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Various Drugs From the Group of A1-Adrenergic Blockers and their Effect

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Abstract: This article describes the effectiveness of various α-blocker drugs. According to in vitro studies, the affinity of silodosin for α1A receptors is more than 160 times greater than the affinity of this drug for α1B receptors and more than 50 times for α1D receptors. The selectivity of silodosin for α1A receptors is approximately 17 times higher than that of tamsulosin. According to the results of a double-blind randomized study, silodosin is not inferior in effectiveness to tamsulosin. According to the results of the studies, silodosin showed high effectiveness in the treatment of benign prostatic hyperplasia and a completely acceptable safety profile.

Key words: Benign prostatic hyperplasia, α-adrenergic blockers, silodosin, uroselectivity.

Drugs that suppress adrenergic receptors have been used in clinical practice for quite a long time since 1918. The first adrenergic blockers were ergot alkaloids, which were used for fairly wide indications - from migraines to long-term treatment of arterial hypertension.

The clinical effects of total blockade of α-adrenergic receptors are very clear - this is the dilation of peripheral vessels, a drop in blood pressure, and tachycardia, which is of a reflex nature. Against this background, the effects associated with the influence on the urinary tract seem insignificant and insignificant. Therefore, adrenergic blockers were previously classified as antihypertensive drugs. The main factor limiting the widespread use of α-adrenergic blockers in general therapeutic practice is the large number of side effects: tachycardia and tachyarrhythmia, hypersalivation, nasal congestion, diarrhea, and visual impairment. These negative effects are more unpleasant than dangerous, but nevertheless they greatly reduce the patient's quality of life and often lead to refusal of further treatment. Side effects of α-adrenergic blockers are a consequence of the direct pharmacological effect of α-adrenergic receptor blockade. Therefore, correction of side effects during long-term use is difficult. On the other side, α-blockers are practically free of their own toxicity. High clinical efficacy, low toxicity and a large number of side effects caused by direct pharmacological effects led to the further development of the studied group of drugs to increase selectivity. Opening various subtypes of α-adrenergic receptors and clarification of their role made it possible to create α1-blockers, selective which, compared to non-selective α-blockers, have a much lesser effect on the cardiovascular system. Against this background, the results acquired clinical significance blockade of α1-adrenoreceptors of the lower urinary tract, which made it possible to use these drugs for the treatment of urological patients. The main goal that was set During the development of these drugs, treatment tolerability was also significantly increased. Despite proven effectiveness in the treatment of benign prostatic hyperplasia, and selective α1-blockers were initially positioned exclusively as antihypertensive agents. Only with the entry onto the market of more effective and safe antihypertensive drugs from other pharmacological groups did it become obvious that

Vasoactive α1-blockers are not competitive in this area. In modern cardiological practice, α1-blockers are reserve drugs and are prescribed only to isolated patients, while the α-blocker has the greatest hypotensive effect in its pharmacological group prazosin has been deregistered in the Russian Federation. However, when treating patients suffering from benign prostatic hyperplasia, the same drugs showed quite acceptable results. Particularly attracted rapid achievement of a therapeutic effect within 2-4 weeks and sometimes earlier. The ability of a drug to lower blood pressure in a given clinical situation turned out to be completely unnecessary, even undesirable. A number of authors recommended the use of selective vasoactive α1-blockers for the treatment of patients suffering from

combined urological and cardiological pathologies, however, real clinical practice has not confirmed the correctness this proposal. Indeed, a large proportion of elderly men receiving long-term conservative treatment for benign prostatic hyperplasia simultaneously require constant use of antihypertensive drugs. However, urologists cannot carry out a full correction of antihypertensive therapy, and cardiologists and therapists cannot adequately assess the function of the lower urinary tract and it is reasonable to prescribe treatment for benign prostatic hyperplasia, Further studies showed that α1-adrenergic receptors are heterogeneous. Of the three identified subtypes, mainly α1A and α1D receptors are present in the prostate gland and bladder neck, while the α1B subtype is characteristic of the cardiovascular system. Thus, it became possible to create highly selective drugs with minimal side effects. The first vasoneactive α1-blocker was tamsulosin, which acts mainly on α1A and α1D receptors and, at therapeutic concentrations, has no effect on systemic hemodynamics. The latest development is the creation of silodosin, an even more selective adrenergic blocker.

