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European Association of Urology

Voiding Dysfunction

Combination of Alfuzosin and Tadalafil Exerts an Additive Relaxant Effect on Human Detrusor and Prostatic Tissues In Vitro

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Article info

Article history:
Accepted April 21, 2009
Published online ahead of print on May 3, 2009

Keywords:
PDE5 inhibitor
α1-adrenoceptor antagonist
Lower urinary tract symptoms
Bladder
Prostate
Smooth muscle

Abstract

Background: Lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) and erectile dysfunction (ED) are highly prevalent in aging men and are strongly linked. Alpha$_1$-blockers such as alfuzosin are effective monotherapies for LUTS. Phosphodiesterase type 5 (PDE5) inhibitors such as tadalafil are the first-line treatment for ED. Both drugs act by two different mechanisms of action on common urogenital target organs and, thus, may have additive effects.
Objectives: We evaluated in vitro the effects of alfuzosin, tadalafil, and the combination of both on human detrusor and prostatic smooth muscle.
Design, setting, and participants: Prostatic and bladder tissue were obtained from patients (n = 20 and n = 17, respectively) undergoing cystoprostatectomy for bladder cancer.
Measurements: In organ baths, isolated prostatic strips and isolated bladder strips were incubated with vehicle, tadalafil (10^{-6} M and 10^{-5} M), alfuzosin (3×10^{-8} M or 10^{-6} M and 10^{-5} M) or a combination. Concentration-response curves (CRCs) to norepinephrine were generated on prostatic strips and detrusor strips precontracted with carbachol. Strips were also submitted to electrical field stimulation (EFS).
Results and limitations: When alfuzosin and tadalafil were combined, the maximal relaxation to norepinephrine on carbachol-precontracted detrusor strips was significantly increased compared with tadalafil alone, and EFS-induced detrusor contractions were better inhibited compared with each compound alone. Tadalafil significantly inhibited norepinephrine-induced prostatic strip contractions by reducing the maximal effect, whereas alfuzosin shifted the CRC of norepinephrine to the right. Combining both tadalafil and alfuzosin resulted in a greater relaxant effect. Likewise, the combination was more effective at reducing EFS-induced contractions compared with each compound alone.
Conclusions: The combination of alfuzosin and tadalafil exerts an additive effect of inhibiting adrenergic smooth muscle tone of prostatic tissue and EFS-induced detrusor contractions and conversely, of enhancing adrenergic relaxation of detrusor precontracted with carbachol. These experiments provide experimental support for the clinical investigation of the combination of α1-blockers and PDE5 inhibitors in the treatment of LUTS.

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0302-2838/$ – see back matter doi:10.1016/j.eururo.2009.04.039

1. Introduction

Lower urinary tract symptoms (LUTS) increase with advancing age [1]. LUTS comprise storage symptoms, often related to detrusor overactivity, and voiding symptoms. The latter could result either from bladder outlet obstruction as a result of benign prostatic enlargement resulting from the histologic condition of benign prostatic hyperplasia (BPH) or from impaired detrusor contractility.

Alpha-adrenoceptor antagonists are considered to be the most effective monotherapy for LUTS suggestive of BPH [2]. They improve both voiding and storage symptoms of BPH and are characterized by a rapid onset of action [3]. All α1-adrenoceptor antagonists are considered to have a comparable efficacy in LUTS. Nevertheless, alfuzosin offers the advantages of good cardiovascular tolerability, even in elderly and hypertensive patients, and less deleterious effect on sexual function [4].

Phosphodiesterase type 5 (PDE5) inhibitors are the first-line treatment of erectile dysfunction (ED) [5]. Moreover, randomized placebo-controlled trials have shown that the three available PDE5 inhibitors (ie, sildenafil, vardenafil, or tadalafil), also improve voiding and storage LUTS in patients with BPH [6–9]. A recent pilot study has also shown that a single vardenafil administration (20 mg) can improve urodynamic parameters in men with spinal cord injuries [10].

LUTS and ED are strongly linked independent of age and cardiovascular comorbidities, as shown in several epidemiologic studies [11,12]. Thus, coprescription of α-adrenoceptor antagonists and PDE5 inhibitors is likely to increase. The concept is currently emerging that treatment with a combination of an α1-adrenoceptor antagonist and a PDE5 inhibitor is the most effective therapy to treat LUTS related to BPH. Specific precautions, however, should be taken regarding the concomitant use of these two therapeutic classes due to their potential additive hypotensive effects. Interestingly, alfuzosin (10 mg once daily [OD]) shows no relevant hemodynamic interaction with tadalafil at the highest prescribed dose (20 mg OD) [13]. Moreover, very recent reports of combination of α-adrenoceptor antagonists and PDE5 inhibitors have each reported no symptomatic hemodynamic effects [14,15]. Finally, a pilot clinical study has shown that combining sildenafil 25 mg OD with alfuzosin 10 mg OD was superior to each therapy alone (same dosages) in relieving LUTS and ED in BPH patients [16].

