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POSSIBILITIES OF PHARMACOLOGICAL CORRECTION OF THE ARTIFICAL BLADDER CONTRACTILE ACTIVITY IN EXPERIMENTAL CONDITIONS *IN VIVO*

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Abstract. Possibilities of pharmacological correction of the artifical bladder contractile activity in experimental conditions in vivo. Savchuk R.V., Kostyev F.I., Shmatkova N.V. *The aim of this work was to study the possibility of pharmacological correction of the neobladder contractile activity of mini-pigs under the influence of new chemical compounds, m-anticholinergic (solifenacin), selective beta-2 sympathomimetic (ginipral (hexoprenaline)) in vivo. Neobladder, formed from the distal section of ileum, pre-denervated along the anti-mesenteric margin, retains peristalsis, and given the sharp thickening of the muscle layer, capable to contractile reactions and tone support. New chemical compounds pyrrole-2-carbaldehyde 2- hydroxybenzoylhydrazone (PChBh) and isatin benzoylhydrazone (IBh) demonstrated spasmodic properties direct at smooth muscle in vivo. Compound PChBh (I) showed more pronounced relaxing properties compared to compound IBh (II), reducing basal pressure against KCl by 40.91%, contraction amplitude by 30.63%, contraction rate by 25.49%. Solifenacin, being an m-anticholinergic antagonist, most clearly demonstrated antispasmodic properties in vivo, reducing hypertonicity by 55.23%, amplitude – by 49.31%, frequency of contractions in 10 minutes – by 57.40%, duration of contractions – by 18.18%. Selective beta-2-sympathomimetic hexoprenaline, previously used to relieve hypertonicity of a pregnant uterus actively affects intestinal motility. Hexoprenaline inhibited bladder overactivity with KCl, decreasing basal pressure by 58.75%, the amplitude of the contractions – by 39.62%, frequency rate – by 57.49%, reductions in the duration – by 54.55%. Preparations from the group of m-anticholinergics and selective beta-2-sympathomimetics showed a pronounced antispasmodic effect in experiment in vivo and can be used to correct incontinence in patients after orthotopic bladder repair. The new chemical compounds pyrrole-2-carbaldehyde 2-hydroxybenzoylhydrazone (PChBh) and isatin benzoylhydrazone (IBh) demonstrated antispasmodic properties in the experiment in vitro, and confirmed an antispasmodic effect in the experiment in vivo, promising further research, determining safety and efficacy.*

Реферат. Возможности фармакологической коррекции сократительной активности артифициального мочевого пузыря в экспериментальных условиях in vivo. Савчук Р.В., Костев Ф.И., Шматкова Н.В. *Целью работы было исследование возможности фармакологической коррекции сократительной активности неоциста mini-pigs in vivo под воздействием новых химических соединений, м-холиноблокатора (солифенацина), селективного бета-2-симпатомиметика (гинипрала (гексопреналина)). Необладдер, сформированный из терминального отдела илеум, предварительно денервированный по противобрыжеечному краю, сохраняет перистальтику и, учитывая резкое утолщение мышечного слоя, способен к сократительным реакциям и поддержке тонуса. Новые химические соединения pyrrole-2-carbaldehyde 2-hydroxybenzoylhydrazone (PChBh) и isatin benzoylhydrazone (IBh) в эксперименте in vivo продемонстрировали спазмолитические свойства, направленные на гладкую мускулатуру. Соединение PChBh (I) продемонстрировало более выраженные расслабляющие свойства в сравнении с соединением IBh (II), снижая базальное давление на фоне KCl на 40,91%, амплитуду сокращений на 30,63%, частоту сокращений на 25,49%. Солифенацин, являясь м-холиноблокатором, наиболее ярко демонстрировал спазмолитические свойства в условиях эксперимента in vivo, снижая гипертонус на 55,23%, амплитуду на 49,31%, частоту сокращений за 10 минут на 57,40%, длительность сокращений на 18,18%. Селективный бета-2-симпатомиметик гексопреналин, используемый*

ранее для снятия гипертонуса беременной матки, активно влияет на перистальтику кишечника, угнетал гиперактивность артифициального мочевого пузыря на фоне KCl, так базальное давление снизилось на 58,75%, амплитуда сокращений на 39,62%, частота сокращений снизилась на 57,49%, длительность сокращений на 54,55%. Препараты из группы м-холиноблокаторов и селективных бета-2-симпатомиметиков продемонстрировали выраженный спазмолитический эффект в эксперименте in vivo и могут быть использованы в коррекции инконтиненции у пациентов после ортотопической пластики мочевого пузыря. Новые химические соединения pyrrole-2-carbaldehyde 2-hydroxybenzoylhydrazone (PChBh) и isatin benzoylhydrazone (IBh) продемонстрировали в эксперименте in vitro спазмолитические свойства, а в эксперименте in vivo подтвердили спазмолитический эффект, следовательно, являются перспективными для дальнейшего исследования, определения безопасности и эффективности.

