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Relationship between Therapy with A1-Adrenoceptor Antagonists (A1-Blockers) for Benign Prostatic Obstruction and Sexual Function

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Abstract

Lower urinary tract symptoms (LUTS) are common in elderly males and have multifactorial aetiology. The impact of LUTS on individual's health and quality of life often motivates patients to search for treatment. The administration of α1-adrenoceptor antagonists (α1-blockers) is considered as a first-line choice for drug treatment, because of its well documented effectiveness and safety. Still side effects are relatively common, but rarely result in discontinuation of therapy. There is a steadily growing interest for the impact of these therapeutical agents on male sexual function. Our aim is to present adequately, through the review of the international relative literature, the effects of currently and mostly used α1-blockers on sexual function of patients suffering from LUTS due to benign prostatic obstruction.

Introduction

Lower urinary tract symptoms (LUTS) are common in elderly males. Based on current knowledge the aetiology of LUTS is multifactorial [1]. One of the main causative factors of LUTS is the benign prostatic obstruction (BPO). The impact of LUTS on individual's health and quality of life often motivates patients to search for medical advice. Urologists usually have to alleviate LUTS and one very popular choice, because of its well documented effectiveness and safety, for first-line drug treatment is the administration of α1-adrenoceptor antagonists (α1-blockers).

Despite good safety profile and high tolerability rates for treatment with α1-blockers, there are known and recorded side effects. Basic cause of these side effects is considered to be the natural presence of α1-adrenoceptors in blood vessels, non-prostatic smooth muscle cells and central nervous system. Cardiovascular side effects, such as dizziness and orthostatic hypotension, represent a major concern for both patients and physicians. Fortunately, the development and use of the more uroselective α1A-blockers have ameliorated the whole "side effects issue". Currently used in a mainstream way are the following α1-blockers: i) doxazosin, ii) terazosin, iii) alfuzosin, iv) tamsulosin and v) silodosin.

Erectile dysfunction (ED) coexists in approximately 70% of males suffering from LUTS [2]. Disorders of sexual function and their bothersomeness were found to strongly correlate with age and severity of LUTS, independently of the existence of other comorbidities [3]. It would be ideal that the medical therapy for LUTS due to BPO would not further impair sexual function, but this not always the case. The most prominent sexual side effect caused by α1-blockers is ejaculatory dysfunction. This fact can result in extra decline of sexual function, which apparently generates an additional deterioration of quality of life. On the other hand, it is mentioned that the use of α1-blockers improves sexual function, including the aspects of satisfaction, erection and ejaculation.

Our aim is to investigate and present the relationship between therapy with α1-adrenoceptor antagonists for BPO and sexual function.

Physiology of Male Sexual Function

Erection and ejaculation are the fundamental components of male sexual function. Both presuppose the presence of erotic desire (libido). Of course the parameter of sexual satisfaction is also substantially important.

Normal penile erection is a composite physiological process involving integration of biochemical signals evoked in response to neurotransmitters and vasoactive factors involved in regulation of penile flaccidity and erection [4]. Studies have shown that the trabecular smooth muscle of corpus cavernosum is an important structure of penis and conduces to control of penile flaccidity and erection [5-7]. The release of norepinephrine (NE), which is a major adrenergic neurotransmitter, as well as the synthesis and release of endothelial vasoconstrictor agents, like endothelins and contractile prostaglandins, are due to adrenergic nerves and mediate local control of trabecular smooth muscle contractility. When penis is flaccid, the smooth muscle fibers of trabeculae and penile cavernosal arteries are contracted. Contractile agonists interact with specific membrane and ion channels, regulating intracellular calcium level and/or amending calcium sensitivity to contractile proteins, resulting in smooth muscle contraction [8,9].

One key pathway of penile flaccidity is the release of NE from adrenergic nerves and its binding to postjunctional α1 and α2 adrenergic receptors (AdRs), localized to the smooth muscle of trabeculae and cavernosal arteries [4]. This reaction activates G-protein coupled alpha-AdRs and signal transduction pathways, causing contraction of smooth muscle fibers. Sexual stimulation, leading in activation of non-adrenergic non-cholinergic nerves,

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redounds in synthesis and release of nitric oxide (NO), which diffuses into the trabecular and arterial smooth muscle of corpus cavernosum [10-13]. NO activates guanylyl cyclase, increasing cyclic guanosine monophosphate (cGMP). The NO/cGMP pathways integrate into the overall regulation of myosin light chain kinase, myosin light chain phosphatase and intracellular calcium concentration. The outcome is reduced intracellular calcium, reduced smooth muscle fibers tone, enhanced smooth muscle relaxation and penile erection [14].

