REGIONAL FEATURES OF THE MICROBIAL LANDSCAPE OF URINE AND COMPARATIVE EVALUATION OF ANTIMICROBIAL THERAPY IN CHILDREN WITH CYSTITIS

REGIONALNA CHARAKTERYSTYKA MIKROORGANIZMÓW IDENTYFIKOWANYCH W POSIEWACH MOCZU ORAZ ANALIZA PORÓWNAWCZA TERAPII PRZECIWBAKTERYJNYCH U DZIECI Z ZAPALENIEM PĘCHERZA MOCZOWEGO

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ABSTRACT

Introduction: Growing resistance of pathogens to antibiotics, including cross-resistance to other antimicrobial classes that are used in the treatment of recurrent infections of the lower urinary system in children demands constant control of issues of regional antibiotic resistance. In the present days, in the empirical treatment of such patients physicians still choose medications with preserved activity in relation to E. coli.

The aim of our study was to investigate the regional features of microbial landscape of urine in children with cystitis and study the efficacy of 7-day administration of Furamag medicinal drug for the treatment of recurrent episodes of this disease in children.

Material and Methods: 65 children aged 5 to 16 years underwent clinical and laboratory examinations. The patients in Group I (33 children) received Furamag as an antimicrobial therapy; the comparison group consisted of patients (32 children) who received cefuroxime axetil. The both therapies course duration was 7 days.

Results: Bacteriological examination results were indicative of prevalence of gram-negative opportunistic microflora; in particular, E. coli prevailed in the structure of isolated causative agents (61.9%). Analysis of detected pathogens susceptibility to antimicrobial agents showed a high level of E.coli resistance to ampicillin, amoxicillin/clavulanate and gentamicin (in 97.4% of cases), and in 50% of cases the E.coli were resistant to cefotaxime, ceftriaxone and cefuroxime. High rates of resistance of Enterococcus spp. (100%) and Enterobacter spp. (96.7%) to cefuroxime, cefotaxime and ceftriaxone were recorded. Furamag demonstrated significantly higher bacteriological efficacy vs. cefuroxime axetil as for eradication of the most clinically significant causative agents of cystitis identified in the Poltava region (93.9% and 68.8%, respectively, $p < 0.05$). During the follow-up study, anti-relapse efficacy of Furamag appeared to be 1.5 times higher as compared to the reference drug in the children examined ($p < 0.05$).

KEY WORDS: infections of lower urinary system, children, antimicrobial resistance, furamag, cefuroxime axetil.

Wiad Lek 2017, 70, 3, cz. II, 566-570

INTRODUCTION

Infections of lower urinary system in children are still a relevant problem both in Ukraine and abroad, being among the first in the structure of pediatric morbidity. Prevalence of urinary tract infections (UTIs) determines not only its medical, but also its social significance. It is indicated by the world statistics on the incidence of this pathology, which states about 150 million cases per 1 year and 6 billion USD of incurred expenses. In USA more than 7 million patients per year seek for medical help on account of this pathology. Besides, cystitis as a reason for visit is observed in more than 2 million cases, and approximately 15% of antibiotic therapy courses are associated with UTIs [1, 2, 11].

In the treatment of community-acquired UTIs empirical approach is used, which is due to the structure of pathogens causing this pathology (in 65–90% of cases the pathogens are presented by E. Coli). Elimination of microbial-inflammatory process in the urinary tract, which is taken as a basis of the therapy, is impossible without antibacterial agents (ABA). Clinicians have a considerable amount of these ABA in their arsenal, and the list of international proprietary names of systemic ABA differs in every country. However, their range is much limited in pediatric practice. Fluoroquinolones (widely used for initial empirical treatment of infections of lower urinary system in adults) due to the age restrictions are prescribed in pediatric practice only in case of pathogen multiresistance to standard regimen drugs. According to the WHO formulary for children, Guidelines of European Association of Urology and American Urological Association, the drugs of choice in the treatment of noncomplicated infections of lower urinary system in children are oral second-third generation cephalosporins or amoxicillin/clavulanate, or trimethoprim (in accordance with the regional data of microflora resistance) administered for 5–7 days (LE 1b), and urinary antiseptics (nitrofurans, fosfomycin according

to EUA guidance, 2015). Due to the relatively high frequency of recurrences of lower urinary system infections that represent 25–30% of cases within the first year after the first episode of the disease, there is often a need for antibiotic retreatment; thus, proper selection of initial antimicrobial therapy for UTI will determine the efficacy of treatment and disease prognosis [3, 15, 21]. Repeated therapeutic and prolonged anti-relapse regimens used for urinary tract sanitation often lead to side effects, such as allergic reactions and changes in physiological composition of child's intestinal microbiota. The disadvantage of most drugs is also represented by a limited number of oral dosage forms adapted for children.

