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FESOTERODINE FOR THE TREATMENT OF OVERACTIVE BLADDER: PHARMACOLOGICAL BASES AND CLINICAL RESULTS

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The results of the clinical use of the new anticholinergic drug fesoterodine in the treatment of patients with overactive bladder was presented in the review. An analysis was made of the pharmacological effects of fesoterodine, which provide its high clinical efficacy and good tolerance.

Keywords: overactive bladder; fesoterodine; anticholinergic therapy; muscarinic receptors.

ФЕЗОТЕРОДИН В ЛЕЧЕНИИ ГИПЕРАКТИВНОГО МОЧЕВОГО ПУЗЫРЯ: ФАРМАКОЛОГИЧЕСКИЕ ОСНОВЫ И КЛИНИЧЕСКИЕ РЕЗУЛЬТАТЫ

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В обзорной статье приведены результаты клинического применения нового антихолинергического препарата фезотеродин при лечении пациентов с гиперактивным мочевым пузырем. Сделан анализ фармакологических эффектов фезотеродина, которые обеспечивают его высокую клиническую эффективность и хорошую переносимость.

Ключевые слова: гиперактивный мочевой пузырь; фезотеродин; антихолинергическая терапия; М-холинорецепторы.

INTRODUCTION

The term overactive bladder syndrome (OAB) refers to a symptom complex manifested by an imperative urge to urinate, with or without urge incontinence, usually accompanied by increased daytime frequency of urination and nocturia in the absence of infectious and other obvious lesions of the bladder [1]. Due to a high prevalence, OAB ranks high among all dysfunctions of the lower urinary tract. The incidence of OAB in adults is estimated to range between 15 and 25% [2, 3], and it is more often detected in women and older patients [3, 4]. The frequency of OAB in Russia, as indicated by the results of various epidemiological studies, is 18% in men and 28% in women [5].

Generally, the social and clinical significance of OAB is determined not only by its high prevalence but also by a significant deterioration in the patient's quality of life – affecting almost all aspects of the patient's life, specifically social, family, professional, and sexual aspects [6, 7]. The degree of such decrease in the quality of life typically depends on the severity and nature of the OAB symptoms, in particular, the presence and severity of urge incontinence [7, 8]. The high prevalence and negative impact on the quality of life further determine the significant attention paid to OAB by urologists and other medical specialists.

Drug therapy is pertinent to the treatment of OAB. While the possibility of using anticholiner-

gic drugs in the treatment of OAB was first demonstrated experimentally in 1975 [9], in 1976, the efficacy of M-anticholinergic drugs was proved in a clinical setting [10]. However, although over the past 45 years, a significant number of drugs with M-cholinolytic action have been proposed and drugs from other groups, in particular β_3-adrenoceptor agonists, have been actively used, the anticholinergic therapy remains the primary one in the treatment of OAB patients [11–13].

The M-anticholinergic drugs block the M-cholinergic receptors, which prevents their activation by the neurotransmitter acetylcholine. In total, five subtypes of M-cholinergic receptors have been identified in humans, which differ in localization and functions. The latter are implemented through signal transduction by heterotrimeric G-proteins. While the M_2- and M_4-cholinergic receptors are inhibitory, and the corresponding protein is designated as Gi, the M_1-, M_3-, and M_5-cholinergic receptors are stimulating (Gq protein) [14]. The activation of M_2- and M_4-receptors suppresses the activity of adenylate cyclase and promotes relaxation of smooth muscles, contrary, the activation of M_1-, M_3-, and M_5-receptors is accompanied by an increase in phosphoinositide hydrolysis, which further leads to an increase in the level of intracellular calcium and contraction of myocytes [14].