Orthotopic urine derivation with the formation of a nebladder from the ileum is recognized worldwide as the best method of urine derivation in patients who have undergone radical cystectomy for invasive bladder cancer [8]. Currently, a large number of different methods of performing ileocystoplasty and variants of urine derivation are known [9]. In addition, several studies have demonstrated that quality surgery using radical cystectomy and pelvic lymph node dissection provides oncologic control over patients with clinically localized or locally advanced bladder cancer, even in long-term follow-up [6, 12].

Volumetric reconstructive intervention has a long-term effect on the urinary, gastrointestinal and sexual function, altering the appearance of the body of patients, which significantly compromises the quality of life of patients who undergo radical cystectomy with various variants of urinary derivation [4, 15]. In the modern world, cancer is not the only criterion in addressing the treatment of bladder cancer patients, since the quality of life of the patient is still very important and a major deterrent for patients in the choice of surgery [13, 14]. Urinary incontinence after orthotopic ileocystoplasty is one of the major complications. According to various authors, it can be up to 81% at night and up to 79% in the daytime [3, 10].

According to some researchers, urinary incontinence was revealed in the postoperative period, which was associated with hyperactivity of the artificial bladder, being confirmed by a comprehensive urodynamic study [7].

The artificial intestinal reservoir, previously detubularized, covered with intestinal epithelium, designed to perform unnatural urodynamic properties is not able to provide satisfactory quality of urination. In the early postoperative period, there occurs hyperactivity of the neocyst due to the reaction of the intestinal wall to a new aggressive environment – urine. Subsequently, the adaptation processes are stabilized and hypoactivity of the nonbladder is manifested due to denervation of the nerve plexuses or the large reservoir initially formed.

In the available literature there are no recommendations and theoretical developments regarding the pharmacological correction of the antispasmodic function of the neocyst at various stages of the postoperative period.

The aim of the study was to investigate the possibility of pharmacological correction of the contractile activity of mini-pigs neocyst *in vivo* under the influence of new chemical compounds – m-cholinoblocker (solifenacin), selective beta-2-sympathomimetics (ginipral (hexoprenaline)).

MATERIALS AND METHODS OF RESEARCH

All manipulations on animals were carried out in accordance with the International Convention on Animals and the Law of Ukraine "On Protection of Animals against Cruelty" 2006, art. 230.

Scientists have proved that pigs' organism in its anatomical and morphofunctional features is closest to humans, therefore, is ideally suited for studying the pathogenesis of various morphological and biochemical processes. Experimental studies were performed on 21 female mini-pigs, average age from 6 to 14 months, the duration of the experiment – 12 months. An experimental model of orthotopic neobladder was reproduced by performing cystectomy in animals with ileocystoplasty under anesthesia [2].

Combined urodynamic study (CUDS) (enterocystotonometry of bladder filling and emptying) we performed on the urodynamic apparatus "Delphis KT" (Laborie, Canada) in accordance with the recommendations of the Committee on Standardization of the International Society for Urinary Incontinence (UI) [5].

Based on the screening and experiment *in vitro*, it was found that the new chemical compounds affect the contractile activity of the ileum segment *in vitro*. Of the new chemical compounds being studied, the antispasmodic properties with tropism to ileum can be distinguished in two of them: pyrrole-2-carbaldehyde 2-hydroxybenzoylhydrazone (PChBh, compound I) and isatin benzoylhydrazone (IBh, compound II), which reduce hypertension by 49.6±3.8% and 39.6±3.1 respectively [11].

The compounds were synthesized at the Department of General Chemistry and Polymers of Odessa I.I. Mechnikov National University, their composition and structure were established by a set of physicochemical methods of research.

For the study *in vivo,* compounds I and II were used in their minimum concentration (C_{ef}), in which the maximum antispasmodic effect was observed. The mass of substance (m, mg/kg) required for administration to the experimental animal was calculated by the formula:

$$\mathbf{m = C_{ef} \cdot M \cdot V,} \qquad \mathbf{(1)}$$

where M is the molar mass of the substance (mol/l),
V – volume of solution of 0.02 l.

