Original Article

Old and new challenges in medical treatment of benign prostatic hyperplasia

ENE Cosmin[1,2] [Dr.], **GEAVLETE Petrisor[1]** [Prof. PhD. Dr.],
ENE Corina Daniela[2] [PhD. Dr.], **NICOLAE Ilinca[3]** [PhD.],
GEAVLETE Bogdan[1] [Assist. PhD. Dr.], **COMAN Oana[2,3]** [Prof. PhD. Dr.]

1. *Clinical Hospital of Emergency „St. John", Bucharest;*
2. *Universitatea de Medicină şi Farmacie „Carol Davila", Bucharest;*
3. *Hospital of Tropical and Infectious Diseases „Victor Babeş", Bucharest;*

Rezumat

Hiperplazia benignă de prostată este o patologie intens studiată al cărei tratament medicamentos reprezintă cea mai facilă şi mai accesibilă modalitate de obținere a unei ameliorări a calității vieții la aceşti pacienți. În prezent sunt utilizate mai multe clase de medicamente: a-blocantele, tratamentul hormonal, anticolinergicele, tratamentul combinat, fitoterapia, precum şi alte variante terapeutice (desmopresina şi inhibitorii de 5 - fosfodiesterază), dar cele mai utilizate sunt prima şi ultima clasă menționată. Alfa-blocantele sunt o clasă de medicamente ce acționează prin intermediul noradrenalinei la nivelul α1 *şi* α2 *- receptorilor din țesutul adenomatos prostatic. Inhibitorii de 5* α *– reductază au la bază principiul deprivării androgenice prin scăderea concentrației dihidrotestosteronului intraprostatic, contribuind în acest mod la scăderea volumului prostatic. În ciuda paletei largi de posibilități terapeutice, trebuie ținut cont de faptul că tratamentul se adapteaza si individualizeaza în funcție de contextului clinic şi biologic.*

Abstract

Benign prostatic hyperplasia is a pathology intensively studied of which, medical treatment is the easiest and the most accessible way of obtaining an improvement in the quality of life in these patients. Currently there are several classes of used drugs: α *- blockers, hormonal therapy, anticholinergics, combination therapy, herbal medicine and other therapeutic options (desmopressin and inhibitors of 5 - phosphodiesterase), but the most used are the first and the last class mentioned. Alpha-blockers are a class of drugs that act via norepinephrine on the receptors* α1 *and* α2*, in prostatic adenomatous tissue. 5* α *– reductase inhibitors are based on the principle of androgen deprivation by decreasing the intraprostatic dihydrotestosterone concentrations, thereby contributing to the decrease of prostate volume. Despite the wide range of therapeutic possibilities, it should be kept in mind that treatment must be adapted and individualized according to the clinical and biological status of the patient.*

Benign prostatic hyperplasia is a highly studied pathology, but still arousing the interest of researchers, especially on finding methods of treatment which to be as effective to affect the least the quality of life and to be at the same time as accessible as possible. Drug treatment of benign prostatic hyperplasia is currently the easiest and the most accessible way of obtaining an improvement in the quality of life in these patients.

It has been described in terms of the patient's symptoms, and particular circumstances, a number of treatment options. Active surveillance (watchful waiting) is addressed to patients with mild symptoms who do not have complicated adenomas, and consists of patient surveillance, without being given treatment for his suffering. In this way, it's trying the improvement of quality of life through adjustments made to the patient's lifestyle, the diet, as well as by treatment related cause, which could lead to the presence of the patient's symptoms.

Medical treatment in patients with benign prostatic hyperplasia is to improve the quality of life of patients, by remission or disappearance of prostatic symptoms, being currently used several classes of drugs: α-blockers, hormonal therapy, anticholinergics, combination therapy, phytotherapy, and other therapeutic options (desmopressin and inhibitors of 5 - phosphodiesterase).

Alpha-blockers are a class of drugs that act via norepinephrine on α1 and α2 receptors in prostatic adenomatous tissue (prostatic stroma). Adrenaline and noradrenaline are catecholamines acting on adrenergic receptors, which belong to the G protein-coupled receptors. The drugs from this class, block the α1 – adrenergic receptors decreasing resistance to the urine flow [1]. Alpha-1 receptors have two subtypes: α - 1H (highly selective) and α -1L (weak selective). From 1H - α subtype the most important are: α - 1A, B, and D [2, 3]. Selective alpha1 - blockers are the treatment of choice in small to medium prostate adenomas. Older generation of drugs such as phenoxybenzamine and prazosin are becoming less common due to their low selectivity on α -adrenergic receptors, leading to significant side effects, more important than the existing ones for new smaller molecules. There are still listed in the guides few therapeutic options for treatment, such as terazosin hydrochloride, doxazosin, alfuzosin, which have the disadvantage of poor selectivity, but also newer molecules such as tamsulosin and silodosin, which are widely used today, due to their high selectivity. Those drugs do not cause hypotension and does not interfere with anti- hypertensive, being well tolerated in combination with phosphodiesterase 5 inhibitors [2].

