UDC 616.64/.69-002.12-022-08-059:615.33

PASECHNIKOV S.P.[1, 2], NASHEDA S.V.[2]
[1]National Medical University named after O.O. Bohomolets, Kyiv
[2]State Institution "Institute of Urology of National Academy of Sciences of Ukraine", Kyiv

EFFICACY EVALUATION OF GRANDAZOL IN THE TREATMENT OF MALE GENITAL ORGANS TRICHOMONAL INFLAMMATORY DISORDERS

Summary. *The article presents the results of research of clinical and microbiological efficacy of Grandazol in the comprehensive treatment for inflammatory disorders of male genital organs of trichomonal bacterial origin.*
Key words: *inflammatory disorders of male genital organs, urogenital trichomoniasis, sexually transmitted infections, Grandazol.*

Inflammatory infections in the urology and issues of their treatment and prevention represent one of the most pressing problems of the contemporary medicine. This is due to their prevalence, frequent recurring, social-economic and reproductive significance as well as to the progressing growth of microorganisms' resistance to antibiotics [1].

Despite significant achievements in the research of origin and pathogenesis in introduction of new methods of diagnostics and treatment, inflammatory disorders of male genital organs (IDMGO) are high on the list among urologic diseases.

Every year an increasing spread of IDMGO is observed, therefore treatment of this pathology becomes currently particularly critical [2].

The etiological factor of IDMGO is both nonspecific microflora and pathogens of sexually transmitted infections (STI).

As of today, the STI reached epidemic proportions in Ukraine. This is determined by a whole number of factors: low level of the population's sexual culture; a broad liberalization of sexual relationships; early sexual debut and lack of awareness about means of contraception; low level of financial security; insufficient and imbalanced nutrition; environmentally unfavorable conditions; hereditary and iatrogenic disorders of local and systemic immunity; active migration processes; decreasing quality and efficiency of preventive and clinical work of medical institutions due to inadequate funding; complexity of diagnostics; change in microflora spectrum and increasing amount of strains of microorganisms that have preserved their pathogenic properties after inferior and inadequate treatment; asymptomatic or pauci-symptomatic course of this disease; lack of immunity after recovery [3, 8, 16, 17].

Urogenital trichomoniasis (UT) is a widespread STI the pathogen of which is *Trichomonas vaginalis* – a protozoan single-celled microorganism adapted in the course of evolution to parasitization in organs of human genito-urinary system [20]. Trichomoniasis is a widespread disease and ranks first among sexually transmitted diseases [4]. The world database receives reports on 170 – 200 millions of trichomoniasis cases annually [5–8]. The infection frequency in the developed countries amounts to 2-10%, and in developing countries – 15-40%. Among

Address for correspondence with authors:
Nasheda Sergei Vasilyevich
E-mail: inflam@ukr.net

patients with a mixed urogenital infection, carriers of trichomonas amount to 40-50%, at that the disease is in 50% of cases asymptomatic. It should be taken into account that carriage of trichomonas leads to an epidemiological dissemination of pathogens among sexual partners [3, 9, 10].

In Ukraine, the official UT incidence rate is 1,263.7 cases for 100,000 of population, however, the real indicator is 5 times higher and amounts to some 6% of the whole population or 12% of sexually active population of reproductive age [11].

Trichomonal infection is the cause of emergence of IDMGO in 23-40% of patients and, respectively, being a widespread disease, it impacts the population's reproductive function and the demographic situation [12, 18]. One characteristic feature of *Trichomonas vaginalis* is their exceptional capacity for the association with other STI pathogens, therefore UT often develops along with a concurrent infection (together with chlamydial, ureaplasma, mycoplasmal infections and gonorrhea), which makes its treatment more difficult and contributes to emergence of complications. Trichomonas often serve as reservoirs, whilst preserving these pathogens in unchanged state (endocytobiosis), and some of them even actively replicate inside of Trichomonas vaginalis [13-15].

Trichomonas vaginalis affects urinary tract, seminal vesicles, prostate gland. UT entails the following complications in men: balanitis, balanoposthitis, urethritis, paraurethritis, cowperitis, epididymitis, prostatitis, vesiculitis, cyctitis [19].

