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AZICLAR IN COMPLEX TREATMENT OF PATIENTS WITH UROGENITAL INFECTIONS

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The results of a comprehensive clinical study for the effectiveness of treatment in 57 patients with chlamydia-mycoplasma infection. The high therapeutic activity and good tolerability of aziclar, as the main etiotropic drug, have been reported.

Keywords: complex treatment, urogenital infections

Urological infections are one of the most common diseases, both among outpatients and patients in specialized hospitals. According to national and foreign studies, approximately 50% of the sexually active population are carriers of mixed urogenital infections, which are mainly sexually transmitted infections [1, 2]. Clinical symptoms of urogenital diseases are variable and often accompanied by quite serious complications. The torpid current is formed against the background of immunosuppression, a decrease in non-specific protective factors and accompanied by an increase in the chronicity of infections. Among the numerous urogenital infections, urogenital chlamydia infection is one of the most common sexually transmitted infections. Currently, there are more than 20 nosological forms of diseases associated with chlamydial infection. Therefore, one of the priority directions of the dermatovenerological service and related specialties (obstetrics, gynecology, urology, etc.) is the treatment of patients with urogenital chlamydia, the incidence of which, according to the WHO, ranks second after urogenital trichomoniasis among sexually transmitted infections (STIs). In recent years, the incidence rate of urogenital chlamydia has a positive trend all over the world. Urogenital chlamydia is annually diagnosed in more than 90 million patients around the world [3]. Numerous and often severe urogenital chlamydia complications, which contribute to a decrease in the birth rate, an increase in congenital anomalies, disability, as well as difficulties and frequent failures in the therapy carried out, are the basis for the fair recognition of this infection as a serious health care problem. Chlamydia are a pathogenic group of gram-negative bacteria that have obligate intracellular parasitism and similar morphological, biochemical and antigenic properties.

Urogenital chlamydia does not have specific clinical and pathognomonic symptoms. Usually it is mild or asymptomatic. The incubation period for chlamydial infection ranges from 5 to 30 days. Chlamydial infection most often takes a subacute or asymptomatic course of the disease. The primary site of infection is more often localized in the mucous urethra and cervical canal. Clinical varieties of chlamydial infection include more than 20 syndromes and pathological conditions that depend on the time of infection, localization of lesions, severity of local and general reactions of the macroorganism. There is no generally accepted clinical classification of the disease. Fresh and chronic urogenital chlamydia is distinguished. The asymptomatic clinical course of chlamydial infection leads to the long-term existence of reservoirs of the pathogen, posing a great danger to the health of patients, affecting new topographical zones. The following male diseases are most common: orchoepididymitis, periorchoepididymitis, deferentitis, funiculitis, prostatitis, Reiter-Fissinger-Leroy disease; female diseases are as follows: bartholinitis, salpingitis, salpingoophoritis, pelvioperitonitis, perihepatitis. Fitz-Hugh-Curtis syndrome, periappendicitis, perisplenitis, perisigmoiditis very often occur after hydrotubation.

Pelvic inflammatory disease (PID) is a complex and poorly understood problem that may cause the development of such complications as infertility, ectopic pregnancy, pelvic pain syndrome, and menstrual disorders. The increased incidence of PID is correlated with the incidence of chlamydial infection, which is evidence of the leading role of *Chlamydia trachomatis* in the occurrence of this pathology [3].

The high incidence of infection of the urogenital tract of pregnant women is the cause of perinatal infections. Most often, infection of newborns occurs during passage through the infected birth canal of the mother. However, there are data indicating the possibility of foetal infection in utero. This is indicated by the presence of chlamydial infection in babies delivered by caesarean section before the rupture of the foetal bladder, and the cases of intrauterine pneumonia in foetuses died in utero and in newborns. The most common symptoms of perinatal chlamydial infection are conjunctivitis and pneumonia of newborns. Among newborns born to a mother with a urogenital infection, conjunctivitis is found in 20-50.5% of cases. Cases of transmission of chlamydial infection from mother to child vary, in particular 20-30% of newborns develop conjunctivitis, 10-20% – pneumonia. The frequency of ophthalmic chlamydial infection has increased in recent years and reaches almost 40% among other conjunctivitis of newborns [4,5]. The generally accepted practice of treating the eyes of newborns with a 1% solution of silver nitrate does not prevent the development of chlamydial conjunctivitis.