Currently there are four α-1 blockers indicated for the treatment of benign prostatic hyperplasia, namely: alfuzosin, doxazosin, tamsulosin and terazosin. The most common side effects of these drugs are: fatigue, dizziness and orthostatic

hypotension due to vasodilatation followed by decrease in blood pressure in the vessels.

Hormonal therapy with 5 α - reductase inhibitors is based on the principle of androgen deprivation by lowering intraprostatic dihydrotestosterone concentrations, thus contributing to a decrease in prostate volume [2]. Dihydrotestosterone is presented as a paracrine hormone and promotes prostate growth due to large number of androgen receptors found in the prostatic level. There are two isoforms of this enzyme: 5 α - reductase type 1, which is present less in the prostate, but is more active at the skin and liver, and 5 α - reductase type 2, which has a dominant expression in the prostate. The inhibitors of 5- α - reductase are indicated in the treatment of larger adenomas (over 50 cm3). The most used molecules are finasteride acting on the subtype 2 of 5 α - reductase and dutasteride, with a dual action on subtypes 1 and 2 of 5 α - reductase. Hormonal therapy shows a lag of about one month between the start of drug administration and the beginning time for feeling its effects. The side effects of this therapy, can be mentioned in the following: reduced libido, erectile dysfunction, retrograde ejaculation, decreased semen volume and less, gynecomastia [4-6].

Combined therapy between α -blockers and 5 alpha- reductase inhibitors, relies on epithelial and stromal components accumulated on the prostate, being more appreciated in clinical practice as first-line therapy. There have also been approved pharmaceutical products in a single tablet including both an alpha-blockers (tamsulosin) and a 5α-reductase inhibitor (dutasteride). Studies have shown that administration of both substances at the same time diminish the symptoms and increased maximum urinary flow, reducing the risk of incurring surgery, in a greater way than each drug separately and compared to placebo [2]. Other ways of combined therapy are: the combination of α - blocker and anticholinergic or α - blocker with 5-phosphodiesterase inhibitors.

Muscarinic receptor antagonists are based on the action of acetylcholine on the urinary bladder. Acetylcholine always produces the onset of an activity on nicotinic receptor, while the action on muscarinic receptors is a modulatory one. At the urinary level it increases ureteral peristalsis, relaxes the muscles of the bladder, the sphincters and stimulates smooth fibers from detrusor surface [6]. Acetylcholine stimulates the postsynaptic muscarinic receptors, which leads to the release of G-protein-mediated calcium in the sarcoplasmatic reticulum, the opening of calcium channels from the cell membrane, which leads to smooth muscle contraction. There are five subtypes of muscarinic receptors, but subtype M2 and M3 are predominantly expressed in the detrusor muscle, the mechanism being involved in bladder contraction [7-9]. From the relaxation of the detrusor muscle, there is an improvement in the irritative symptoms in patients with benign prostatic hyperplasia. Recommended drugs for the treatment of overactive bladder

are darifencacin hydrobromide, fesoterodine fumarate, oxibutin hydrochloride, propiverine hydrochloride, solifenacin succinate, trospium chloride and tolterodine tartrate. As side effects of this therapy, there were noted: dry mouth, nasopharyngitis, constipation, urination, dizziness and, less commonly, urinary retention.

Combination therapy between antagonists of muscarinic receptor and α - blockers had a complementary effect, being useful in reducing the frequency of voiding, the nocturia, and in improving IPSS score and quality of life in these patients. The most common side effect was dry mouth recorded.

Phytotherapy may be a treatment option carefully selected cases of prostate adenoma. Among the most commonly used extracts is included: *Rooperi Hypoxis* root fruit of *Serenoa rerpens / Sabal serrulata*, pumpkin seeds, pollen extracts, Echinceea purpurea roots and more [10].

Regarding the active substance or substances from these products, there are studies that consider the free fatty acids and sitosterol as being active compounds of them [3].

Another composition and concentration of active substances, can be found in the structure of each product, due both to the manufacturing methods differences, and also to mixtures of different plants used.

The phytotherapic mechanism of action is in study. There are three mechanisms of action described in the literature : the inhibition of 5-alpha reductase inhibitors, the anti-inflammatory effect and altered cell growth [11].

Regarding the improvement of symptoms in patients with benign prostatic hyperplasia treated with phytotherapics compared to placebo, it was observed an increased quality of life revealed by IPSS score, relieving symptoms and decreasing postmicțional residual volume (PVR) in the first months of starting treatment [12, 13].

Other molecules used in benign prostatic hyperplasia are: desmopressin (a vasopressin analogue) - arginine antidiuretic hormone, with a role in the homeostasis of water, which promotes the reabsorption of water by lowering the amount of excreted urine, which is useful in decreasing the polyuria and nocturiei episodes in patients with benign prostatic hyperplasia. The side effects of this medication are: diarrhea, nausea, headache, abdominal pain, dizziness and the emergence of hyponatraemia.