The alpha-adrenergic neuroeffector system has a crucial physiological role in erection [8,9,15-22]. In vivo and in vitro studies have indicated that adrenergic nerves (sympathetic nervous system), source of physiologically active NE, innervate human penile corpus cavernosum [9,23,24]. Release of NE from sympathetic nerve fibers of the human corpus cavernosum is modulated by presynaptic α2 AdRs and cholinergic nerves (parasympathetic) via prejunctional muscarinic acetylcholine receptors. Contraction of trabecular smooth muscle under the influence of NE depends on expression of postjunctional α1 and α2 AdRs [8,9,20]. Systemically administered antagonists of alpha AdRs (blockers) ease penile erection and, in some cases, provoke prolonged erection, even episodes of priapism [25-31]. In vitro studies with tissue strips of corpus cavernosum have found that prazosin (α1-blocker) and yohimbine (α2-blocker) produced right-ward parallel shifts in the phenylephrine concentration-response curve [18,20,32-35]. Prazosin had a greater affinity for the receptor, implying predominance of α1 AdRs over α2 ones in human erectile tissue [20,32]. These studies revealed the significant role of α1 AdRs in normal erection.

Ejaculation is distinguished in the following phases: i) seminal emission, ii) formation of a high-pressure chamber and iii) antegrade expulsion of fluid from the urethra [36].

Emission is the deposition of the ejaculate in the prostatic urethra via the ejaculatory ducts. Sympathetic nervous system controls emission. Originating from the cerebral cortex (thalamus, spinothalamic centers) efferent fibers responsible for emission, proceed through the anterolateral columns to the thoracolumbar and sympathetic chain (T10 to L3). From there postsynaptic adrenergic nerve fibers march through the superior hypogastric plexus overlying the bifurcation of aorta en route to the end organs [3]. Another synaptic junction and short adrenergic fibers, branches of which innervate individual smooth muscle cells, exist within the thin adventitial tissue of the end organs [37].

As emission continues, simultaneous bladder neck closure and contraction of distal external sphincter mechanism formulate a high-pressure chamber [3].

The opening of the urogenital diaphragm and the rhythmic contraction of ischiocavernous, bulbocavernous and pelvic floor muscles result in having an antegrade ejaculation. The contraction of these muscles is controlled by the somatic nervous system. At the same time, somatic muscle control is a part of the ejaculatory reflex, which is not considered to be under voluntary control [38].

Currently used A1-Adrenoceptor Antagonists (A1-Blockers) and Sexual Function

Terazosin is associated with relatively low incidence of ejaculatory dysfunction [3]. The Veterans Affaires Cooperative Studies in 1996 compared placebo, terazosin, finasteride and combination therapy for benign prostatic hyperplasia and reported an incidence rate equal to 0.3% for ejaculatory dysfunction in the group of patients treated with terazosin [39]. Another study, the Hytrin Community Assessment Trial study, reported a rate of 1.4%, but this result was found to be statistically significantly different from placebo [40].

No available data currently exist for the relationship between doxazosin and sexual dysfunction, including the erectile one. Contrariwise, there are supporting data for the improvement of erection and sexual health in patients who are treated for LUTS or diagnosed benign prostatic hyperplasia with doxazosin [41-44].

Rosen R *et al.* studied the impact of alfuzosin (extender-release form in a dosage of 10 mg) on sexual function in men suffering from symptomatic benign prostatic hyperplasia. According to their findings alfuzosin significantly improved erection and had no adverse effect on ejaculation compared to placebo [45]. Kim MK *et al.* determined the effect of alfuzosin on sexual function by using the Male Sexual Health Questionnaire (MSHQ) in men with LUTS. They found that alfuzosin significantly improved the ejaculatory function and had also positive impact on erection and sexual satisfaction [46]. Similarly, two other studies, conducted in Taiwan and Korea, included men with benign prostatic hyperplasia under therapy with alfuzosin and concluded that alfuzosin significantly improved erection, ejaculation and sexual satisfaction [47,48].

