

## BIOLOGICAL RESEARCH

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## RESEARCH OF THE INFLUENCE OF MELANIZOL PESSARIES ON BACKGROUND OF “CHEMICAL” VAGINITIS IN RATS

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**The aim.** to study the therapeutic influence of new pessaries Melanizol based on metronidazole and tea tree oil on the background of model of “chemical” vaginitis in female rats.

**Materials and methods.** The therapeutic effect of pessaries Melanizol was studied in female rats on the model of “chemical” vaginitis with using argentum nitrate, which provokes vaginitis not burdened by infection. Against the background of vaginitis, the general condition of animals, the dynamics of body weight, the morphological composition of peripheral blood and the erythrocyte sedimentation rate (ESR), pH, biochemical parameters (total protein, ALT and glucose), temperature in the vagina of rats, macroscopically assessed changes in the vaginal mucosa (VM) were studied.

**Results and discussion.** Against the background of pathology in the animals, a shift in the studied indicators was observed. Pessaries Melanizol at the dose of 21 mg/kg make a therapeutic effect on the model of experimental “chemical” vaginitis, caused by argentum nitrate, as indicated by the restoration of the VM state, reduced the number of leukocytes, restored the percentage composition of the leukocyte formula, reduced the amount of total protein and the cytolytic enzyme ALT in blood serum and vaginal contents, which indicates the anti-inflammatory and cytoprotective effect of the studied agent. The recovery of vaginal temperature, pH and the amount of glucose in the vaginal contents was also observed, which indicates the normalization of homeostasis in the vagina of experimental animals. According to these effects, the studied pessaries Melanizol were superior to the reference drug “Gravagin” at the dose of 30 mg/kg and were not inferior to the reference drug Hippophaes oleum pessaries (HOP) at the dose of 17.64 mg/kg.

**Conclusions.** The therapeutic effect of new pessaries Melanizol based on metronidazole and tea tree oil on the model of “chemical” vaginitis in female rats has been proven. The investigated pessaries Melanizol are a promising drug for the treatment of non-specific vaginitis and require further research in this direction

**Keywords:** experimental vaginitis, argentum nitrate, pessaries, metronidazole, tea tree oil, rats

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**1. Introduction**

Infectious-inflammatory diseases of the genitals are a common problem throughout life for women, for a long time do not give way to the position and have an increasing trend, and are also the reasons of the impact on the state of reproductive health. Vaginal symptoms can not only affect a woman's quality of life, but also make it difficult for clinicians to assess and prescribe the right treatment [1–3], because they accompany a significant number of diseases, the most common of which are bacterial vaginosis, candidal vaginitis, trichomoniasis [4]. Data from the literature show that non-specific vaginitis (NV) is diagnosed most often among vaginitis, the frequency of which reaches 76–80 % among vulvovaginal diseases [5].

Depending on the pathogenetic mechanisms of inflammation in women of reproductive age, NVs of infectious and non-infectious genesis are distinguished. Although, despite the cause of NV, non-infectious inflammation, within a few days, still acquires the features of a bacterial inflammatory process, due to the involvement

of flora mainly from the intestines [6] and the activation of opportunistic microflora.

The reason for the violation of the integrity of the skin and mucosal barriers can be chemical, mechanical, thermal factors that damage the epithelium of the VM, such as constant douching, the introduction of chemical contraceptives into the vagina, etc., which leads to inflammation and disruption trophic tissues and increases sensibility to infection [7].

The issue of treatment of patients with NV remains debatable, since the body's reaction depends on a number of circumstances, determined by individual characteristics. Unfortunately, the irrational treatment of vaginitis due to their latent course, as well as the difficulty of timely clinical and laboratory diagnosis explain the frequency of cases of “undeciphered” disease [8].

Thus, based on the prevalence of vaginitis and the constant increase in the number of visits to gynecologists, a number of side effects that significantly affect the condition, functioning of the reproductive

system and the quality of life of a woman, the study of their pharmacocorrection is relevant today.

Currently, there is an arsenal of means for the treatment of vaginitis, both mono- and multi-component, on the market. But the domestic assortment of medicines is insignificant and needs to be replenished with new promising pharmacologically active medicines with minimal side effects [9]. Such medicines can be combinations of synthetic and natural components, which today are presented in small quantities and have a limited spectrum of action. Therefore, to search for new effective means with minor side effects due to the combined use of synthetic and natural components is important and topical.

Therefore, our aim was to study the therapeutic influence of new pessaries Melanizol based on metronidazole and tea tree oil on the background of model of "chemical" vaginitis in female rats.