The complexity of clinical laboratory diagnostics of a bacterial infection lies in the availability of simultaneously 2-3 and more various pathogens. Certain difficulty in identification of the disease in men is related to peculiarities in the genital system's constitution. In case of a trichomonal lesion of the prostatic urethra part and prostate at the expense of a barrier function of the membranous sphincter, it is not always possible to reveal a pathogen in excretes [24].

As to the morphology of trichomonas, the number of their atypical forms has increased. These forms possess low mobility and have an ameboid or spherical shape, which complicates a bacterioscopical diagnosis.

Frequent absence of pathognomic clinical implications of urogenital trichomoniasis, its course with minimal clinical implications make laboratory methods a basis for diagnosis of the disease. Judgments of many kinds with respect to diagnosis methods can be found in literature, which to a certain degree misleads practicing physicians. The selection of research methods when identifying sexually transmitted infections depends on many factors: anamnestic data, examination results, preliminary research (direct smear), list of laboratory tests conducted in a clinic, their cost, the patient's wherewithal. Thus, the selection of methods and examination algorithm should not only correspond to the regulatory environment (protocols, standards) but also be individual for each patient. Preparation of a patient and material sampling technique certainly have an effect on the quality of the diagnosis process.

In order to receive more reliable data, the following rules must be adhered to:

– a negative result of any examination does not exclude the presence of trichomonas;

– examination of material obtained should be carried out by all accessible methods simultaneously;

– it is necessary to use for the assessment not only urethral discharge and prostatic secretion, but also uropsammus of freshly voided urine, secretion of bulbourethral glands, sperm [18, 21].

The complexity of IDMGO treatment is due to the high virulence and resistance of pathogens to antibacterial drugs applied in urological practice, with persistent course of a disease and weakening of body defenses.

When determining a background therapy for treatment of STI, account should be taken of the WHO recommendations as to the criteria for antibacterial drug selection. The requirements envisage:

– high efficacy;

– low toxicity and good tolerability;

– slow development of the pathogen's resistance to applied medicinal products;

– opportunity to reduce administration frequency;

– opportunity to take drugs orally.

The quality of an efficient and timely therapy against trichomoniasis contributes greatly to the disease's expansion, course and prognosis. The treatment success depends on a right individual selection of the medicinal product, its pharmacokinetics and pharmacodynamics. The therapy's inefficiency is often linked to the non-compliance with the recommended treatment regimen or re-infection.

During a combination treatment of IDMGO, it is advisable to use antibacterial drugs with a broad spectrum of action. With reference to the wide spectrum of possible pathogens the structure of which includes, as a rule, anaerobic microbes, the tendency of *Trichomonas vaginalis* to endocytobiosis, the treatment regimens with inclusion of antibiotics and imidazoles are the most rational and practice-proven, in particular, during the acute and subacute periods of disease. Two, or sometimes more individual medications are included into these regimens. The combined antibacterial medications that became available in recent years, allow conducting treatment with a single medicinal product, thus enhancing patient compliance, considerably increasing the treatment efficacy and reducing the drug load on the organism [13].

These properties are displayed by the combined antibacterial medication Grandazol which contains active substances levofloxacin (2.5 mg/ml) + ornidazole (5 mg/ml). The medication is available in 100 ml vials (250 mg levofloxacin + 500 mg ornidazole) and 200 ml (500 mg levofloxacin + 1,000 mg ornidazole); in tablets (250 mg levofloxacin + 500 mg ornidazole).

The availability of various drug forms of Grandazol enables the use in the acute period of infusion (intravenous) administration route, ensuring 100% bioavailability and high concentration of the active ingredient in blood plasma within shortest time, with subsequent transfer of the patient to oral administration without dose adjustment [27].

Levofloxacin is an antibiotic that belongs to the group of fluoroquinolones. The fluoroquinolones are fundamentally different from other antimicrobial drugs by their mode of action. Their bactericidal effect is attributable to inhibition of two vitally important ferments of a microbial cell – DNA-gyrase and topoisomerase IV which results in a disturbance of synthesis of a bacterial DNA. Levofloxacin is active in respect of gram-positive and gram-negative pathogens including strains resistant to penicillins, cephalosporins and aminoglycosides. The advantages of levofloxacin: administration once a day; favourable pharmacokinetics; high level of penetration of prostate tissues; good bioavailability; similar pharmacokinetic parameters at oral and parenteral administration; high activity in respect of STI pathogens (*Mycoplasma hominis, Ureaplasma urealyticum, Chlamydia trachomatis, Neisseria gonorrhoeae*) [25, 26].