Tamsulosin correlates with a significant incidence (4-18% in clinical trials) [49] of ejaculatory dysfunction, even reaching to the level of 30% of patients receiving this treatment [50]. Possibly this represents an outcome of its higher pharmacological selectivity for α1A-receptors of the bladder neck, seminal vesicles and vas deferens. In an animal model (rat) tamsulosin and alfuzosin were administered in dosages sufficient enough to decrease urethral pressure. The researchers measured bladder neck pressure and seminal vesicle pressure in response to electrostimulation of the hypogastric nerve and found that tamsulosin induced more detrimental effects on both pressures [49]. Barqawi AB *et al.* concluded that men taking tamsulosin for LUTS appear to be at an advantage over men taking other alpha-blockers, when the effect of LUTS on sexual health is considered [51]. Song SH *et al.* presented no significant difference between baseline and follow-up in erectile function, ejaculatory function, satisfaction, sexual activity and libido in a cohort of 177 men who received tamsulosin (0.2 mg once daily for 12 weeks) as therapy for LUTS [52]. Finally, Seo DH *et al.* compared tamsulosin based monotherapy (0.2 mg every day) versus combination therapy with tamsulosin and solifenacin (0.2 mg and 5 mg respectively) in men with LUTS with regard to their impact on erectile function. While the IIEF-5 score (International Index of Erectile Function) significantly improved as the IPSS-ST domain score (International Prostate Symptom Score - storage symptoms) improved in the monotherapy arm, no significant association was found in patients under combination therapy [53].

Silodosin is a recently developed uroselective α1A-blocker. Kobayashi K *et al.*, after comparing silodosin versus placebo in healthy male volunteers, concluded that orgasm is preserved regardless of ejaculatory dysfunction [54]. Another study on healthy volunteers revealed statistically significant worsening of subjective quality of orgasm by causing abnormal ejaculation (decreased

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volume or absence of ejectable semen) and a diminution in the number of bulbocavernosus/pelvic floor muscle contractions [55]. Yokoyama T *et al.* compared the effects of silodosin (4 mg twice daily), tamsulosin (0.2 mg once daily) and naftopidil (50 mg once a day) on LUTS, erectile and ejaculatory functions in patients with benign prostatic hyperplasia (BPH). According to their results, only naftopidil improved erection, while the group under silodosin had the greatest rate (24.4%) of total absence of antegrade ejaculation [56]. Even higher rate of ejaculatory disorder (42%) is reported by Sakata and Morita, who assessed the problem in sexually active patients with BPH. The reporting rate of ejaculatory disorder reached 95%, when authors constricted the finding on those who practiced sexual action (intercourse, masturbation) after oral intake of silodosin [57]. Montorsi F. in his review reports that the most usual adverse reaction related to the use of silodosin is ''retrograde ejaculation'' (anejaculation), resulting to a low discontinuation rate though [58]. A recent, Spanish, cross-sectional, observational study of quality of life in patients with BPH under treatment with silodosin found that the patients' scores in EQ-5D and SFI (Sexual Function Index) questionnaires were statistically lower with older age, severe LUTS and greater size of prostate, but no differences were acknowledged related to time on therapy with silodosin [59]. In closing, we would refer to another multicenter randomized trial, in which silodosin was compared with naftopidil, a highly selective α1D-blocker, regarding to their impact on sexual function of men with LUTS/BPH. Both agents did not affect erection, but the sexually active patients in the silodosin group experienced more intensive ejaculatory impairment, reporting namely statistically significant decrease of ejaculation volume, prolongation of time to ejaculation and decrease of orgasm [60].

Naftopidil, a selective α1D-blocker, is licensed only in Japan, since 1996, for treating males suffering from benign prostatic hyperplasia [61]. Masumori *et al.* investigated, in the context of a randomized multicenter study, the incidence of ejaculatory disorders caused by naftopidil (50 mg) and tamsulosin (0.2 mg) in patients with LUTS. The sexually active patients under therapy with tamsulosin reported with higher frequency reduced ejaculatory volume and an abnormal feeling on ejaculation, but the difference was significant only in the first issue [62]. In the abovementioned study by Yokoyama T *et al.* only naftopidil, in comparison with tamsulosin and silodosin, significantly improved erection, as demonstrated by the improvement of the IIEF-5 score at 4 and 12 weeks after treatment had ended [56]. Another finding of this study was that the reported rate of a de novo reduced volume of ejaculation was 2.4% in naftopidil group of patients [56]. Yamaguchi K *et al.*, in an already mentioned study, found that both silodosin and naftopidil had no significant effect on IIEF-5 score [60]. They additionally concluded that naftopidil offers a statistically significant lower degree of ejaculatory dysfunction [60]. It is noteworthy that it is unknown whether the reported data on naftopidil can be generalized, taking into account that: i) no clinical trial has compared naftopidil to placebo in western countries, ii) all available clinical trials were conducted exclusively in Japan, iii) long-term evaluation, beyond 18 weeks, of drug safety is unavailable and iv) the dose of tamsulosin used in the comparative studies was smaller than the recommended one in western countries [63].