Respiratory chlamydia is the second most frequent form of chlamydial infection of newborns, which develops in 10-30% of children born to infected mothers. In addition to ophthalmic chlamydial and respiratory forms of chlamydial infection, newborns and children develop acute otitis, gastroenteritis, proctitis, and reactive arthritis [6].

In recent years, more and more attention has been paid to urogenital chlamydia in children. Infection of children occurs in utero or during passage through the infected birth canal, and during close domestic contact due to violations of sanitary and hygienic norms. We often find cases of familial chlamydia. Established chlamydial and trichomonad infection of children from parents and other relatives living in the same apartment allows to talk about family urogenital infection. Most often, girls are infected with chlamydia. Chronic asymptomatic chlamydial urogenital infection is registered in the families of children with urogenital chlamydia.

Constant improvement of urogenital chlamydia diagnostic methods has ensured the creation of conditions where the diagnosis of chlamydial infection does not pose any

particular difficulties.

Treatment of urinary tract infections, on the one hand, is easier compared to infections of other localizations, due to this fact, an accurate etiological diagnosis is almost always possible. A determining factor in the possibility of using an antibiotic for urogenital infection is its activity against the dominant pathogens of the inflammatory process. The use of antibiotics in the treatment of urogenital infection has a number of features that must be taken into account when choosing a drug.

Treatment of patients with urogenital infection continues to be one of the most urgent problems of practical health care, which is caused not only by the steady growth of infection in the population, the presence of a large number of serious complications, but also by a high percentage of disease recurrences in patients who received etiotropic antibiotic therapy in accordance with current instructions and treatment regimens. According to various researchers, the frequency of recurrence of urogenital infection after the treatment is from 2 to 50% [7,8]. In this regard, the development and improvement of treatment methods for patients with urogenital infection is necessary and promising.

The purpose of this study was to determine the effectiveness of treatment of patients with urogenital infections using the drug Aziclar as an etiotropic therapy.

Materials and methods

We studied 57 patients with urogenital infections aged 13 to 52 (30 men, 20 women, 7 children). Etiological diagnosis of all patients was carried out in accordance with directive documents regulating microbiological, bacteriological and non-cultural research methods. Informed consent was obtained from each patient for the proposed treatment.

Dry urethroscopy, transrectal ultrasound examination of the prostate gland, seminal vesicles, bladder and kidneys were performed in men to clarify the localization, features and nature of pathological changes. Ultrasound examination of the pelvic organs, bladder and kidneys, and an extended colposcopy were performed in women.

The complex treatment included the use of hepatoprotectors, adaptogens, antioxidants, drugs that improve the state of microbiocenosis, and vitamin therapy. Local therapy, its methods and duration were based on the results of topical diagnostic analyses.

Aziclar (clarithromycin), manufactured by Flamingo Pharmaceuticals Ltd., India, was used as an etiotropic drug for the treatment of patients with urogenital infection. Aziclar was prescribed at a dose of 0.5 g twice a day. The course dose of Aziclar was 10-14 g.

Aziclar, manufactured by Flamingo Pharmaceuticals Ltd., India, is a representative of the class of macrolides with a 14-membered lactone ring and has an indirect effect on the immune response processes macroorganism due to the changed synthesis of the most important mediators of the immune response by monocytes and macrophages, such as tumor necrosis factor, interleukins, colony-stimulating factor, etc. [11,12]. This became the basis for its inclusion in the group of antibiotics that have an immunomodulatory effect on macroorganisms.

