical field stimulation (EFS, 0–64 Hz, 3 ms, 10 seconds, 300 mA) were generated in the presence of vehicle, alfuzosin, tadalafil, or both drugs combined. EFS (20 Hz, 1 ms, 10 seconds, 300 mM)-induced nitrergic relaxation on NE-precontracted strips was studied in the presence of vehicle, alfuzosin, tadalafil, or both drugs combined.

Main Outcome Measures. Functional measurement of cavernosal smooth muscle relaxation in the presence of tadalafil and alfuzosin.

Results. The relaxation induced by tadalafil (10^{-10} to 10^{-5} M) on precontracted strips was enhanced by alfuzosin at both 10^{-8} and 10^{-7} M. The combination of alfuzosin (3.10^{-8} M) and tadalafil (10^{-7} M) was more efficient to inhibit FRC-induced contractions than each compound alone. The combination of tadalafil (10^{-6} M) and alfuzosin (10^{-8} M) increased the relaxation induced by EFS and its effect was greater than tadalafil alone. In addition, the combination of tadalafil (10^{-6} M) and alfuzosin (10^{-7} M) prolonged EFS-induced relaxation to a greater extent than each compound alone.

Conclusions. In vitro, the combination of alfuzosin and tadalafil is more efficient than each compound alone to relax adrenergic tone or to enhance nitrergic relaxation of the human corpus cavernosum. Such a combination deserves further investigation in placebo-controlled studies to evaluate its benefit in ED patients who are not sufficiently improved by PDE5 inhibitors. **Oger S, Behr-Roussel D, Gorny D, Tremeaux JC, Combes M, Alexandre L, and Giuliano F. Combination of alfuzosin and tadalafil exerts in vitro an additive relaxant effect on human corpus cavernosum. J Sex Med 2008;5:935–945.**

Key Words. Erectile Dysfunction; PDE5 Inhibitors; α1-Blockers; Smooth Muscle; Pharmacology

Introduction

Erectile dysfunction (ED) is a highly prevalent condition in aging men [1] that may considerably affect their quality of life, although it is a frequently neglected aspect of health care [2]. The main predictors of ED are age and cardiovascular comorbidities such as hypertension, heart disease, hypercholesterolemia, and diabetes [3]. Recently, lower urinary tract symptoms (LUTS) associated

with benign prostatic hyperplasia (BPH) have also been identified as a risk factor for ED, independent of age or other comorbidities [4–7]. The mechanisms explaining this link between ED and LUTS remain unclear, but several theories have been suggested [6,8].

Phosphodiesterase type 5 (PDE5) inhibitors are the treatment of choice for ED [9]. PDE5 isoenzymes are the predominant PDE expressed in the corpus cavernosum [10]. They are selective for the hydrolysis of cyclic guanosine monophosphate (cGMP), which is the key second messenger involved in the nitric oxide (NO)-mediated penile smooth muscle relaxation [11]. Therefore, the elevation of cGMP in the cavernosal tissue via PDE5 inhibition enhances smooth muscle relaxation, improving erectile function. Tadalafil is a long-acting PDE5 inhibitor, which has been shown to be safe and efficacious [12,13]. On the other hand, α1-adrenoceptor blockers are considered the most effective monotherapy for LUTS suggestive of BPH [14]. They act mainly on the dynamic component of obstruction by reducing the adrenergic tone of the prostate, prostatic urethra, and bladder neck. All α1-adrenoceptor blockers share the same efficacy [14] but differ in their cardiovascular and sexual side effect profile. Alfuzosin, has been shown to provide a rapid and sustained relief of LUTS, with minimal cardiovascular and sexual side effects [15–17]. Moreover, it shows no clinically relevant hemodynamic interaction with tadalafil at the highest prescribed dose (20 mg) [18].

Because of the close association between ED and LUTS, physicians are increasingly in a position to manage both conditions simultaneously and the concept of a combined therapy that could improve the benefits of each drug administrated alone is currently emerging. Several pilot clinical studies have evaluated the effect of combining a PDE5 inhibitor with an α1-adrenoceptor blocker. Hence, in a retrospective analysis of 42 men with ED, considered nonresponders to tadalafil (20 mg on demand), the addition of alfuzosin 10 mg once daily to tadalafil on demand improved ED in 71% of patients and was well tolerated [19]. Similar results have been obtained when daily doxazosin was combined to sildenafil on demand in ED patients nonresponding to sildenafil alone [20]. Lastly, a pilot randomized study found that the daily administration of alfuzosin 10 mg and sildenafil 25 mg for 12 weeks in men with LUTS and untreated ED was safe and more effective than monotherapy with either agent to improve ED and LUTS [21].

The aim of the present study was to further investigate from a pharmacologic perspective if the combination of tadalafil and alfuzosin was more effective than each compound alone in relaxing human corpus cavernosum. In the first step, we examined the potential enhancing effect of alfuzosin on the relaxation induced by tadalafil on norepinephrine (NE)-precontracted corpus cavernosum tissue. Then, we investigated the effects of alfuzosin and/or tadalafil on corpus cavernosum contractions induced by electrical field stimulation (EFS) and on nitrergic nonadrenergic noncholinergic (NANC) relaxation of precontracted cavernosal tissue.

Material and Methods

Human Corpus Cavernosum Strips Preparation

Tissue samples were obtained from 10 patients (aged 42–76 years, mean age 61 ± 3 years) undergoing penile surgery for penile implant as treatment of ED, penile congenital curvature or Peyronie's disease. All patients provided their informed consent. Once collected, the tissue samples were stored at 4°C in Krebs–HEPES buffer (118 mM NaCl; 4.7 mM KCl; 1.2 mM $MgSO_4$; 1.2 mM KH_2PO_4; 2.5 mM $CaCl_2$; 4.2 mM $NaHCO_3$; 11.1 mM glucose; and 20.8 mM HEPES; pH 7.4) containing penicillin (100 IU/mL) and streptomycin (0.1 mg/mL) for optimal conservation until use (within 24 hours maximum). The samples were cleaned of adherent tissue and blood, and the sections were excised from each donor sample for each experiment.

In Vitro Contractile Studies

Cavernosal strips were suspended in 5-mL organ chambers filled with Krebs–HEPES buffer maintained at 37°C and continuously bubbled with 95%O_2 and 5%CO_2 to maintain the pH at 7.4. The strips were connected to force transducers for isometric tension recording (Pioden controls Ltd, Newport, UK) and an initial tension of 1 g was applied, as previously described [22,23], in order to obtain a resting tension of 374.7 ± 55.6 mg at the end of the equilibration period. Following amplification, the tension changes were computerized with Mac Lab/8 using Chart 5 software (AD Instruments Ltd, Chalegrove, UK). The tissue preparations were allowed to equilibrate for 60 minutes, while being washed periodically with fresh Krebs–HEPES buffer. The tissues were primed by KCl (80 mM, 10 minutes) and after washings, by NE (10^{-6} M, 5 minutes) followed by