Mainly suppressing α1A receptors themselves, which will minimize the effect on the cardiovascular system and improve treatment tolerability. According to in vitro studies, the affinity of silodosin for α1A receptors is more than 160 times greater than the affinity of this drug for α1B receptors and more than 50 times to α1D receptors[1,2]. The selectivity of silodosin for α1A receptors is approximately 17 times higher than that of tamsulosin.

RESULTS

RESEARCH ON SILODOSIN

Table 1 shows the pharmacokinetic characteristics of silodosin. The bioavailability of the drug is 32%, the half-life is quite long - 11 hours, which determines its long-term effect (24 hours or more) and the possibility of use once a day. The drug is metabolized in the liver by the cytochrome P-450 system, after which the biotransformation products are excreted in the urine and feces. Influence Silodosin has minimal effects on cardiac activity and systemic blood pressure [3, 4].

However, it is worth noting that selectivity towards any subpopulation of receptors is a relative phenomenon and strictly dose dependent. Selectivity is fully manifested only when low and medium therapeutic doses of the drug are used. With increasing concentration of the drug in the blood, this property progressively weakens.

Table 1. Pharmacokinetics of α-blockers

Medicine	Prazosin	Doxazosin	Tamsulosin	Silodosin
Bioavailability %	50	65	100	32
Duration: hour	7-10	24	24	24
Half-life hour	2-3	19-22	13	11
Introduction Liver\Kidneys %	90/10	63/37	0/100	55/45
Hypotensive effect	++	+	0/+	0
Selectivity	0	+	++	++++

Therefore, the use of high dosages is inappropriate in most cases. These statements in pharmacology are an axiom regarding α-blockers, this was further confirmed by the results of a systematic review carried o t by TJ. Wilt et al, (2003). Increasing tamsulosin dosage more than 0.4 mg/day. did not lead to an increase in the effectiveness of treatment, but was accompanied by a significant increase in the frequency of side effects [5]. This is directly related to the weakening of the selectivity of the drug, since directly toxic reactions (another reason for the increase in the frequency of undesirable effects) are not typical for α-adrenergic blockers

EFFECTIVENESS OF SILODOSIN IN THE TREATMENT OF BENIGN PROSTATE HYPERPLASIA.

The effectiveness of silodosin for the treatment of benign prostatic hyperplasia has been confirmed by three double-blind randomized studies. Two of them were conducted in the USA, one in European

countries. In American studies, silodosin was compared with placebo [3, 6]. A European study compared silodosin with placebo and tamsulosin [7, 8]. The course of therapy was 12 weeks. Treatment results were assessed using both subjective (IPSS scale) and objective methods (uroflowmetry). In all studies conducted, silodosin significantly reduced the clinical manifestations of benign glandular hyperplasia compared with placebo ($p<0001$).

Moreover, patients in the main groups noted subjective improvement already on days 3-4 from the start of treatment (-4.2 vs -23 on the IPSS scale, $p<0.0001$). An increase in Omax was noted within 3-6 hours after taking the first dose of silodosin. To the moment

At the end of the study, the maximum urinary flow rate in the groups of patients receiving silodosin was significantly higher compared to the control groups ($p < 0.002$). The average increase in this indicator was 2.9-3.8 ml/s [6,7].

Across all studies, the proportion of patients who reported simultaneous subjective improvement in the feeling of incomplete emptying of the bladder, pollakiuria, and nycguria among those receiving silodosin was higher than among those receiving placebo, and this pattern was noted for both the general sample (30.5 vs. 20. 2% $p<0.0001$), and in relation to the group of patients who initially had nocturnal pollakiuria (two or more urinations per night) (349 vs 23.2% p.<.0001).