5 - phosphodiesterase inhibitors - nitric oxide is a neurotransmitter non – adrenergic and non -cholinergic, synthesized from amino acids (L -arginine), involved in the transmission of signals in the urinary tract. At the cellular level, NO stimulates the synthesis of cyclic guanosine monophosphate (cGMP) which activates phosphodiesterases, leading to smooth muscle relaxation by depletion of calcium. 5 phosphodiesterase inhibitors reduce the tone of the detrusor smooth

muscle, of urethra and of prostate [14, 15]. There are three drugs approved to EAU 2013 Guidelines for treatment of pulmonary hypertension at European level, namely sildenafil, tadalafil and vardenafil, but these drugs have not been approved for being used in benign prostatic hyperplasia. Side effects may include: dizziness, dyspepsia, visual disturbances, headache, myalgia, nasal congestion, conjunctivitis, syncope, tinnitus. Treatment of LUTS (lower urinary tract symptoms) with these drugs is still experimental.

Conclusions

Despite the wide range of therapeutic possibilities, it should be kept in mind that the treatment must always be individualized and adjusted according to clinical and laboratory context. Also, despite the progress made in this area, and despite the hard research that is carried out to develop new molecules, drug therapy in benign prostatic hyperplasia is for the moment without a curative visa, only helping to improve the patients' quality of life.

Conflicts of interests:

The authors have nothing to disclose.

References:

1. Fulga I, Corciovei Constantinescu I, Coman OA, Constantinescu MC, Zugravu A, Coman L, Cristescu IG, Stoleru S, Zugravu G - *Farmacologie*. Editura Medicală, 2006: 120-124; 82-84.

2. Sinescu I, Gluck G. - *Tratat de urologie*. Vol. 4, Ed.Medicala 2008.

3. Dhingra N, Bhagwat D. - *Benign prostatic hyperplasia: An overview of existing treatment.* Indian Journal Of Pharmacology 2010.

4. Naslund MJ, Miner M. - *A review of the clinical efficacy and safety of 5α-reductase inhibitors for the enlarged prostate.* ClinTher 2007, 1:17-25.

5. McConnell JD, Roehrborn CG, Bautista O, Andriole GL, Dixon CM, Kusek JW, Lepor H, McVary KT, Nyberg LM Jr, Clarke HS, Crawford ED, Diokno A, Foley JP, Foster HE, Jacobs SC, Kaplan SA, Kreder KJ, Lieber MM, Lucia MS, Miller GJ, Menon M, Milam DF, Ramsdell JW, Schenkman NS, Slawin KM, Smith JA. - *Medical Therapy of Prostatic Symptoms (MTOPS) Research Group.The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia*. N Engl J Med 2003, 25:2387-98.

6. Roehrborn CG, Siami P, Barkin J, Damião R, Major-Walker K, Morrill B, Montorsi F. - *CombAT Study Group. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombATstudy.* EurUrol 2010, 1:123-31.

7. Chess-Williams R, Chapple CR, Yamanishi T, Yasuda K, Sellers DJ. - *The minor population of M3-receptors mediate contraction of human detrusor muscle in vitro*. J Auton Pharmacol 2001, 21:243-8.

8. Matsui M, Motomura D, Karasawa H, Fujikawa T, Jiang J, Komiya I, Takahashi S, Taketo MM. - *Multiple functional defects in peripherial autonomic organs in mice lacking muscarinic acetylcholine receptor gene for the M3 subtype*. Proc Natl Acad Sci USA 2000, 97,17: 9579 - 84.

9. Braverman AS, Doumanian LR, Ruggieri MR. - *M2 and M3 muscarinic receptor activation of urinary bladder contractile signal transduction. II. Denervated rat bladder.* J Pharmacol Exp Ther 2006, 316:875-80.

10. Fitzpatrick JM, Dreikorn K, Khoury S. - *The medical management of BPH with agents other than hormones or alpha-blockers*, SCI. 1993: 445-450.

11. Dreikorn K. - *The role of phytotherapy in treating lower urinary tract symptoms and benign prostatic hyperplasia.* World J Urol. 2002, 19,6:426-435.

12. Chatelain C, Autet W, Brackman F. - *Comparison of once and twice daily dosage forms of Pygenumafricanum extract in patients with benign prostatic hyperplasia: a randomized, double-blind study, with long term open label extension.* Urology 54 1999: 473-478.

13. Berges RR, Kassen A, Senge T. - *Treatment of symptomatic benign prostatic hyperplasia with beta-sitosterol: an 18-month follow-up.* BJU Int. 2000, 85:842-846.

14. Ückert S, Küthe A, Jonas U, Stieff CG. - *Characterization and functional relevance of cyclic nucleotide phosphodiesteraseisoenzymes of the human prostate.* J Urol 2001, 166:2484-90.

15. Ückert S, Oelke M, Stief CG, Adersson KE, Jonas U, Hedlund P. - *Immunohistochemical distribution of cAMP- and cGMPphosphodiesterase (PDE) isoenzymes in the human prostate.* EurUrol 2006, 49:740-5.