As shown by numerous immunological, functional, and molecular studies, the bladder wall comprises of M_2- and M_3-cholinergic receptors. The number of M_2-receptors is significantly greater than that of M_3; their ratio is generally 3–4:1 [15, 16]. Despite the predominance of M_2-cholinergic receptors in the bladder, detrusor contractions are mediated by the stimulation of M_3-cholinergic receptors [15, 17]. The function of M_2-cholinergic receptors in the bladder has long been unclear. However, M_2-cholinergic receptors have been shown to play a role in ensuring the contractile ability of the detrusor, although this role can be regarded as indirect. It has also been proven that the activation of M_2-cholinergic receptors inhibits the relaxation of the detrusor mediated by the sympathetic nervous system, thereby increasing its contraction [18]. It is known that the activation of β-adrenergic receptors by norepinephrine released from sympathetic nerves increases the level of cyclic adenosine monophosphate in smooth muscles, which is a key trigger for their relaxation [19]. In this regard, the results of the first study on the efficacy of the combined use of M_2-, M_3-anticholinergic drug fesoterodine, and β_3-adrenoceptor agonist Mirabegron [20] seem to be very promising in OAB treatment.

However, interestingly, in some diseases, the role of M_2-cholinergic receptors is significantly increased. For instance, in cases of neurogenic bladder dysfunctions in patients with spinal cord injury and myelodysplasia, it has been proven that the density of M_2-cholinergic receptors is increased and their function is changed; therefore, they, together with M_3-receptors, are directly involved in providing detrusor contraction [21]. Similar changes occur with detrusor hypertrophy [22]. With the denervation of the bladder, the density of M_2-cholinergic receptors increases by 60%, while the density of M_3-receptors does not change [23].

Thus, if the detrusor contractions are normally mediated by M_3-cholinergic receptors, in patients with neurogenic bladder dysfunctions and detrusor hypertrophy, these contractions can be mediated by M_2-receptors. Since the main reasons for the development of OAB are precisely neurogenic and myogenic disorders, this circumstance is clinically extremely important. Since there are much more M_2-cholinergic receptors in the bladder than M_3, such a transformation of the receptor composition and function inevitably leads to an increase in the contractile activity of the bladder. Therefore, for this category of patients, a significantly greater effect can be expected when using drugs that are both M_2- and M_3-anticholinergic drugs.

For a long time, a decrease in detrusor contractile activity due to blockade of M-cholinergic receptors of smooth muscle cells was considered as the main goal for using anticholinergic drugs in OAB patients. However, in recent years, data have shown that M-anticholinergic drugs can also decrease the afferent activity of the urinary bladder [24]. The urothelium has proven to be capable of releasing acetylcholine [25], and cholinergic modulation of afferent excitability of the urinary bladder is provided by M_2- and M_3-cholinergic receptors [26]. In this case, the cholinergic influence on afferent activity is implemented indirectly, through secondary mediators. The stimulation of M-cholinergic receptors in the urothelium causes the release of neurotransmitters that decrease or increase the sensitivity of the bladder, in particular, ATP and nitric oxide [27]. This effect is due to the presence of M-cholinergic

receptors in the urinary bladder mucosa, and their species characteristics, density, and affinity are similar to those in the detrusor. Thus, in the urothelium, the predominance of M_2- over M_3-receptors has also been found [28]. The blocking of the M-cholinergic receptors of the urothelium and submucosa by anticholinergic drugs contributes to the effectiveness of these drugs in OAB.

Thus, the use of M-anticholinergic drugs in the treatment of OAB patients has a substantial scientific basis and pharmacological rationale. The main points of action of these drugs are M_2- and M_3-cholinergic receptors in the detrusor and urothelium, which provides a decrease in both efferent and afferent activities. The value of the possibility of influencing the M_2-cholinergic receptors increases in patients with neurogenic OAB, as well as OAB caused by detrusor hypertrophy, which is often noted in patients with infravesical obstruction due to benign prostatic hyperplasia.

Furthermore, fesoterodine (Toviaz) is one of the modern anticholinergic drugs used in the treatment of OAB. Fesoterodine was approved by EMA in 2007 and FDA in 2008, and in 2013 it was registered in Russia as a drug for the treatment of OAB. Fesoterodine is a competitive blocker of muscarinic receptors of both the M_2- and M_3-subtypes, which is an undoubted advantage of the drug, since both the mechanisms of detrusor contraction (M_3-receptors) and the mechanisms that prevent its relaxation (M_2-receptors) are blocked [29]. As a result, the sensitivity of the bladder is also reduced. Thus, the balanced M_2- and M_3-receptor affinity of fesoterodine leads to a double effect of controlling both the contractile activity and sensitivity of the bladder.