Ornidazole is a synthetic drug of nitroimidazole group with antibacterial (anti-anaerobic) and antiprotozoal action. Its antitrichomonal activity is due to the presence of a nitro group in the molecule. The nitro radical is able to break down DNA strings of a trichomonal cell. The effect emerges quickly. Cell division and cell mobility are terminated within 1 hour, and the cell itself dies within 8 hours [22].

The spectrum of action of Grandazol corresponds to its components – ornidazole and levofloxacin:

Staphylococcus spp., Streptococcus spp., Enterococcus spp., Enterobacter spp., H.influenzae, Legionella spp., E.coli, Klebsiella spp., Salmonella spp., Proteus spp., Shigella spp., N.gonorrhoeae, Chlamydia trachomatis, Mycoplasma hominis, Ureaplasma urealyticum, Bacteroides fragilis, Clostridium spp., Peptostreptococcus spp., Peptococcus spp., Gardnerella vaginalis, and also Trichomonas vaginalis etc.

Objective of paper: to study efficacy, safety and tolerability of Grandazol (manufactured by Yuria-Pharm) as well as its impact on the clinical course and laboratory indicators when treating IDMGO of trichomonal and bacterial origin.

Materials and Methods

37 males aged between 19 and 54 years (average age 34.1 ± 2.5 years) with IDMGO caused by UT participated in the study. In the study were included males who earlier did not take antiprotozoal medications and did not take medications from the fluoroquinolones group within preceding 30 days. Also sensitivity of potentially pathogenic flora to levofloxacin was taken into consideration. Clinical manifestations of the disease and laboratory indicators were registered before treatment and also 3-5, 7-10 days after the beginning of treatment and 1 month after its completion.

The UT diagnosis was determined on the basis of anamnesis, disease pattern, and also laboratory data. The laboratory diagnosis of trichomoniasis and bacterial burden was conducted with the aid of:

– bacterioscopy of urethra scraping;

– bacterioscopy of prostatic secretion;

– biomolecular method (polymerase chain reaction – PCR) of a study of urethral discharge and prostatic secretion on *Trichomonas vaginalis, Chlamydia trachomatis, Mycoplasma hominis, Ureaplasma urealyticum, Neisseria gonorrhoeae*;

– culture study of urethral discharge and prostatic secretion on *Trichomonas vaginalis*;

– bacteriological examination of urethral discharge and prostatic secretion on potentially pathogenic flora.

Furthermore, a common clinical examination was conducted: complete blood count, common urine test, blood glucose, biochemical blood assay (urea, creatinine, total protein, total bilirubin, alanine aminotransferase, aspartate transaminase).

All patients had ultrasound investigation of kidneys, bladder, prostate, organs of scrotum (if required).

The males with the proven IDMGO diagnosis of trichomonal and bacterial origin, their sexual partners (with the partner's consent) were informed on the character and peculiarities of the treatment course. All sexual partners were also recommended examination and treatment. The following recommendations were given: to exclude sexual contacts during treatment, to use barrier contraception methods during sexual contacts until recovery of both partners is verified. We considered clinical and etiological recovery as full recovery.

Study Results

According to the data of our study, trichomoniasis as a monoinfection was found only in 8.1% of patients, and its mixed forms in association with other infections – in 91.9% of patients.

The spectrum of sexually transmittable infectious agents was the following:

T.vaginalis – 19 (51.3 %), T.vaginalis + Mycoplasma spp. – 3 (8.1 %), T.vaginalis + Neiseria spp. – 2 (5.4 %), T.vaginalis + C.trachomatis — 6 (16.3 %), T.vaginalis + U.urealyticum – 3 (8.1%), T.vaginalis + U.urealyticum + C.trachomatis – 2 (5.4 %), T.vaginalis + C.trachomatis + Mycoplasma spp. – 1 (2.7 %), T.vaginalis + U.urealyticum + Mycoplasma spp. – 1 (2.7 %).