Discussion

α1-adrenoceptor antagonists (α1-blockers) lack major effects on sexual desire (libido) as shown in placebo-controlled studies [64].

Regarding to erection we have inconsistent reports describing both beneficial and adverse effects. The improvement of erection and sexual function due to α1-blockers could be explained by two ways. Firstly, the indisputable reduction of bothersomeness due to the improvement of LUTS make patients feel less ''disabled'' by their LUTS and more able to enjoy pleasures of life without feeling inhibited or limited [65]. Secondly, inhibition of α1- and α1D-adrenoreceptor subtypes facilitates erection via relaxation of the smooth muscle in the penile arteries or the corpora cavernosum, thus improving the blood inflow [66]. Zorgniotti and Lefleur first suggested the erectogenic properties of the α-blocker phentolamine [67]. Additionally, concentration-dependent relaxation of corpus cavernosum muscle strips was demonstrated in isometric tension studies with prazosin, tamsulosin, doxazosin and terazosin, with tamsulosin being the most potent [68]. On the contrary, the ejaculatory dysfunction is a constant, treatment related problem. The prevalence of ejaculatory dysfunction has been estimated to be 82.6% in patients with LUTS treated with α-blockers [69]. Blockade of α1A subtype adrenergic receptors in the bladder neck causes muscle relaxation, allowing semen to flow back into the bladder during orgasm (retrograde ejaculation). At the bladder neck, in prostatic smooth muscle, seminal vesicle and on the vas deferens there are in abundance α1A receptors, getting involved in evoking contraction [70-72]. For this reason a relative or complete anejaculation rather than retrograde ejaculation is postulated. Hisasue S *et al.* as well as Hellstrom WJ *et al.* have supported with their studies the anejaculation thesis [73,74]. Maybe it would be better to use the more generalized term ''ejaculatory dysfunction'', since patients' description of the problem varies a lot, including decreased frequency, delay, dryness, decreased strength/force, decreased volume, decreased pleasure and sense of discomfort or even pain at ejaculation.

The subjective perception of orgasm is also a matter for consideration. Although orgasm is maintained, patients report usually a discount of satisfaction derived from orgasm. A possibly realistic explanation could be that this finding is due to the combination of reduced or no semen passing through the urethra with insufficient rhythmic contraction of the pelvic floor [55].

Investigators have also tried to determine the potential correlation between baseline parameters of patients with LUTS, such as age, IPSS score and prostate volume, therapy with α-blockers and impact on sexual function. Obviously, there is a twofold objective: i) to make a prognosis of which patients will experience, after α-blocker-based medical therapy, alterations in their sexual function according to baseline parameters and ii) to dissuade further deterioration of sexual function in males who already present relative problems. Leliefeld HHJ at al. implemented logistic regression analysis to identify factors that determined changes in sexual function, after therapy for BPH, and did not observe stong and consistent patterns that could explain changes in sexual function post treatment [75].

Nevertheless, discontinuation rates of therapy with α-blockers for LUTS are relatively low, for example 3.9% for silodosin [58]. The indubitable improvement of LUTS, generating an improvement of quality of life in general, apparently surmounts the contingent

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influence on quality of sexual life. Additionally, we need to take into account that men suffering from LUTS are usually old enough to already present sexual dysfunction and lower libido and that the effect of α-blockers is often blended, comprised of erectile upturn and ejaculatory dysfunction.

In conclusion, males suffering from LUTS due to BPO/BPH are extensively treated with α1-adrenoceptor antagonists. This therapy impacts on sexual function. Urologists have to take into consideration that sexual health is a fundamental human right, important to overall health and quality of life and that sexual satisfaction provides benefits to patients and their partners. An extra amelioration of an already impaired sexual function must be avoided, but we currently lack of prognostic factors that we could rely on moving towards this direction. We could regard alfuzosin, among all uroselective α-blockers, as the best available choice for younger patients, who are sexually active and need to be treated for LUTS. Finally, elderly patients with relative scarcity of sexual interest and major concern about voiding dysfunction represent ideal candidates for therapy with either tamsulosin or silodosin.

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