## 2. Materials and methods

The drug under study was the pessaries Melanizol (1 pessary contains 250 mg of metronidazolium, 100 mg of tea tree oil, a mixture of PEO-1500 and PEO-400 (9:1), used in the [10]. The reference drugs employed were the Gravagin (unpatented denomination, production of "Sperco Ukraine", Ukraine; 1 pessary contains 500 mg of metronidazolium), Hippophaes oleum pessaries (unpatented denomination, production of "Monpharm", Ukraine; 1 pessary contains 350 mg of oleum Hippophaes), which have anti-inflammatory activity [9].

The study was conducted on 50 non-linear white laboratory female rats weighing  $210 \pm 10$  g. The animals were kept on a standard diet of the vivarium. Care of them (including euthanasia) during the experiment was carried out according to the available documents, which regulate organization of the work using experimental animals. The principles of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" were observed (Strasbourg, 18 March 1986) [11], adopted by The 1st National Congress on Bioethics (Kyiv, 2000), which is coordinated with the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes", Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals, used for experimental and other scientific purposes, Order of the Ministry of Health of Ukraine from February 13, 2006 No. 66, Law of Ukraine "On protection of animals from cruelty" (No. 3447-IV 21.02.2006) [12].

After completion of the experiment, the rats were taken out from the experiment in accordance with the ethical principles of animal testing.

Before the beginning of the experiment, the oestrous cycle was examined in female rats and the animals in prooestrus-oestrus phases were selected, in order to minimize the differences in the assessment of the functional state of the vaginal mucosa when comparing the obtained results.

Vaginitis was modeled by a single intravaginal application of the 10 % solution of argentum nitrate [13]. Each experimental group consisted of 10 female rats. The animals were divided into 5 groups as follows:

Group 1 – intact animals (intact control, IC, no pathology); Group 2 – control pathology (CP, positive control); Group 3 – animals, treated with the vaginal pessaries Melanizol; Group 5 – animals, treated with the reference drug, the vaginal pessary Gravagin; Group 6 – animals, treated with the reference drug HOP.

The studied pessaries and reference drugs were injected vaginally once a day at doses, calculated using the specific sustainability factors by Y.R. Rybolovliev, applied in the experimental pharmacology. The studied drugs were being injected into the vagina during 7 days, once a day. After treatment, the animals were taken out from the experiment by the method of euthanasia.

Changes in MV to evaluate according to three parameters: edema, hyperemia, hemorrhages in points and the percentage ratio of the area of the affected area of the vagina (mm) to the area of the entire vagina (mm) by the macroscopic method. The indicators of the morphological composition of peripheral blood were evaluated: the number of leukocytes, indicators of the leukocyte formula, ESR [14]. The course of the pathology was also assessed by indicators of pH (indicator test strips "pH-test" (TOV "NORMA", Ukraine) and  $t^{\circ}$  C (electrothermometer "Microlife", Switzerland) in the vagina. Given the fact that inflammatory processes in the body are accompanied by changes in blood biochemical indicators, the main marker indicator under such conditions is the level of total protein, and any inflammatory reactions are accompanied by cytolysis [15], the level of total protein, ALT in blood serum and vaginal contents, as well as glucose in vaginal contents were determined [14].

Statistical treatment of the obtained results was carried out with the program "Statistica 6.0", using parametric and nonparametric criteria.

## 3. Results

During the observation of animals of the CP group, hyperemia and swelling of the external genitalia in the absence of abundant secretions was noted against the background of vaginitis in female rats. For a more detailed study of the course of vaginitis against the background of pathology and under the conditions of pharmacological correction, indicators characterizing the state of MV (hyperemia and swelling of the external genitalia, the area of damage to the vagina and discharge from it), clinical blood test, temperature and pH in the vagina were studied.

The body weight of animals was studied at the peak of pathology and under conditions of pharmacological correction. The analysis of this indicator in the group of IC animals showed its increase by 4.0 % during the experiment in comparison with the initial data. On the background of pathology, the body weight of animals decrease on 4.7 % ( $p < 0.05$ ) to the initial data, which indicates the severity of its course.

In the group of animals, treated with Melanizol at the dose of 21 mg/kg, a recovery of the body weight of the animals was observed compared to the animals of the CP group. There was no statistically significant difference between the effect of Melanizol and the comparison drugs.

Considering the fact that any inflammation is characterized by an increase in local temperature [13], and vaginitis is accompanied by changes in the acid-base reaction in the vagina [16], in order to control the development of the

pathology and pharmacological correction of the studied vaginitis, the local temperature and the pH value in the vagina of experimental animals were measured.