The high frequency of isolation of *T.vaginalis* in association with *C.trachomatis* in comparison with association with other pathogens should be noted. This peculiarity can be seen as a possible characteristic of a symbiosis of said microorganisms. The results obtained point to the effectiveness and necessity to conduct comprehensive laboratory studies during STI screening.

During culture study on potentially pathogenic flora, the following pathogens were identified: *Staphylococcus spp.* – 11 (28.2%), *Esherichia coli* – 9 (23.1%), *Enterococcus spp.* – 9 (23.1%), *Streptococcus spp.* – 3 (7.7%), *Proteus spp.* – 2 (5.1%), *Klebsiella spp.* – 2 (5.1%), *Enterobacter spp.* – 2 (5.1%), *Pseudomonas aeruginosa* – 1 (2.6%).

In 5 (13.5%) patients two patogens by a culture technique were found, in 3 (8.1%) males the potentially pathogenic flora was not identified in clinically significant concentration.

Table 1. Clinical efficacy of treatment with Grandazol of patients with IDMGO

Efficacy	Number of patients, abs.	Number of patients, %
Good	34	91.9
Partial	2	5.4
Absent	1	2.7
Total	37	100.0

Table 2. Bacteriological efficacy of treatment with Grandazol of patients with IDMGO of trichomonal and bacterial origin

Pathogen type	Number of strains	Bacteriological result, abs. number (%)		
		Pathogen eradication	Pathogen replacement	Pathogen preservation
Staphylococcus spp.	11	10 (90.9)	1 (2.6)	–
Esherichia coli	9	8 (88.9)	–	1 (2.6)
Enterococcus spp.	9	8 (88.9)	–	1 (2.6)
Streptococcus spp.	3	3 (100)	–	–
Proteus spp.	2	2 (100)	–	–
Klebsiella spp.	2	2 (100)	–	–
Enterobacter spp.	2	2 (100)	–	–
Pseudomonas aeruginosa	1	1 (100)	–	–
Total	39	36 (92.3)	1 (2.6)	2 (5.1)

The analysis of results of application of the combined antibacterial medication Grandazol in a combination therapy of IDMGO, conducted one month after the course completion, has shown the following outcomes (tables 1, 2).

Under a good clinical effect the full elimination of symptoms and signs of the disease was meant. Reduction in disease symptoms and intensity of complaints were interpreted by us as a partial clinical efficacy. Under absence of effect, the full preservation of clinical manifestations was meant. Absence of a clinical result was noted by one patient, in whom during a follow-up laboratory test atypical forms of trichomonas were found and Esherichia coli was seeded repeatedly.

It has been noted, at a dynamics of subsiding of clinical symptoms, that in the course of the treatment the main infectious manifestations are

neutralized sufficiently rapidly. This fact enabled us to transfer the patient, already on days 4-5 of treatment, to the oral administration, shorten the period of his hospital stay and continue treatment in the outpatient setting without the dose adjustment.

Grandazol had a pronounced positive effect with relation to opportunistic pathogens in 92.3% of patients. One strain of *Esherichia coli* and one strain of Enterococcus turned out to be insensitive. Besides, in one case the pathogen was replaced: *Staphylococcus* for *Esherichia coli*. During a follow-up examination 1 month after treatment, *Trichomonas vaginalis* was found in 3 (8.1%) patients.

Apart from the results of clinical and laboratory tests, any adverse events that emerged from the beginning of the treatment, were taken into consideration.

The side effects of treatment as gastrointestinal disorders were observed in the form of nausea in 4 (10.8%) of patients, metallic aftertaste – in 1 (2.7%) male, loosening of stool – in 2 (5.4%). In two patients, a transient modest rise of hepatic transaminases after treatment was observed. Modest side effects that emerged in some patients during the treatment did not require drug withdrawal.

Conclusions

The application of Grandazol for treatment of patients with IDMGO of trichomonal and bacterial origin has demonstrated a clinical efficacy of 91.9%.

The bacteriological efficacy of Grandazol with relation to opportunistic pathogens amounted to 92.3%, with relation to Trichomonas vaginalis – 91.9%.

Grandazol is well tolerated by patients, it does not cause serious adverse effects and changes in laboratory indicators, is convenient in application (once a day) and suitable for application as a sequential therapy.