A number of patients, upon completion of the twelve-week course of therapy prescribed by the protocol, continued treatment with silodosin for 40 weeks. Basic yet the purpose of these studies was to assess the safety of the drug. Against the background of long-term use of silodosin, the decrease in IPSS scores continued. However, changes turned out to be relatively small: 0.82-1 point ($p < 0.01$ compared to the initial level) [6].

When patients receiving placebo were switched to silodosin, an average reduction in overall IPSS score of 2.7 to 3.0 points was achieved over 40 weeks ($p < 0.001$ compared to baseline) [7,9]. Of particular interest is a non-comparative prospective study performed by Y. Matsukawa et al (2009). A four-week course of silodosin led to a significant decrease in bladder outlet obstruction, which was confirmed by the results of uroflowmetry ($p < 0.0001$). The same study noted a significant increase in bladder volume at the time of the first urge from 113 ml initially to 140 ml after a course of treatment with silodosin [10]

COMPARISON OF SILODOSIN

WITH TAMSULOSIN

According to the results of a double-blind randomized study, silodosin is not inferior in effectiveness to tamsulosin. By the end of the twelve week.

During the course of treatment, a slightly more pronounced decrease in the subjective manifestations of benign prostatic hyperplasia was noted, but the differences did not reach a statistically significant level (-7.0-67 on the IPSS scale $p> 0.05$). However, the proportion of patients who reported simultaneous subjective improvement in the feeling of incomplete emptying of the bladder, pollakiuria, and nocturia among those receiving silodosin was higher compared with the same proportion of patients receiving tamsulosin or placebo ($p > 0.05$). This was noted both in the general sample and in the group of patients who initially noted two or more urinations per night [ll].

SAFETY OF SILODOSIN THERAPIES

Along with effectiveness, a very important parameter is the frequency of side effects, that is, the tolerability of therapy. According to a comprehensive analysis of the results of the three above-mentioned double-blind randomized studies

side effects (regardless of their severity) were noted by 34% of patients, and in 23.6% of patients the drug caused ejaculation disorders. The vast majority of these

Patients, knowing about the high therapeutic effect of silodosin on BPH symptoms, preferred to continue treatment. Only a few patients (3.9%) refused further use of silodosin due to the occurrence of ejaculation disorders [11].

In a detailed analysis, it was noted that in the group of patients who developed ejaculation disorders while taking silodosin, the effectiveness of treatment was higher. “The improvement in the overall IPSS score by three points or more, as well as the maximum urinary flow rate by 3 ml/s or more by the end of the course of therapy was 1.75 times higher in patients with ejaculation disorders that occurred while taking silodosin than in patients who did not experience this side effect ($p = 0.0127$)” [12].

The incidence of side effects from the cardiovascular system while taking silodosin is 1.2%, which did not differ significantly from the control groups receiving placebo (1%) ($p > 0.05$) [11]. When taking antihypertensive drugs and silodosin simultaneously, the probability of developing orthostatic hypotension is 1.4%, however, the differences also turned out to be unreliable as with the groups receiving

monotherapy with silodosin and control groups. It is quite obvious that patients who initially suffered from orthostatic hypotension or had at least one such episode in history, as well as those taking vasoactive drugs, were excluded from the analysis.

α1-blockers for antihypertensive purposes. Comprehensive cardiac monitoring performed on patients during the aforementioned double-blind randomized studies also did not reveal a clinically significant effect of silodosin on the myocardium.

To confirm the low toxicity of silodosin in relation to the effect on the heart muscle, a separate study was conducted on the effect of a five-day course of silodosin at dosages of 8 mg and 24 mg. It was performed on healthy male volunteers and did not reveal clinically or statistically significant changes in heart rate contractions and the state of the cardiac conduction system according to the results of electrocardiography [13].

