SPECIFIC PROPERTIES OF THE DRUG METRONIDAZOLE, GALAVIT AND ITS EFFECT ON INFECTION

Tursunov Dilshodjon O'tkir o'g'li

Faculty of Medicine, International University of Asia, Uzbekistan.

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Abstract. *Inflammatory diseases have an extremely unfavourable impact on the reproductive function of women, causing chronic pelvic pain syndrome (24%), infertility (40%), pregnancy failure (45%), ectopic pregnancy (3%) [5, 6]. The main trigger mechanism in the development of inflammation is microbial invasion (microbial factor). Analysis of the results of numerous bacteriological studies in gynaecology performed over the last 50 years revealed a change in the causative agents of pelvic inflammatory diseases. In the 40s-60s of the XX century the leading place was occupied by streptococcus (31.4%); in the 60s-70s - by staphylococcus (54.5%). Since the 1980s, most researchers have been unanimous in the opinion that the leading initiator of UTIs are associations of non-spore-forming Gram-negative (Bacteroides, Prevotella, Fusobacteria) and Gram-positive anaerobic microorganisms (peptostreptococci and clostridia), aerobic Gram-negative (Escherichia coli, Klebsiella, Proteus, Enterobacteriaceae) and less frequently Gram-positive microbial flora (Streptococcus, Enterococcus, Staphylococcus aureus).*

Almost all microorganisms present in the vagina (with the exception of lacto- and bifidobacteria) can take part in the inflammatory process. Since the 80-90s of the XX century, great importance in the genesis of STIs has been given to sexually transmitted infections (STIs) (chlamydia, mycoplasmosis, ureaplasmosis, viral infection, candidiasis), 50-70% of pelvic organ diseases are caused by chlamydia and ureaplasmas. The ways in which infection affects the female reproductive system are manifold.

Keywords: *Inflammation, bifidobacteria, Trichomonas vaginalis, Galavit, Clion-D-100, Miconazole, obligate anaerobes, protozoal-bacterial-candida, anti-inflammatory therapy,*

СПЕЦИФИЧЕСКИЕ СВОЙСТВА ПРЕПАРАТА МЕТРОНИДАЗОЛ, ГАЛАВИТ И ЕГО ВЛИЯНИЕ НА ИНФЕКЦИЮ

Аннотация. *Воспалительные заболевания крайне неблагоприятно сказываются на репродуктивной функции женщин, вызывая синдром хронической тазовой боли (24%), бесплодие (40%), невынашивание беременности (45%), внематочную беременность (3%) [5, 6]. Основным пусковым механизмом в развитии воспаления является микробная инвазия (микробный фактор). Анализ результатов многочисленных бактериологических исследований в гинекологии, проведенных за последние 50 лет, выявил смену возбудителей воспалительных заболеваний органов малого таза. В 40-60-е годы XX века ведущее место занимал стрептококк (31,4%), в 60-70-е годы - стафилококк (54,5%). Начиная с 1980-х*

годов большинство исследователей единодушно сходятся во мнении, что ведущими возбудителями ИМП являются ассоциации неспорообразующих грамотрицательных (Bacteroides, Prevotella, Fusobacteria) и грамположительных анаэробных микроорганизмов (пептострептококки и клостридии), аэробной грамотрицательной (Escherichia coli, Klebsiella, Proteus, Enterobacteriaceae) и реже грамположительной микробной флоры (Streptococcus, Enterococcus, Staphylococcus aureus).

В воспалительном процессе могут принимать участие практически все микроорганизмы, присутствующие во влагалище (за исключением лакто- и бифидобактерий). С 80-90-х годов XX века большое значение в генезе ИППП придается инфекциям, передающимся половым путем (ИППП) (хламидиоз, микоплазмоз, уреаплазмоз, вирусная инфекция, кандидоз), 50-70% заболеваний органов малого таза вызываются хламидиями и уреаплазмами. Пути воздействия инфекции на женскую репродуктивную систему многообразны.

Ключевые слова: *Воспаление, бифидобактерии, Trichomonas vaginalis, Галавит, Клион-Д-100, Миконазол, облигатные анаэробы, протозойно-бактериально-кандидозная, противовоспалительная терапия.*

On the central nervous system.

Morphological and functional changes in the organs of the reproductive system during inflammation cause pathological afferentation to the parts of the CNS that regulate the hypothalamic-pituitary-ovarian system. As a result of these changes there is a decrease in the endocrine function of the ovaries, which often violates the process of ovulation.

On the endocrine system.

Inflammatory changes in the ovaries inevitably affect their function, leading to impaired production of estrogen and progesterone. The most common consequence of chronic oophoritis is absolute or relative progesterone deficiency, i.e. luteal phase failure (LPF). Lack of adequate endometrial responses to hormonal stimulation can be explained not only by morphological changes in endometrial tissue, but also by impaired function of its receptors due to inflammation.