In the animals of the IC group, the temperature in the vagina was  $37.39 \pm 0.09$  °C and the pH value of the vaginal contents was  $6.45 \pm 0.12$  units. It was determined, that on the background of "chemical" vaginitis, caused by argentinum nitrate, a significant increase in temperature by  $1.14$  °C ( $p < 0.05$ ) and pH by  $0.5$  units ( $p < 0.05$ ) was observed in the vagina of experimental animals compared to the IC group. Such changes in intravaginal parameters in animals indicate an inflammatory process without excessive activation of opportunistic microflora (OM).

On the background of treatment with pessaries Melanizol, the disappearance of external manifestations of inflammation (hyperemia and swelling of the external genital organs) in female rats was noted, as well as a decrease in vaginal temperature by  $0.9$ °C ( $p < 0.05$ ) and pH by  $0.35$  unit ( $p < 0.05$ ) vaginal contents in comparison with animals of the CP group.

According to the ability to reduce the temperature in the vagina of female rats on the background of "chemical" vaginitis, pessaries Melanizol were more effective

( $p < 0.05$ ) than the reference drug Gravagin and was almost not inferior to the comparison drug HOP. According to the ability to restore pH, no significant difference between the groups of animals, treated with pessaries Melanizol and reference drugs, was noted.

In female rats,  $67\%$  ( $p < 0.05$ ) of inflammation of MV were observed on the background of argentinum nitrate administration (Table 1). Pessaries Melanizol reduced inflammation of MV by  $3.0$  times ( $p < 0.05$ ) in comparison with the group of CP animals. According to this ability, pessaries Melanizol surpassed the reference drug Gravagin by  $1.6$  times ( $p < 0.05$ ) and exerted a more pronounced effect compared to HOP by  $1.3$  times ( $p < 0.05$ ). The obtained data indicate a clear therapeutic effect of "Melanizol" on the model of "chemical" vaginitis.

The severity of the course of the pathology was assessed by the integral indicator of the state of MV – the sum of points (Table 1), which reflect the expressiveness of edema, hyperemia and the number of hemorrhages. The sum of the points of damage of MV was  $7.6$  ( $p < 0.05$ ). The obtained data are correlated with changes in body weight, local temperature and pH indicators during the experiment.

Table 1

The influence of Melanizol on the state of VM in female rats on the background of "chemical" vaginitis on the 7th day (n=10, M±m)

Conditions of the experiment	Indicator	
	Vaginal lesions, %	Total points
IC	$0.00 \pm 0.00$	$0.00 \pm 0.00$
CP	$67.27 \pm 2.44^*$	$7.60 \pm 0.36^*$
Melanizol	$22.19 \pm 0.76^{*\#@\S}$	$3.50 \pm 0.40^{*\#@}$
Gravagin	$36.31 \pm 1.64^{*\#}$	$4.90 \pm 0.31^{*\#}$
HOP	$27.51 \pm 2.06^{*\#@}$	$3.30 \pm 0.45^{*\#@}$

Note: \* – significant in relation to IC ( $p < 0.05$ ); # – significant in relation to CP ( $p < 0.05$ ); @ – significant in relation to Gravagin ( $p < 0.05$ ); § – significant in relation to HOP ( $p < 0.05$ ); n – the number of animals in the group

Pessaries Melanizol reliably reduced the intensity of the manifestations of MV lesions by  $2.2$  times ( $p < 0.05$ ) in relation to the CP group (Table 1), and according to the ability to restore the state of the damaged MV, pessaries Melanizol surpassed the reference drug Gravagin by  $1.4$  times ( $p < 0.05$ ) and were not inferior to the reference drug HOP.

The course of "chemical" vaginitis was also accompanied by changes in the parameters of the clinical blood test: the number of leukocytes, a shift of the leukocyte formula to the left and a change in the indicator of ESR (Table 2). Thus, on the 7th day of the experiment, on the background of pathology, leukocytosis was observed in the animals of the CP group. An increase in the total number of leukocytes by  $1.5$  times ( $p < 0.05$ ) in relation to the IC group was detected, as well as a shift of the indicators of the leukocyte formula to the left (the number of neutrophils significantly increased). The course of inflammation, in turn, confirms the increase in ESR by  $1.6$  times ( $p < 0.05$ ) in relation to the IC group.

It should be noted, that the treatment of the model pathology in animals with pessaries Melanizol suppressed the inflammatory process, as evidenced by a decrease in ESR by  $1.3$  times ( $p < 0.05$ ) and the number of

leukocytes by  $1.5$  times ( $p < 0.05$ ) in comparison with the CP group, as well as restoration of the percentage ratio of leukocyte formula indicators to the level of the IC group. In the course of the experiment, it was proven, that the reference drugs Gravagin and HOP were inferior to pessaries Melanizol in terms of the expressiveness of the therapeutic effect.