High efficacy, good tolerability and safety of Grandazol in a combined treatment of IDMGO of trichomonal and bacterial origin allow us to recommend this medication for use in the clinical practice.

References

1. *Perepanova T.S., Palagin I.S. Topical issues of therapy and prevention of urological infections, standards and recommendations on management of patients with urological infections // Bulletin of Practising Physician. — 2014. — No. 3. — S. 14-17.*
2. *Gurzhenko Yu.N., Boyko A.I., Kogut Yu.Ya., Krasovskiy V.M. Study of efficacy of medication Lomadei in a combined treatment of imflammatory diseases of male genital organs // Man's Health. — 2012. — No. 1. — P. 77-82.*
3. *Melnikov S.N. Treatment of chronic imflammatory diseases of genital organs of trichomonal and bacterial origin // Man's Health. — 2013. — No. 1. — P. 162¬163.*
4. *Dyudin A.D. Efficacy, tolerability and compliance of application of secnidazole in a combined treatment of patients with urogenital trichomoniasis / A.D. Dyudin, N.N. Polion, I.A. Byubyuk, V.V. Gorbuntsov, D.G. Bashmakov // Ukrainian journal of dermatology, venereology, cosmetology. — 2013. — No. 3 (50). — P. 144-148.*
5. *Gorpynchenko I.I. Therapy of metronidazole-resistant trichomoniasis by combination of ciprofloxacin and tinidazole / I.I. Gorpynchenko, M.G. Romanyuk, A.M. Kornienko [et al.] // Man's Health. — 2014. — No. 1. — P. 95-98.*
6. *Gotsulyak O.L. Urogenital chlamydia infection associated with trichomoniasis // News of medicine and pharmacy. — 2007. — No. 1 (205) — P. 15-17.*
7. *Kogan B.G. Urogenital trichomoniasis: new solution for an old problem // Health of Ukraine. — 2008. — No. 11 (192) — P. 68.*
8. *Gorpynchenko I.I. Study of efficacy of appliaction of medication Ornizole in patients with chronic urogenital trichomoniasis / I.I. Gorpynchenko, Yu.N. Gurzhenko // Man's Health. — 2010. — No. 3. — P. 198-200.*
9. *United Kingdom national guideline on the management of Trichomonas vaginalis (2007). Available from: http//www. bashh. org/documents/87/87. pdf.*
10. *Workowsri K.A., Berman S. Centers for Disease Control and Prevention (CDC). Sexually Transmitted Diseases Treatment Guidelines, 2010 // MMWR Recomm Rep. 2010; 59 (RR-12): 1-10.*
11. *Kornatska A.G., Vovk I.B., Chubey G.V. Imflammatory diseases of pelvic organs caused by sexually transmitted infections // Health of Ukraine. — 2012. — No. 4 (8). — P. 38-39.*
12. *Klimenko B.V. Trichomoniasis. — M.: Meditsina, 1987. — 158 P.*
13. *Leontyev I.G. Modern combined drugs in treatment of urogenital trichomoniasis and associated urethrogenic infections in men/ I.G. Leontyev, D.I. Leontyev // Clinical dermatology and venereology. — 2013. — No. 3. — P. 63-68.*
14. *Molochkov V.A. Urogenital trichomoniasis, associated urethrogenic infections (epidemiology, clinic, diagnostics, treatment, prevention)// Russian journal of skin and venereal diseases. — 2000. — N 3. — P. 48-56.*
15. *Kubanova A.A. Urogenital infectious diseases caused by genital mykoplasms / A.A. Kubanova, M.R. Rakhmatulina // Bulletin of dermatologist and venereologist. — 2009. — No. 3. — P. 78-82.*
16. *Gerasimova T.V. Combined therapy of trichomonal urogenital infection / T.V. Gerasimova, E.N. Gopchuk // Woman's Health. — 2012. — No. 10 (76). — P. 136-138.*
17. *Pasechnikov S.P. Efficacy assessment of medication Orzipol in treatment of chronic imflammatory diseases of male genital organs of trichomonal and bacterial origin / S.П. Pasechnikov, S.V. Nasheda // Man's Health. — 2014. — No. 4. — P. 116-119.*
18. *Kadenko O.A., Bolotyuk. M.V. Comparative efficacy characteristics of laboratory diagnostics methods of urogenital trichomoniasis (own studies) // Journal of dermatology and cosmetology named after M.O. Torsuyev. — 2012. — No. 1-2. — P. 86-94.*
19. *Kubanova A.A. Management of patients with sexually transmitted infections and urogenital infections. Clinical recommendations / A.A. Kubanova, A.L. Baluyev, M.I. Gluzmin, N.P. Yevstigneyeva, D.V. Zaslavskiy [et al.]. — M.: Business express, 2012. — 111 p.*
20. *Ryzhikh P.G. To the matter of laboratory diagnostics of urogenital trichomoniasis taking into account concentration of Trichomonas vaginalis in biological material / P.G. Ryzhikh, A.E. Gushchin // Clinical dermatology and venereology. — 2013. — No. 5. — P. 44-48.*
21. *Dermatoveneorology: teaching guide / Edited by V.P. Fedotov, A.D. Dyudin, V.I. Stepanenko. — 2nd edition, rus. — Dnepropetrovsk; Kiev. Svidler A.L. Publishing house, 2011. — 652 p.*
22. *Kogan B.G., Gordeyeva G.D. Role of combined antibacterial drugs in the combination therapy of inflammatory diseases of female genital organs of mixed origin // Woman's Health. — 2014. — No. 5. — P. 86-90.*
23. *Myronyuk I.S. Urogenital mycoplasmosis caused by Mycoplasma genitalium: perspective on issue in treatment in physician's practice // Health of Ukraine. — 2015. — No. 2 (3). — P. 14-15.*
24. *Bednova V.N., Pogorelskya L.V.,Vasilyev M.M. et. al. Tactics for examination and therapy of patients with infectious urogenital diseases complicated by disbacteriosis (manual for physicians). — M.: Meditsina, 1996. — P. 14-32.*