Macrolide antibiotics inhibit the synthesis of proteins in the cells of the microorganism. The mechanism of action of macrolides is due to their interaction with the 23S RNA component of the catalytic center of the 50S peptide transferase (or 30S for some microorganisms), which is a subunit of the membrane-associated ribosomes of bacterial cells. The indicated binding is an irreversible covalent and, apparently, complementary binding, which ensures the species specificity of the action of macrolides. Binding of macrolides to ribosomes of sensitive microorganisms leads to disruption of peptidyl transferase activity and inhibition of translocation and transpeptidation reactions, as a result of which the normal process of protein synthesis is disrupted [25]. Clinical observations on adult patients have revealed an increase in chemotaxis of neutrophils under the influence of erythromycin, roxithromycin, clarithromycin and shown a high therapeutic effectiveness of the drugs in the treatment of patients with urogenital infection [13]. The study by J. Lefevre et al., determining the sensitivity of Chlamydia trachomatis to various antibiotics, has shown that clarithromycin exhibits better activity against chlamydia [14].

Currently, macrolides are the drugs of choice in the treatment of patients with urogenital infection. It should be noted that the derivatives of erythromycin – roxithromycin, clarithromycin, azithromycin, josamycin, etc., are practically devoid of the disadvantages characteristic of erythromycin. They have good bioavailability, and high antichlamydial activity has ensured wide use in the treatment of patients with chlamydial infection. The macrolides have a special ability to penetrate into cells with subsequent intracellular accumulation, creating at the same time high concentrations that many times exceed their bactericidal activity, against a number of intracellular pathogens of the infectious process, such as chlamydia, mycoplasma, etc. [9,10]. Macrolides are relatively easily absorbed from the gastrointestinal tract. The absorption occurs mainly in the small intestine. The absorption of macrolides occurs most completely in an alkaline environment, and in an acidic environment they undergo partial or complete hydrolysis. An exception to this is clarithromycin, which shows pronounced resistance to the action of hydrochloric acid [15]. Therefore, the modern macrolides are in the form of dragees or enteric capsules.

Adverse events in people taking macrolides are rarely observed and usually not serious. Dyspeptic phenomena, such as nausea, heaviness and pain in the epigastrium, vomiting, diarrhea, which is associated with stimulation of gastrointestinal motility, have been reported [16, 17]. In the vast majority of cases, macrolides are metabolized in the liver with the participation of cytochrome P450. In contrast to erythromycin, which can irreversibly inhibit the enzyme; josamycin, clarithromycin and midekamycin reversibly inhibit it. Metabolism of macrolides in the liver takes place with the participation of cytochrome P-450 (isoform CYP3A4) with the formation of metabolites, the antibacterial activity of which is significantly lower than the drug itself. Of all the metabolites of clarithromycin, only 14-OH clarithromycin (R-hydroxyl derivative) and S-hydroxyl derivative have an antibacterial effect, but the antibacterial activity of the latter is extremely low [18,19].

Macrolides and their metabolites are excreted by the liver with bile and kidneys with urine. Ways of drug elimination depend on the water/fat solubility of the compounds: lipophilic substances are excreted with bile, and hydrophilic substances with urine. Macrolides themselves are lipophilic substances, and hydrophilic compounds can be formed only as a result of their metabolism.

In addition, it should be noted that lipophilic compounds can excrete into breast milk and pass through the placental barrier during pregnancy. The antimicrobial activity of clarithromycin is similar to erythromycin in many respects, while the spectrum of antibacterial action is somewhat wider. Clarithromycin has activity against many gram-positive, gram-negative bacteria, as well as some anaerobic bacteria and non-bacterial infectious agents [19,20].

Clarithromycin is a macrolide antibiotic with the most pronounced lipophilic properties. When eating fatty food, a partial redistribution of the drug into food may occur, thereby reducing its bioavailability. In this regard, the diet correction with the exception of eating fatty food is required. It should be noted that in obese people, clarithromycin may accumulate in adipose tissue, as a result the concentration of the drug in blood serum changes.