The antispasmodic properties of the test compounds - m-cholinoblocker (solifenacin) and selective beta-2-sympathomimetics (ginipral) were measured against sedation of experimental animals by enterocystometry. Given sedation, it was possible to estimate part of the enterocystometric parameters only. The comparison group was the indicators obtained in the injection of hyperkalium solution in the neocyst and of the control group, then within 7 days the studied compounds were injected intraperitoneally, followed by enterocystometric study and fixed during 60 minutes.

Statistical processing of the results was performed using descriptive and variational statistics using the Student's t test. The results were calculated on a personal computer using Statistica for Windows and Microsoft Excel 7.0 licensed software. The differences were determined to be significant at $p<0.05$ [1].

RESULTS AND DISCUSSION

The problem of nocturnal and diurnal urinary incontinence, hyperactivity of the nebladder in patients after radical cystectomy with ileocystoplasty is very urgent, the use of new drugs with antispasmodic properties aimed at smooth muscles reduce the tone and stabilize the volume of the neobladder.

It was determined that the hyperkalium solution introduced into the artificial bladder causes a contractile reaction of the neobladder. This property was used as an experimental simulation of neocyst hyperactivity.

Considering that enterocystometry in experimental animals is only possible under conditions of anesthetic care, most parameters cannot be evaluated, but some of them are subject to dynamic control. The results obtained are presented in the table.

When performing enterocystometry of the neobladder, the basal pressure in the control group was 2.11±0.54 cm H_2O, the amplitude of contractions was 5.33±1.06 cm H_2O. We evaluated the activity of peristalsis as the rate of contractions for 10 minutes. (it was 8.3±0.5 cm H_2O), the duration of contraction, in turn, was 1.4±0.14 s.

According to the results of enterocystometry against introduction of hyperkalium solution with concentration of 60 mmol/l into the artificial bladder of experimental animals, basal pressure increased by 181.52% – 5.94±0.25 cm H_2O ($p<0.05$), the amplitude of contractions increased by 89.87% – 10.12±2.21 cm H_2O ($p<0.05$). The rate of contractions also increased over a 10-min period by 159.04% – 21.5±2.4 times ($p<0.05$)), the duration of detrusor contraction increased by 57.14% – 2.2±0.15 s. ($p<0.05$).

The new chemical compound showed antispasmodic properties according to enterocystometry data *in vivo* in experimental animals against stimulation of neobladder with 60 mmol/l hyperkalium solution. Thus, with the introduction of PChBh (I), a statistically significant decrease in basal tone by 40.91% – 3.51±0.51 cm H_2O ($p_1<0.05$) was observed, and amplitude of contractions – by 30.63% – 7.02±1.02 cm H_2O ($p_1<0.05$), the rate of contractions – by 25.49% – 16.02±0.9 times ($p_1<0.05$) compared with the group of animals stimulated with hyperkalium solution. The duration of contractions was 2.1±0.15 s. ($p_1\geq0.05$), which is not statistically significant for the comparison group.

The chemical compound IBh (II) also showed antispasmodic properties against the stimulation of the neobladder with hyperkalium solution, but to a lesser extent. Thus, the basal pressure decreased by 15.49% – 5.02±0.26 cm H_2O ($p_2<0.05$), the amplitude of contractions – by 18.87% – 8.21±1.27 cm H_2O ($p_2<0.05$), the rate of contractions for 10 min – by 15.72% – 18.12±0.7 times ($p_2<0.05$). The duration of contraction was 2.0±0.16 s. ($p_2\geq0.05$), which was unreliable in terms of enterocystometry in experimental animals against stimulation with 60 mmol/l KCl.

The introduction of selective beta-2-sympathomimetics of hexoprenaline (ginipral) significantly suppressed the contractile activity of mini-pigs' neocyst due to the selective effects on intestinal smooth muscles.

The maximal antispasmodic effect of sympathomimetic in enterocystometry registration against stimulation of the artificial bladder with hyperkalium solution was observed 25 min. after its administration. Basal pressure decreased by 58.75% – 2.45±0.18 cm H_2O ($p_3<0.05$), the amplitude of contractions – by 39.62% – 6.11±2.07 cm H_2O ($p_3<0.05$), rate of contractions – by 57.49% – 9.14±1.20 times ($p_3<0.05$), duration of contractions – by 54.55% – 1.00±0.14 s ($p_3<0.05$), approaching the value in the control group.