PHARMACOKINETICS AND PHARMACODYNAMICS OF FESOTERODINE

The active metabolite of fesoterodine, which determines its antimuscarinic activity, is 5-hydroxymethyltolterodine (5-HMT) which is formed during the cleavage of fesoterodine by nonspecific esterases in blood plasma [30]. The average concentration of 5-HMT in blood plasma increases in proportion to the dose of the drug administered [31]. Due to the involvement of fesoterodine in the process of elimination, in addition to renal, of many other metabolic pathways, the influence of internal and external factors on its pharmacokinetics is less than that of tolterodine [31].

Fesoterodine is normally available in the form of tablets with prolonged-release of the active ingredient, which compared to the immediate-release dosage form provides an effective concentration in blood plasma, thereby reducing the risk of adverse events [32]. The maximum concentration of 5-HMT is noted in the blood 5 hours after the drug intake, and the pharmacokinetic profile has a smooth shape that ensures good tolerability to the therapy. In addition, with long-term use, 5-HMT is not accumulated, and the maximum therapeutic effect is achieved within two–eight weeks of regular administration of the drug.

The active metabolite of fesoterodine 5-HMT is metabolized with the participation of the CYP3A4 isoenzyme. This must be taken into account in the clinical use of fesoterodine. Accordingly, with the simultaneous administration of CYP3A4 inhibitors, such as clarithromycin, ketoconazole, saquinavir, and ritonavir, the daily dose of fesoterodine should not exceed 4 mg [33]. In addition, taking potent inducers of CYP3A4 isoenzyme (carbamazepine, rifampicin, phenobarbital) together with fesoterodine is also not recommended, as this may reduce the effectiveness of the treatment. Fesoterodine does not undergo presystemic metabolism in the liver, that is, biotransformation before it enters the systemic blood circulation, which makes the effect stable and predictable [34]. The presence of renal failure does not affect significantly the mean time to reach the maximum concentration of the drug and the mean terminal half-life of 5-HMT [35].

Moreover, food intake does not have a clinically significant effect on the fesoterodine pharmacokinetics, so it can be prescribed regardless of the food intake. Although the recommended starting dose is 4 mg/day, it can be increased to 8 mg/day. The possibility of prescribing fesoterodine either 4 or 8 mg/day suggests dosing flexibility and dose titration. Of note, the gender and age of patients do not affect the fesoterodine efficacy [36].

CLINICAL EFFICACY AND TOLERABILITY OF FESOTERODINE IN THE TREATMENT OF OAB PATIENTS

The results of the clinical use of fesoterodine indicate a high efficacy of the drug in reducing the severity of the main clinical manifestations of OAB, namely increased frequency of urination, urgency, and urge incontinence [37–39].

The clinical efficacy of fesoterodine from the perspective of evidence-based medicine has been studied thoroughly, and the results of the first clinical trials were published in 2007. In the study by N.W. Nitti et al. [39], 836 OAB patients were under case follow-up; 283 of them received fesoterodine at a dose of 4 mg/day, 279 at 8 mg/day, and 274 patients received placebo. The duration of the treatment was 12 weeks. The patients receiving fesoterodine had a significant improvement in the disease symptoms compared with the placebo group, namely decrease in the frequency of urination, the number of urgencies, urge incontinence, as well as increase in the average volume of urination. The treatment was mostly well-tolerated, with dry mouth and constipation being the most frequent side effects [39]. Similar results have been obtained in several other studies that confirm the efficiency of the two doses (4 and 8 mg) of fesoterodine in the treatment of OAB patients [38, 40]. Likewise, in the study by J.P. Weiss et al. [41], a significant decrease in the severity of nocturia and the frequency of urgency at night in OAB patients that were treated with fesoterodine was revealed.

While the clinical effect of fesoterodine in OAB patients typically manifests itself as early as two weeks after the start of the treatment for both doses [40], the maximum effect is achieved by week 3 or 4 of the treatment [42].