On the immune system.

IUCD leads to immune disorders manifested in a decrease in interferon activity (interferon system); a decrease in the activity of natural killer cells; a decrease in the activity of macrophages; suppression of the cellular link of immunity in the form of an imbalance of T-cell immunity and polyclonal stimulation and B-lymphocytes; an increase in the number of immunoglobulins of all classes.

In addition to affecting the general immune system, infectious agents cause major changes in local immunity, which are manifested by:

- increase in the number of T-lymphocytes, NK-cells, macrophages;
- predominance of T-cell immunity over T2;
- increase in the amount of IgM, IgA, IgG, which contributes to embryo rejection reactions.

Thus, changes in the immune system, whose function is to recognise and eliminate foreign antigens, may be the cause of inadequate maternal response to the onset and development of pregnancy, which may lead to infertility or miscarriage [5].

Fetus.

In the early stages of embryogenesis (zygote, morula, free blastocyst) inflammatory response in the mother-placenta-fetus system does not occur at all, and the only possible response to the action of any stimulus is an alterative process and death of the product of conception. During the implantation period, a full-fledged inflammatory response is also absent. During the placentation stage, the inflammatory response is documented only within the maternal portions of the parietal and basal endometrium. Only in the 3-4th week, placental macrophages - Hofbauer-Kaschenko cells - appear in the stroma of mesenchymal immature villi, which have a protective effect against a number of pathogens, but can also be a reservoir for the reproduction of some of them (human papillomavirus). In later life, the infection can be transmitted to the foetus by different routes, but most often transplacental, leading to malformations, foetoplacental insufficiency and other complications of gestation.

Anti-inflammatory therapy of patients with chronic endometritis was carried out according to generally accepted schemes with the use of broad-spectrum antibiotics or taking into account the sensitivity of bacterial microflora, eubiotics, antimycotic, immunomodulatory, metabolic drugs, physiotherapeutic procedures. In the presence of mycoses, treatment started with prescription of antimycotic drugs: orungal 100 mg 2 times a day orally for 3 days, ginopevaril 1 suppository 150 mg a day for 3 days, or 1 suppository 50 mg for 15 days. In all cases, taking into account the presence of chronic infection, immunomodulators increasing specific and non-specific defence of the organism were prescribed. In chronic endometritis it is most appropriate to use immunotropic drugs affecting the macrophage link of immunity, since phagocytosis plays a crucial role in the elimination of opportunistic microorganisms, which are a constant component of inflammation; in addition, the activation of phagocytic cells causes natural, easily reversible activation of all components of the immune system. In this regard, the optimal immunomodulatory drug for the treatment of patients with chronic endometritis is Galavit.

Galavit (5-amino-1,2,3,4-tetrahydrophthalazine-1,4-dione sodium salt) is a domestic drug, which, depending on the dose and method of administration, is capable of both suppressing

excessive manifestations of immune inflammation and increasing the immune response in case of its insufficient effectiveness. The effectiveness of anti-inflammatory therapy is due to the ability of the drug to reduce the synthesis of tumour necrosis factor, IL-1 and other acute-phase proteins from hyperactivated macrophages [3]. Characteristically, halavit practically does not affect normally functioning cells, which favourably distinguishes it from most immunomodulatory drugs. Thus, galavit increases non-specific resistance to infectious diseases, has a protective effect on manifestations of toxaemia, promotes antimicrobial defence. This contributes to normalisation of vascular permeability, improvement of microcirculation, nerve trophics, acceleration of epithelialisation and regeneration of endometrium without structural defects, which is especially important for patients planning pregnancy. In chronic endometritis it was administered intramuscularly in a dose of 100 mg daily for 5 days, then 100 mg every other day for 10 days simultaneously with the use of antibiotics and other antimicrobials.

In the presence of viral infection (HPV, CMV) in cases of active or frequently recurrent process, chemotherapy with acyclovir (0.2 g 4-5 times a day for 10-30 days), valacyclovir (0.5 g 2 times a day for 5-10 days) or famciclovir (0.25 g 2 times a day for 5-10 days) was used. All patients were prescribed drugs improving metabolic processes in tissues (vobenzyme), complexes of metabolites and adaptogens (B vitamins, folic acid, calcium pantothenate, cocarboxylase, ascorbic acid, vitamin E, etc.). Hormonal rehabilitation was carried out with gestagen-estrogen preparations with the content of estrogenic component not less than 30 mcg: Regulon (30 mcg estradiolvalerate) or Diane-35 (contains 35 mcg estradiolvalerate) 1 tablet from the 5th to the 25th day of menstrual cycle during 3 months.