It was also established, that on the background of "chemical" vaginitis in the rats of the CP group, changes in blood biochemical parameters were observed (Table 3), as evidenced by an increase in the amount of total protein and activity of ALT, both in blood serum ( $1.1$  times and  $1.2$  times respectively;  $p < 0.05$ ), as well as in vaginal contents ( $1.4$  times and  $1.5$  times respectively;  $p < 0.05$ ). The changes of these parameters in the vaginal contents were more indicative in comparison with blood serum, which indicates a more pronounced local reaction. On the background of pathology, a decrease in the amount of glucose in the vaginal contents by  $2.0$  times ( $p < 0.05$ ) in relation to the CP group was noted. But the fluctuations did not exceed  $50\%$ , which indicates a moderate activation of OM. Pessaries Melanizol statistically significantly reduce the amount of total protein and the activity of ALT in blood serum and vaginal contents of

female rats compared to the CP group, but these changes did not reach the IC group.

Compared to the reference drugs, Melanzol showed a better therapeutic effect than reference drug Gravagin and HOP according to the ability to restore indicators of the amount of total protein and activity of

ALT in blood serum and vaginal contents, but no statistical difference was observed between the groups. According to the ability to restore the amount of glucose in the vaginal contents, pessaries Melanzol significantly surpassed the reference drug Gravagin and were not inferior to the reference drug HOP (Table 3).

Table 2

The influence of "Melanzol" on the parameters of the clinical blood test on the background of the "chemical" vaginitis model in female rats on the 7th day (n=10, M±m)

Indicator	Groups of experimental animals				
	IC	CP	Melanzol	Gravagin	HOP
Leukocytes, 10 <sup>9</sup> /l	9.50±0.40	15.53±0.30*	10.40±0.34 <sup>#</sup>	12.25±0.64 <sup>#</sup>	12.35±0.63
Neutrophils, %	26.35±0.90	32.67±0.55*	27.87±0.35**	31.15±0.28*	29.35±0.33 <sup>#</sup>
Eosinophils, %	1.60±0.21	1.90±0.17	1.80±0.17	1.68±0.28	1.74±0.24
Monocytes, %	3.75±0.47	4.15±0.17	3.63±0.14	3.98±0.33	3.63±0.14
Lymphocytes, %	66.80±0.75	60.20±0.53*	64.58±0.29 <sup>#</sup>	65.24±0.25 <sup>#</sup>	64.67±0.35 <sup>#</sup>
ESR, mm/h	2.70±0.26	4.10±0.31*	2.90±0.31 <sup>#</sup>	3.40±0.16 <sup>#</sup>	3.00±0.33 <sup>#</sup>

Note: \* – significant in relation to IC ( $p < 0,05$ ); # – significant in relation to CP ( $p < 0,05$ ); n – the number of animals in the group

Table 3

The influence of Melanzol on the biochemical indicators of blood and content of the vagina on the background of the "chemical" vaginitis model in female rats on the 7th day (n=10, M±m)

Indicator	IC	CP	Melanzol	Gravagin	HOP
Blood serum					
Total protein, г/л	64.65±1.05	71.10±0.42*	65.82±0.99 <sup>#</sup>	67.45±0.69 <sup>#</sup>	65.21±1.19 <sup>#</sup>
ALT, mmol/(l•h)	0.50±0.02	0.62±0.02*	0.53±0.03 <sup>#</sup>	0.55±0.03	0.54±0.02 <sup>#</sup>
Vaginal contents					
Total protein, g/l	4.36±0.21	6.31±0.31*	5.25±0.22 <sup>#</sup>	5.60±0.14 <sup>#</sup>	5.14±0.21 <sup>#</sup>
ALT, mmol/(l•h)	0.21±0.01	0.35±0.02*	0.25±0.01 <sup>#</sup>	0.29±0.02 <sup>#</sup>	0.27±0.02 <sup>#</sup>
Glucose, mmol/l	2.29±0.16	1.14±0.13*	1.77±0.15 <sup>#</sup> @	1.21±0.12 <sup>#</sup>	1.74±0.11 <sup>#</sup> @

Note: \* – significant in relation to IC ( $p < 0,05$ ); # – significant in relation to CP ( $p < 0,05$ ); @ – significant in relation to Gravagin ( $p < 0,05$ ); n – the number of animals in the group

Thus, "Melanzol" had a positive effect on the course of "chemical" vaginitis, caused by argenticum nitrate. Against the background of vaginitis, the agent reduced the amount of total protein as a marker of inflammation, reduced the activity of the cytolytic enzyme ALT in cow serum and vaginal contents, and increased the amount of glucose in vaginal contents.