The data of European and domestic studies confirm the global trends towards increasing resistance of uropathogenic strains of E. coli to antibacterial agents included into treatment regimens for community-acquired infections of lower urinary system, especially to co-trimoxazole (resistance – 20–30%), ampicillin (more than 30%), first-generation quinoline (5–27%) [6–9]. Another disturbing feature is increasing resistance to amoxicillin/clavulanate and fluoroquinolones (norfloxacin, ciprofloxacin) in some European countries: 9 and 15%, respectively [9].

The results of multicenter studies demonstrated resistance of more than 80% of E. coli cultures to third- and fourth-generation cephalosporins ("MARAPHON", 2011–2012, Russia); increasing resistance of this uropathogen to cefuroxime and ciprofloxacin in 14.3 and 13.6% of cases, respectively (ARESC – the pan-European research on UTI causative agents); and significantly increased proportion of cultures (25 % and higher) that are resistant to third-generation cephalosporins in Southern and South-Eastern Europe [17–20]. This fact necessitates constant dynamic monitoring of antibiotic resistance in general and in each country, in particular [16].

According to the conception of Infectious Diseases Society of America and the European Society for Clinical Microbiology and Infectious Diseases concerning the treatment of acute noncomplicated cystitis in women (IDSA/ESCMID), ABAs lead to selection of resistant uropathogen strains. For example, treatment with cephalosporins may cause selection of vancomycin-resistant enterococci, and treatment with fluoroquinolones – selection of methicillin-resistant staphylococci and gram-negative microorganisms resistant to fluoroquinolones. In contrast, long-term use of nitrofurans, fosfomycin, mecillinam does not increase resistance of E. coli to other drugs [10] In addition, during a quite long period of documented usage (more than 60 years), the level of uropathogen resistance to nitrofurans remains stationary low [4, 5, 10, 15].

This enables wide usage of them at the present time in order to eliminate infectious inflammatory process in the lower urinary system in children.

Furamag® ("OlainFarm") is an original fixed combination dosage form of 5-nitrofuran furagin. Magnesium carbonate, which is a part of the drug, prevents conversion of furagin potassium salt to furagin under acid pH of stomach, improves its absorption in the small intestine, thereby increasing its bioavailability by 2.5–3 times as compared to furagin [5, 12–14], and reduces side effects. Furamag is acceptable for use in pediatric patients; it is produced in capsules of 25 mg and 50 mg; its therapeutic and preventive doses can be calculated for children since 3 years of age (package insert).

THE AIM

The aim of our study: to investigate the regional features of microbial landscape of urine in children with cystitis and to study the efficacy of 7-day administration of Furamag medicinal drug for the treatment of recurrent episodes of this disease in children.

MATERIALS AND METHODS

65 children aged 5 to 16 years with recurrent cystitis underwent clinical and laboratory examinations; all of them were treated at the outpatient and in-patient units of Poltava Regional Pediatric Clinical Hospital and Kremenchuk Municipal Pediatric Clinical Hospital. This work is a part of a research work of State Higher Education Institution of Ukraine "Ukrainian Medical Stomatological Academy" of the Ministry of Health of Ukraine: "Optimization of diagnosis, treatment, and detection of predictors for co-morbid disease formation in children with gastrointestinal disorders and allergic diseases", 2011–2015 (State Register #0111.U005141).

The patients in Group I (33 children) received Furamag 5 mg/kg/day in 2–3 divided doses; the comparison group consisted of patients (32 children) who received cefuroxime axetil 10 mg/kg/day in 2 divided doses for 7 days. The patients did not differ in major demographic, sex and anamnestic parameters which could have affected the results of the study. Children with the new onset of cystitis, or complicated and noncomplicated infections of the upper urinary tract, as well as diseased children under 5 years were excluded from the study. Examinations of the children and all therapeutic measures were carried out with the patients' and their parents' consent.

Past history was obtained and the following studies performed in all children: clinical tests (complete blood count and clinical urine analysis), biochemical blood analysis (including creatinine, BUN, nonprotein nitrogen, total protein, bilirubin and its fractions), differential count of urinary leukocytes, Nechiporenko's test, Zimnitskiy's test, and daily proteinuria level measurement. Before inclusion into the study, all patients provided urine samples for identification of causative agents and their sensitivity to antibiotics. Clinical significance of microorganisms isolated in urine was evaluated qualitatively and quantitatively. When studying the midstream specimen of urine, shedding of microorganisms in amount of $\geq 10^{3-4}$ cfu/ml and more was considered clinically significant. General clinical, instrumental, clinical laboratory and biochemical tests in

the patients were performed by conventional methods.

The assessment of treatment results included the following parameters: bacteriological efficacy after treatment (on day 7); clinical efficacy in early period (on day 3), immediately after treatment, and in 7–14 days after treatment; present/absent relapses during 3 months after treatment; and sensitivity of isolated infectious agents to the investigated antimicrobial drugs. Follow-up period lasted for 3 months.