25. Maley M. Treatment of urinary tract infections: focus on fluoroquinolones // Medical aspects of man's health. — 2015. — № 2 (17). — P. 27-31.

26. Rakhmatulina M.R. Urogenital infections in urology /M.R. Rakhmatulina, T.S.Perepanova, V.A. Bozhedomov// Efficient pharmacotherapy (urology and nephrology). — 2013. — No. 2 (16). — P. 2-10.

27. Netyazhenko V.3. Non-intensive infusion therapy in practice of internal medicine physician / V.3. Netyazhenko, O.A. Galushko// Ukrainian chemotherapeutic journal. — 2012. — No. 3 (26). — P. 164-167.

Received on 08.07.15

Пасічників С.П.[1,2], Нашеда С.В.[2]
[1]Національний медичний університет імені О.О. Богомольця, м. Київ
[2]ДУ «Інститут урології НАМН України», м. Київ

ОЦІНКА ЕФЕКТИВНОСТІ ЛІКУВАННЯ ЗАПАЛЬНИХ ЗАХВОРЮВАНЬ ЧОЛОВІЧИХ СТАТЕВИХ ОРГАНІВ ТРИХОМОНАДНО-БАКТЕРІАЛЬНОЇ ЕТІОЛОГІЇ ПРЕПАРАТОМ ГРАНДАЗОЛ

Резюме. У статті наведено результати досліджень клінічної та мікробіологічної ефективності препарату Грандазол у комплексній терапії запальних захворювань чоловічих статевих органів трихомонадно-бактеріальної етіології.

Ключові слова: запальні захворювання чоловічих статевих органів, урогенітальний трихомоніаз, інфекції, що передаються статевим шляхом, Грандазол.

Pasechnikov S.P.[1,2], Nasheda S.V.[2]
[1]National Medical University named after O.O. Bohomolets, Kyiv
[2]State Institution «Institute of Urology of National Academy of Medical Sciences», Kyiv, Ukraine

EVALUATING THE EFFECTIVENESS OF THE TREATMENT FOR INFLAMMATORY DISORDERS OF MALE GENITAL ORGANS OF TRICHOMONAL BACTERIAL ORIGIN USING GRANDAZOL

Summary. The article presents the results of studying clinical and microbiological efficacy of Grandazol in the comprehensive treatment for inflammatory disorders of male genital organs of trichomonal bacterial origin.

Key words: inflammatory disorders of male genital organs, urogenital trichomoniasis, sexually-transmitted infections, Grandazol.