A very important moment of prevention of unfavourable outcome of planned pregnancy in patients with TCDD is the assessment of the effectiveness of the therapy, which was carried out according to the following criteria:

-absence of inflammatory changes in the endometrium and its adequate secretory transformation in phase II of the cycle in the histological study of endometrial paipel biopsy specimens;

-AMGF content in the uterine cavity flush is not less than 10525.2±12.5 ng/ml;

-ultrasound (corpus luteum not less than 19 mm, endometrial thickness not less than 10 mm).

According to WHO, up to 40% of all drugs prescribed to patients for one indication or another, do not have scientifically proven efficacy. However, recently, along with the clinical efficacy of medicines, the safety of their use has been put at the centre of the practical application of a drug. In this regard, it seems appropriate to analyse the efficacy and safety of the existing drugs on the market for the treatment of female genital infections, especially since their safety is

particularly important when used by women of childbearing age, from the point of view of the possible impact on the foetus [1, 2]. The use of combination antimicrobials for the treatment of female genital tract infections in the last decade is due to a number of factors. Currently, there is a certain choice of combined preparations of the mentioned group (Ginalgin, Klion-D, Meratin combi, Mycoginax, Neo-Penotran, Terjinan, etc.), and therefore the issue of its optimal choice in the practical work of gynaecologist, dermatovenerologist and urologist is important [2-4]. Statistical data show that at present the spectrum of occurrence of various infectious diseases of the female genital sphere is: - trichomoniasis -40-80 %; - nonspecific bacterial vaginitis - about 70 %; - candidal vaginitis - 3-15 %; - bacterial vaginosis - 40-50 %; and mixed infections prevail - from 50 to 60 % of cases. It is considered that a mixed protozoal-bacterial-candida process is observed in 80-89.5 % of patients [3, 5, 6]. At the same time, certain variants of infections have a certain frequency associated with pregnancy. Thus, according to I. V. Ilyin et al. [5], vaginal candidiasis outside pregnancy is noted in 10-17% of the examined Moscow residents, and in pregnant women and before delivery it is noted, respectively, in 30-40% and 44.4% of the examined. Three out of four women have a history of vaginal candidiasis at least once in their lives.

Chlamydia salpingitis and salpingoophoritis are the most frequent manifestations of ascending infection, the peculiarity of which is their prolonged subacute, sterile course without tendency to ‘aggravation’, leading to obstruction of fallopian tubes, ectopic pregnancy, tubal-peritoneal infertility, adhesions in the pelvis, pregnancy failure. Quite often infertility is the only complaint of patients with UC.

Acute uncomplicated urethritis in men and especially in women is poor in symptoms. Most often the condition does not worsen, the temperature is normal or subfebrile, may bother burning, itching, painful urination, hyperaemia around the external opening of the urethra. In women, signs of acute inflammation of the urethra are observed in only 4-5% of patients. During the chlamydial process, relapses and exacerbations may occur. If a patient is diagnosed with chronic persistent UC, it should be remembered that ‘defective’ persistent forms can revert to normal forms. Such a patient may develop an exacerbation of the process and may become a source of infection. Thus, patients with persistent forms should be treated with individualised regimens, usually without antibiotics, including immunocorrective therapy.

Widespread use in clinical practice has found the drug ‘**Klion’**, produced in the form of tablets for oral use, containing 250 mg of metronidazole in its composition. Penetrating inside the microbial cell, metronidazole turns into the active form, binds to DNA and blocks the synthesis of nucleic acids, which leads to the death of the microorganism. The drug is rapidly adsorbed in the gastrointestinal tract, and its maximum concentration in blood plasma is reached in 1-3 hours. The

elimination half-life of clion is 8 h. Most of the drug is excreted with urine (60-80%), less - with faeces (6-15%). Clione is used 250 mg 4 times a day per os for 5-7 days. An alternative treatment regimen is the use of Clion once in a dose of 2 g. Clion-D-100 is an intravaginal combined preparation, which contains 100 mg of metronidazole and 100 mg of miconazole nitrate. Metronidazole is active against the obligate anaerobes, Trichomonas vaginalis, as well as Entamoeba histolitica. Miconazole nitrate has antifungal action, mainly against C. albicans.

During intravaginal use metronidazole is subjected to systemic absorption. The maximum concentration in blood during intravaginal use is about 50% of the maximum concentration achieved during a single administration of an equivalent oral dose of metronidazole. Miconazole nitrate is insignificantly absorbed during topical administration. The half-life of the drug is 8 h.

Administration regimen: 1 tablet intravaginally at night for 10 days. Before insertion into the vagina the tablet should be moistened with water for better dissolution. To achieve therapeutic effect, treatment should be carried out by both partners.

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