DISCUSSION

According to the results of the studies, silodosin showed high efficacy in the treatment of benign prostatic hyperplasia and a completely acceptable safety profile. However, the question remains about the place of this drug in clinical practice.

Silodosin was generally comparable in effectiveness to tamsulosin. There are clinical situations where silodosin has demonstrated significantly greater efficacy compared to tamsulosin. In general, the conclusion made by M.P. Curran (2011) based on the results of the studies “silodosin is not inferior in effectiveness to tamsulosin” is formulated absolutely correctly from a pharmacological point of view. The fact is that generations of α-blockers differ not in effectiveness, but in tolerability. This setting has been repeatedly confirmed in studies, including double-blind, randomized ones. As an example, let us note the work of .M. Buzeln ct al. (1993), which showed equal clinical efficacy of alfuzosin and prazosin for the treatment of benign prostatic hyperplasia. Significant differences were noted only in the frequency of side effects [15].

To paraphrase the above thesis, it can be noted that the selectivity that determines the generation of an α-blocker is reflected only in the frequency of side effects without significantly affecting the clinical effectiveness. Generally to

α-blockers, even the earliest ones, have never been claimed to be insufficiently effective.

The frequency of side effects of silodosin and tamsulosin, according to the combined data of double-blind randomized studies, was almost identical. In our opinion, a situation has arisen here, not uncommon in modern clinical pharmacology, when one has to choose between two drugs - good and very good. Both good and very good drugs are equally effective in a typical situation. But a very good drug requires special conditions to realize its potential. Large studies usually include average patients, thus excluding severe and complicated patients. Therefore, with this approach, it is not possible to identify overwhelming advantages. α-blockers may be subject to increased selective requirements in

terms of clinical conditions in conditions similar to the side effects of α-blockers. For example, a pre-existing tendency to hypotension, especially against the background of coronary heart disease (α-blockers increase myocardial oxygen demand and can provoke an attack of angina or arrhythmia) used to be a reason for refusing treatment for benign prostatic hyperplasia α-blockers. Now it is quite reasonable to use silodosin. Tachycardia and tachyarrhythmia are currently well corrected with medication, but if there is a need to prescribe an α-blocker to such a patient, then higher selectivity is needed. Thus, we will reduce the risk of recurrence of rhythm disturbances. Due to its highest uroselectivity, silodosin is preferable if the patient is taking antihypertensive drugs and PDE-5 inhibitors (tadalafil, sildenafil). Considering the predominantly elderly age of patients with BPH, the safety factor

With regard to the cardiovascular system, when taking α-blockers simultaneously with antihypertensive drugs / PDE-5 inhibitors, it becomes especially relevant.

α-blockers can increase gastric secretion and gastrointestinal motility. Gastroenterological contraindications do not appear in the annotations of all drugs in this group. However, if the patient suffers from ulcers or erosions of the stomach, esophagus, duodenum, recurrent hyperacid gastritis and at the same time has indications for taking α-blockers then the drug of choice will be the most selective of them - silodosin.

SUMMARY

The new α-blocker silodosin is a highly effective and safe drug for the treatment of benign prostatic hyperplasia. Silodosin is characterized by a rapid development of effect; it can be used in all patients suffering from DIP and having indications for taking α-blockers. Due to its selectivity superior to all commercially available analogues, silodosin has safety advantages in the treatment of BPH in patients suffering from hypotension, tachycardia, tachyarrhythmia, especially against the background of coronary heart disease, gastric and duodenal ulcers, hyperacid gastritis. Silodosin does not increase the risk of hypotension in patients taking antihypertensive therapy (drugs acting on the renin-angiotensin system, beta-blockers, calcium channel blockers and diuretics) or in patients taking PDE 5 inhibitors.

Silodosin is compatible with all groups of antihypertensive drugs, except vasoactive α-blockers. When silodosin is co-administered and antihypertensive therapy, no dosage adjustment is required.

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