Macrolides, which have a high level of penetration into tissues, have the ability to accumulate in cells, creating higher tissue concentrations and to be considered the most effective antibiotics in the treatment of patients with urogenital infections, where the etiological agent has an intracellular or membrane form of parasitism. On average, the macrolides tissues concentration is about 10 times higher than the concentration in blood plasma. The highest tissue concentrations are typical for josamycin, azithromycin and clarithromycin, exceeding 10-100 times higher than plasma concentrations, the lowest – for erythromycin, only 5-10 times higher than plasma concentrations [21]. Antibiotics of this group are well tolerated by patients. There are isolated reports of allergic reactions to macrolides. Drugs of the macrolide group do not have cross-allergic reactions with antibiotics containing β-lactam ring (penicillins, cephalosporins) that allows to use such drugs for people with allergic reactions to β-lactam antibiotics. In isolated cases, intoxication, due to the impaired drug metabolism in liver diseases, may occur [22,23]. The low toxicity of macrolides allows them to be used even during pregnancy and lactation, and in paediatrics for the treatment of premature newborns and older children. Even with long-term use of macrolides, there are rare cases of intestinal dysbacteriosis, which is one of the main complications of antibacterial therapy, and inhibition of hematopoiesis is practically absent. Macrolides of new generations have high bioavailability, pronounced antibacterial activity and minimal toxicity, They are also well tolerated by patients [22,24,26].

Results and discussion

A comprehensive examination of the patients has revealed urogenital chlamydia in the form of monoinfection in 42 (73.7%), and a combination of chlamydial and mycoplasma infections in 15 (26.3%), respectively. Aziclar was well tolerated by patients. Adverse reactions requiring cancellation or dose adjustment of Aziclar were not observed during treatment. Indicators of general clinical and biochemical blood tests and urine analysis indicators were within the physiological parameters of healthy people both before and after the therapy. This indicates that the etiotropic drug Aziclar has no significant negative impact on the hepatobiliary, hematopoietic and genitourinary systems.

Control of the effectiveness of etiotropic therapy along with the concomitant use of any two diagnostic methods allowing to determine both the direct etiological agent and the antibodies produced to it (PIF, ELISA, PCR, cultural methods) was carried out 3-4 weeks after the end of treatment.

Disappearance of clinical symptoms of the disease and complete elimination of the causative agent were the criteria for curing patients. Only those patients in whom clinical recovery is combined with etiological treatment were considered to be treated. Dispensary follow-up of patients were carried out within 6 months with a full clinical and laboratory examination was performed 3-4 weeks after the end of treatment, then once every 2-3 months. When evaluating the dynamics of clinical symptoms, if there was a need to take into account topical changes, additional adequate instrumental methods of examination (urethroscopy, colposcopy and others) were used. The complex of laboratory examination of convalescent patients also included the evaluation of leukocyte reaction and the cytological pattern of scrapings from available mucous membranes.

Dynamic monitoring of patients in the course of therapy made it possible to establish that on the 4th-5th day, subjective sensations completely disappeared and objective signs of inflammation regressed in almost all patients with certain complaints.

The comprehensive clinical and laboratory examination have shown that with the help of the proposed method of etiotropic treatment of the patients with urogenital infection, it was possible to achieve clinical treatment in 57 (100%) and etiological treatment in 55 (96.49%). In two patients, during the curability control, the chlamydia infection was confirmed and *Ureaplasma urealyticum* was detected. Antibiotic therapy was additionally prescribed to two patients to cure mycoplasma infection.

Analysis of the data shows that Aziclar, manufactured by Flamingo Pharmaceuticals Ltd., India, has a pronounced activity against chlamydial and mycoplasma infections, which are characterized by intracellular and membrane parasitism.

Thus, Aziclar (clarithromycin), manufactured by Flamingo Pharmaceuticals Ltd., India, like other antibiotics of the macrolide group, has high bactericidal activity against gram-positive and some gram-negative microorganisms, as well as pathogens with intracellular and membrane parasitism. It is able to accumulate in high concentrations in macrophages, neutrophils and other immunocompetent cells. Aziclar, having a prolonged effect, is a low-toxic drug.

Good biopharmacological characteristics and tolerability, high therapeutic efficiency of the drug Aziclar allow to recommend it for wider use by practicing physicians in the complex treatment of patients with chlamydial-mycoplasma infection.

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