Further, P.E. Van Kerrebroeck et al. [43] have investigated the safety, tolerability, and efficacy of long-term courses of treatment with fesoterodine. In their study, all patients were first administered with a dose of 8 mg fesoterodine/day, which at week 4, was either reduced to 4 mg or kept the same. The duration of the treatment was between 24 and 32 months. Of the 471 patients included in the study, 61% continued treatment for 24 months or more; 71% chose a maintenance dose of 8 mg throughout the treatment; 88 patients rated the treatment tolerance as good; and dry mouth was noted in 34% and led to discontinuation of treatment in only 2% (n = 8) of the patients. Nevertheless, the effect of treatment persisted throughout the entire 24 months of treatment without a tendency to decrease [43].

Moreover, several studies have shown that the efficacy of fesoterodine at a dose of 8 mg/day is superior to that of tolterodine ER (extended release) at a dose of 4 mg/day in reducing the severity of the main OAB symptoms, namely urge incontinence, urgency, and increased urination frequency [38, 44].

J.J. Wyndaele et al. [45] in their study analyzed the efficacy of fesoterodine in OAB patients who were dissatisfied with previous treatment with tolterodine. At first, patients took fesoterodine at a dose of 4 mg/day for four weeks, then, based on a subjective assessment of efficacy and tolerability, they continued to take this dose or increased it to 8 mg; the total duration of treatment was 12 weeks. Approximately 50% of the 516 patients treated increased the dose of fesoterodine to 8 mg at week 4 of the therapy. By the end of the treatment, a significant improvement in the symptoms of OAB was noted. In addition, when analyzing the Patient Perception of Bladder Condition questionnaires, 83% of the patients noted an improvement by week 12 of fesoterodine intake, and 59% had an improvement by 2 or more points. Thus, fesoterodine has demonstrated high efficacy in the treatment of OAB patients after previous unsuccessful treatment with tolterodine [45]. Similar results were obtained in a number of other studies [46, 47]. H.B. Goldman et al. [48] also showed the clinical efficacy of fesoterodine at a dose of 4 mg/day to patients who had no benefit from previous treatment with tolterodine ER. By the end of week 1 of the treatment, the patients noted significant improvement in the OAB symptoms. By this time, urgent urinary incontinence was arrested in 38% of patients [48]. The clinical results suggest that fesoterodine can be considered as the drug of choice for patients in cases when M-anticholinergic drugs used previously are not effective enough [49].

However, of note, the results of prescribing fesoterodine to OAB patients do not depend on the urodynamic diagnosis, as the drug is effective both in the presence and the absence of increased detrusor contractile activity (detrusor overactivity) [50].

J. Heesakkers et al. [51] indicate the advisability of administration of fesoterodine to patients from the so-called special groups. These include: (1) women with genitourinary syndrome, so fesoterodine is recommended to them in combination with local (vaginal) estrogen replacement therapy; (2) patients at a risk of cognitive impairment, since fesoterodine has a limited ability to penetrate through the blood–brain barrier and have a negative effect on the central nervous system (CNS); and (3) elderly patients due to the high safety profile of

the drug [51]. Interestingly, to date, fesoterodine is the only anticholinergic drug recommended for the treatment of OAB in elderly patients. According to the FORTA classification (Fit fOR The Aged classification for lower urinary tract symptoms), fesoterodine is assigned to category B [52]. The FORTA system defines clear criteria for drug therapy, taking into account age, and its recommendations are based on the principles of evidence-based medicine and data of real practice. The efficacy and safety of fesoterodine at doses of 4 and 8 mg/day in elderly patients have been confirmed by the results of clinical studies [53].

Moreover, a decrease in the severity of symptoms in OAB patients treated with fesoterodine is accompanied by a significant improvement in their quality of life. Accordingly, in the study by K.J. Mansfield et al. [54], the administration of fesoterodine resulted in significant improvements in various aspects of the quality of life in seven out of nine domains of the KHQ questionnaire, and in the study by C.R. Chapple et al., it was noted in eight out of nine domains of the same questionnaire [44].