The mechanism of action responsible for the greater benefit of the combination in LUTS is not yet fully understood and should be explored. Increasing recent data indicate that the benefit observed from the combination in clinical practice on LUTS could be due to an effect of both drugs, not only on the prostate but also on the smooth muscle of the bladder [17–19]. Thus, our goal was to evaluate in vitro whether the combination of alfuzosin and tadalafil was more effective than each compound alone in inhibiting pharmacologically induced or electrical field stimulation (EFS)–induced contractions of human prostatic smooth muscle and/or in enhancing pharmacologically induced relaxation of human bladder smooth muscle.

2. Materials and methods

2.1. Preparation of human prostatic strips and detrusor strips

Prostatic samples (from the transition zone) and bladder samples (from the dome) were obtained from 20 patients (age: 69 ± 3 yr) and from 17 patients (age: 67 ± 2.5 yr), respectively, undergoing cystoprostatectomy for infiltrating bladder cancer. The subjects had no history of bladder dysfunction according to their medical charts and had not received radiotherapy. All patients provided their informed consent.

Tissue samples were stored at 4 °C in Krebs-HEPES buffer (118 mM sodium chloride, 4.7 mM potassium chloride (KCl), 1.2 mM magnesium sulfate, 1.2 mM potassium dihydrogen phosphate, 2.5 mM calcium chloride, 4.2 mM sodium bicarbonate, 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 h maximum). Samples were cleaned of adherent tissue and blood, and sections (4 × 2 × 2 mm) were excised from each donor sample for each experiment.

Strips were suspended in 5-ml organ chambers filled with Krebs-HEPES buffer (37 °C, pH: 7.4) that was continuously bubbled with 95% O_2 and 5% CO_2. They were connected to force transducers for isometric tension recording (Pioden Controls Ltd, UK) and an initial tension was applied (0.5–1 g). Following amplification, the tension changes were computerized with Mac Lab/8 using Chart 5 software (ADInstruments Ltd, Oxfordshire, UK). The tissue preparations were allowed to equilibrate for 60 min while being washed periodically with fresh Krebs-HEPES buffer, and they were primed by KCl (100 mM, 10 min).

2.2. In vitro contractile experiments with prostatic strips

Concentration-response curves (CRCs) to norepinephrine (10^{-8} M to 10^{-4} M) were constructed on each strip. Then, after washings, and following a 20-min incubation period with either vehicle (corresponding to the high dose combination), tadalafil (10^{-6} M or 10^{-5} M), alfuzosin (3×10^{-8} M), or two combinations of both compounds (10^{-6} M tadalafil plus 3×10^{-8} M alfuzosin or 10^{-5} M tadalafil plus 3×10^{-8} M alfuzosin), CRCs to norepinephrine were repeated.

In another set of experiments, frequency response curves (FRCs) (at 5 Hz, 10 Hz, 15 Hz, 20 Hz, 30 Hz, and 40 Hz; 5-ms pulse duration, 5-s train duration; 300 mA) were constructed. After washings, and following a 20-min incubation period with the same conditions as for norepinephrine CRCs, FRCs were repeated.

The concentrations used for alfuzosin were in the same range as its pKi determined for the α1-adrenoceptor in human prostate [20]. The concentrations used for tadalafil were previously reported to be efficient concentrations in prostatic tissue [21] and were used to evaluate whether the combination could improve the efficacy of each compound.

2.3. In vitro contractile experiments with detrusor strips

Strips were incubated for a 20-min period with alfuzosin alone (at 10^{-6} and 10^{-5} M), tadalafil alone (at 10^{-6} M and 10^{-5} M), or both compounds combined at two different concentrations (10^{-6} M tadalafil plus 10^{-6} M alfuzosin or 10^{-5} M tadalafil plus 10^{-5} M alfuzosin) and vehicle (corresponding to the dosage combination). Strips were then precontracted with carbachol (10^{-6} M) and allowed to reequilibrate until a stable response was obtained (20 min), and then CRCs for norepinephrine (10^{-9} M to 3×10^{-5} M) were performed.

In a second set of experiments, the detrusor strips were submitted to EFS (20 Hz; 5-ms pulse duration, 5-s train duration; 300 mA) applied by