#### 4. Discussion of research results

Topical therapy is the therapy of choice in case of treatment of a non-specific infectious process: acute or chronic processes in the vagina and cervix. In addition, according to experts, an ideal drug for local therapy of NV should take into account the following important requirements [5]: pronounced influence on gram-negative and gram-positive bacilli and cocci flora, anaerobes, simpler ones; creation of high concentrations of the drug in the focus of inflammation; rapid clinical effect in the elimination of symptoms of inflammation; prevention of the development of vaginal candidiasis; convenience and ease of use, etc. Among local drugs in urogynecological practice, vaginal suppositories (pessaries) are the most widely used [17].

Active research into the properties of tea tree oil continues today, which is widely used in medicine,

in the pharmaceutical, food, and cosmetic industries due to a number of biological properties (antimicrobial, antioxidant, antitumor, etc.) [18,19]. Currently, tea tree oil is one of the few essential oils that is contextually included in the 7th European Pharmacopoeia and, at the same time, included in the monograph of the European Medicines Agency (EMA), which recognized its traditional use [20]. Today, metronidazole is actively used for the treatment of NV and is included in the treatment protocol [21]. PEO (polyethylene oxide), as a base, has a number of significant positive properties, because such bases are hydrophilic bases capable of drying abundant vaginal secretions [17]. Therefore, the creation of pessaries based on tea tree oil and metronidazole is justified.

Considering the difficulty of studying the anti-inflammatory and reparative properties of the vaginal drugs due to the burden of bacterial infection [6], we developed a model of vaginitis [13] using argenticum nitrate, which causes damage to the vagina, unburdened by infection due to antimicrobial properties. So, this model satisfied our requirements in the study of anti-inflammatory properties of drugs that are recommended for vaginal use.

The course of "chemical" vaginitis, caused by a non-infectious factor, the introduction of a 10 % solution

of argenticum nitrate into the vagina, caused changes in indicators (for example, pH), which confirm the suppression of OM reproduction [13]. An increase in the temperature in the vagina, a change in the indicators of the clinical blood test (an increase in the total number of leukocytes by 1.5 times, and a shift of the leukocyte formula to the left) indicate an inflammatory reaction in the animal's body, as well as, most likely, stimulation of phagocytosis [22]. Given the fact that inflammation is always accompanied by various changes in biochemical indicators in the body, an increase in the amount of protein and activity of ALT, which indicates cytolytic processes on the background of pathology, we conducted research on these indicators in blood and vaginal contents. The change in the studied indicators also confirmed the systemic nature of the disease [15].

Also the amount of glucose in the vaginal content as a substrate for the vital activity of bacteria (lactobacilli) and an indicator of the amount of glycogen were determined in experiment [23].

The recovery of indicators in animals, treated with the studied pessaries Melanizol, indicates a decrease in the manifestations of inflammation and cytotoxicity and confirms the data of the literature on the anti-inflammatory effect of tea tree oil [22]. An increase in the level of glucose in the vaginal contents indicates the normalization of homeostasis [23] and restoration of vaginal protection [24]. At the same time, pessaries Melanizol had a significantly ( $p < 0.05$ ) better therapeutic effect than Gravagin, but was not inferior to the drug of HOP.

**Study limitation.** There is a need to use drugs with anti-inflammatory properties under conditions of this pathology. Promising in this regard is the study of

the mechanism of action of anti-inflammatory activity of pessaries Melanizol.

**Prospects for further research.** The obtained experimental data provide a basis for further study and make pessaries Melanizol promising for introduction into practical medicine and pharmacy, which will expand the arsenal of drugs for treatment of vaginitis.

## 5. Conclusions

Thus, pessaries Melanizol at the dose of 21 mg/kg had a therapeutic effect on the background of model of experimental "chemical" vaginitis, caused by argenticum nitrate. It's confirmed by the restoration of the state of VM, parameters of the clinical blood test, total protein and cytotoxic enzyme ALT in blood serum and vaginal contents, by the restoration of vaginal temperature, pH and amount of glucose in vaginal contents. According to these effects, the studied pessaries Melanizol surpassed the reference pessaries "Gravagin" at the dose of 30 mg/kg and were not inferior to the reference Hippophaes oleum pessaries at the dose of 17.64 mg/kg.

Based on the obtained results, it can be concluded, that pessaries Melanizol are a promising drug for implementation in the practice of treatment of non-specific vaginitis and require further research in this direction.

## Conflict of interests

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results, presented in this article.

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