Fesoterodine prescription to men with irritative symptoms, who take alpha-adrenoblockers, has been proven to be very effective. This is evidenced by the results of a clinical study conducted by S.A. Kaplan et al. [55]. Nine hundred and forty-three men with accumulation symptoms were randomized into fesoterodine and placebo groups. Patients in the fesoterodine group were first treated with a dose of 4 mg/day, which was increased to 8 mg later. At week 4 of the treatment, 251 (53%) patients from the fesoterodine group indicated the need to increase the dose. The addition of fesoterodine to alpha-adrenoblocker therapy decreased significantly the urinary frequency and improved the quality of life, both compared with baseline and with placebo [55]. The use of fesoterodine has demonstrated its efficacy in the treatment of men with irritative symptoms after a transurethral resection of the prostate gland for benign hyperplasia. According to the data of urination diaries, compared with patients in the control group who received standard therapy, patients treated with fesoterodine for one month had a statistically significant decrease in the frequency of daytime urination and nocturia; additionally, the maximum urine flow rate increased according to uroflowmetry, the mean score on the IPSS scale increased, and the quality of life improved. The authors concluded that the use of fesoterodine for the treatment of accumulation symptoms in patients after transurethral resection of the prostate is advisable [56].

In 2019, the first publication appeared, which indicated the effectiveness of fesoterodine for patients with neurogenic OAB. T. Yonguc et al. [57] prescribed fesoterodine at a dose of 4 mg/day to 63 patients with Parkinson's disease complicated by OAB, and noted the high efficacy and good tolerability of the treatment. The clinical effect was expressed as decrease in the number of urinations, urgency and episodes of urge incontinence, and decrease in the severity of nocturia. The authors noted the absence of the effect of fesoterodine on the patients' cognitive function [57]. A significant clinical effect of fesoterodine administration to children with neurogenic dysfunctions of the lower urinary tract was also noted [58].

In fact, the affordability of the drug is also an important aspect of prescribing it. After analyzing the cost of treatment with various anticholinergic drugs O.V. Filippova came to a conclusion that the cost of treatment with fesoterodine is not only low, but, as a rule, is lower than many other antimuscarinic drugs. When using the drug at a dose of 4 mg/day, treatment costs an average of 23.11 rubles, and when using 8 mg, it is 31.67 rubles [59].

Moreover, the safety profile of M-anticholinergic drugs is due to the localization of M-cholinergic receptors. In addition to the urinary bladder, M-cholinergic receptors are also located in the ganglia, secretory glands, myocardium, and smooth muscles. Since there are currently no anticholinergic drugs that are absolutely selective for the bladder, their use can lead to adverse events caused by generalized blockade of muscarinic receptors. The most common side effect of anticholinergic therapy is dry mouth, while constipation, nausea, diarrhea, dizziness, drowsiness, and visual impairment that are registered less often. These side effects are dose-dependent and stop without any consequences after the end of the treatment [60]. While an increase in the heart rate is the only side effect with a higher frequency as compared to when using non-selective M-anticholinergic drugs, including fesoterodine, in comparison with selective ones, the incidence of other side effects, however, does not differ with these drugs [61]. In an extensive epidemiological study that examined the effect of M-anticholinergic drugs on the risk of occurrence of cardiovascular diseases

and associated complications, no significant differences were found after the administration of different anticholinergic drugs [62].

An important advantage of fesoterodine is its limited ability to penetrate the blood–brain barrier, which is manifested clinically by a low incidence of side effects in the CNS [39, 63]. As a result, fesoterodine has no limitations for use in patients with the CNS diseases. When prescribing fesoterodine, there is no risk of impairment of cognitive activity, including memory, which is especially important in elderly patients [63].

CONCLUSION

Fesoterodine is the drug of choice in the treatment of OAB patients. The pharmacological mechanisms of therapeutic action of the drug have been studied in detail, and the results of a large number of clinical studies indicate the high efficacy of fesoterodine in reducing the severity of OAB symptoms. In addition, the pharmacokinetic and pharmacodynamic characteristics provide a high safety profile of fesoterodine, due to which it can be prescribed to vulnerable groups of patients, such as the elderly patients, patients with CNS diseases, or cognitive impairments. The ease of administration, the possibility of dose titration, and the ratio of treatment cost to its effectiveness are important advantages of fesoterodine.

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