Enterocystometry parameters in experimental animals under the influence of studied substances *in vivo* (M±m)

Studied substance	Basal pressure (cm H_2O)	Amplitude (cm H_2O)	Rate of contractions during 10 min., times	Duration of contractions, s
Control group NaCl (n=10)	2,11±0,54	5,33±1,06	8,3±0,5	1,40±0,14
KCl 60 mmol/l (n=10)	5,94±0,25	10,12±2,21	21,50±2,40	2,20±0,15
PChBh (I) + KCl 60 mmol/l (n=10)	3,51±0,51	7,02±1,02	16,02±0,9	2,10±0,15
IBh (II) + KCl 60 mmol/l (n=10)	5,02±0,26	8,21±1,27	18,12±0,70	2,00±0,16
Hexoprenaline (ginipral) + KCl 60mmol/l (n=10)	2,45±0,18	6,11±2,07	9,14±1,20	1,00±0,14
Solifenacin 0,1mg/kg + KCl 60 mmol/l (n=10)	2,66±0,18	5,13±1,09	9,16±1,3	1,8±0,4

Notes: 1. p - significance of differences with regard to control group with NaCl, 2. p_1 - significance of differences of compound I with regard to the group of animals with KCl, 3. p_2 - significance of differences of compound II with regard to the group of animals with KCl, 4. p_3 - significance of differences of beta-2-sympathomimetics with regard to the group of animals with KCl, 5. p_4 - significance of differences of m-cholinblocker with regard to the group of animals with KCl.

M-cholin blockers are widely used for the treatment of conditions caused by detrusor hypertension, simultaneously affecting not only the smooth muscles of the bladder but the intestine as well. The antispasmodic properties of solifenacin were the most clearly demonstrated when performing enterocystometry of neocysts in experimental animals. High basal pressure on the background of hyperkalium solution under the influence of m-cholin blocker decreased by 55.23% – 2.66±0.18 cm H_2O ($p_4<0.05$), amplitude – by 49.31% – 5.13±1.09 cm H_2O ($p_4<0.05$)), the rate of contractions for 10 min. – by 57.40% – 9.16±1.30 times ($p_4<0,05$), duration of contractions – by 18.18% – 1.8±0.4 s. ($p_4<0.05$).

The neobladder, formed from the terminal ileum, previously denervated along the anti-mesenteric margin, retains peristalsis and, considering a sharp thickening of the muscular layer, is capable of contractile reactions and tone maintaining. The novel chemical compounds pyrrole-2-carbaldehyde 2-hydroxybenzoylhydrazone (PChBh) and isatin benzoylhydrazone (IBh) demonstrated spasmolytic properties in the experiment *in vitro*, and in the experiment *in vivo* confirmed the antispasmodic effect, hence the need for further study of safety and efficacy.

CONCLUSIONS

1. The novel PChBh (I) and IBh (II) chemical compounds in the experiment in vivo demonstrated antispasmodic properties aimed at smooth muscles. Compound PChBh (I) exhibited more pronounced relaxing properties compared to compound IBh (II), reducing basal pressure against KCl by 40.91%, amplitude of contractions – by 30.63%, rate of contractions – by 25.49%.
2. Solifenacin, being an m-cholinoblocker, most clearly showed antispasmodic properties in the experiment in vivo, reducing hypertonus by 55.23%, amplitude – by 49.31%, rate of contractions for 10 min. – by 57.40%, duration of contractions – by 18.18%.
3. Selective beta-2-sympathomimetic hexoprenaline, previously used to relieve hypertonus of the pregnant uterus, actively affects the intestinal peristalsis, inhibiting hyperactivity of the artificial bladder against KCl: so, the basal pressure decreased by 58.75%, amplitude of contractions – by 39.62%, rate of contractions by – 57.49%, duration of contractions – by 54.55%.
4. Drugs from the group of m-cholinblockers and selective beta-2 sympathomimetics demonstrated a pronounced spasmolytic effect in the experiment in vivo and can be used for the correction of incontinence in patients after orthotopic plastic of the urinary bladder.

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topical diagnostics and treatment of dysfunctional pelvic pain syndromes and neurogenic disorders of urination" (state registration number O006 6656).

Conflict of interests. The author declares that there is no conflict of interest.

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