Subjective assessment of clinical symptoms severity (urethrodynia during urination, discomfort and lower abdominal pain, feeling of incomplete bladder emptying, urinary urgency) was performed using a questionnaire and scored as following: 0 – no symptom, 1 – mild, 2 – moderate, 3 – severe. Frequency of urination at night: 0 – no symptom, 1 – once, 2 – twice, 3 – three times or more. Minimum and maximum scores on symptom scale ranged from 0 to 15. Objective assessment of clinical efficacy of treatment included: recovery (elimination of clinical and laboratory signs of urinary tract infection, no need for additional antibacterial therapy), or lack of efficacy (no clinical improvement, a need for additional antibacterial therapy).

Bacteriological efficacy assessment was performed on the basis of the following criteria. Eradication – the pathogen that was isolated before treatment is not detected in further studies. Persistence – the pathogen that was isolated before treatment is detected in further studies in a clinically significant titer. Superinfection – elimination of the primary pathogen during treatment and occurrence of another clinically significant microorganism after treatment in the presence of clinical signs of infection. Assessment is not available – no microbial growth.

Mathematical processing of results was performed using STATISTICA for Windows 7.0 (StatSoft Inc) and MS Excel spreadsheets. The mean values and standard deviation ($M \pm \sigma$) for parametric values and frequency of signs for nonparametric values were calculated. The values were compared by means of chi-squared test and t-test. For all analyses performed, with the values of $p < 0.05$ the observed differences were considered statistically significant; with the values of $p \leq 0.1$ there was a trend to a difference. Differences in clinical and bacteriological efficacy were assessed by Wilson's method with 95% confidence intervals (CI) calculation.

RESULTS AND DISSCUSION

Patient characteristics. 65 children with the recurrent cystitis were included into the study. The mean age of randomized patients in Group I and II made up 6 and 7.7 years, respectively; the differences between the groups were not statistically significant. Girls prevailed over boys in percentage correlation in both groups (I – 90.9%; II – 93.8%, respectively). Concomitant diseases were found in the majority of patients in both groups, significant differences between the groups were not observed. The vast majority of comorbidities in both groups (72.7% and 75%, respectively) were presented by functional gastroduodenal and gallbladder diseases in remission (functional dyspepsia, biliary malfunctions, gastroesophageal reflux, duodenogastric reflux). Time of occurrence and duration of the first episode (onset) of the disease before inclusion into the study did not differ significantly between the groups. Before inclusion into the study, 24.2% and 21.9% of patients in Group I and II, respectively, were pre-treated with antibiotics that may be regarded as a risk factor for antibiotic resistance of pathogens.

Study of regional features of the microbial landscape of urine and sensitivity to antimicrobial therapy in children with cystitis. Bacteriological examination results were indicative of prevalence of gram-negative opportunistic microflora in all examined children. In particular, E. coli prevailed in the structure of isolated causative agents (61.9%), which is consistent with the literature data [15, 17, 20], and is accounted for by prevailing initial way of infecting and reservoir of the microflora in the intestinal tract. The data are also confirmed by frequently observed association between the pathology in the studied patients and functional gastroduodenal diseases. Enterococcus spp. (19%) and Enterobacter spp. (14.3%) ranked second and third; other detected gram-negative pathogens included: Klebsiella spp. (7.9%), Staph epidermidis (3.2%) and Pr. Mirabilis (3.2%). Microbial associations were registered in 6.3% of cases, wherein they were represented by associations with Ps. aeruginosa or cocci. In 1.3% of cases the microflora could not be defined. Potential reasons for negative results of bacteriological study could possibly be represented by the presence of intracellular or viral infection as an etiologic factor. It should be noted that Klebsiella significantly prevailed in Group I, while enterococci and enterobacteria with almost equally significant frequency were observed in both groups, with a little prevalence in Group II.

Analysis of detected pathogens susceptibility to antimicrobial agents showed a high level of E.coli resistance to ampicillin, amoxicillin/clavulanate and gentamicin (in 97.4% of cases); in 50% of cases the E.coli were resistant to cefotaxime, ceftriaxone and cefuroxime, and in 7.7% of cases – to azithromycin. High rates of resistance of Enterococcus spp. (100%) and Enterobacter spp. (96.7%) to cefuroxime, cefotaxime and ceftriaxone were observed; in more than 30% of cases both were resistant to gentamicin, which is consistent with the literature data related to significant increase of uropathogens resistant not only to aminopenicillins and aminoglycosides, but also to second and third generation cephalosporins [17, 16, 20]. It should be noted that Furamag demonstrated significantly higher activity against enterococci and enterobacteria as compared to cefuroxime axetil to which these bacteria are naturally inactive. A trend was observed towards greater frequency of the E. coli strains susceptible to Furamag rather than to cefuroxime axetil – 95% and 73%, respectively ($p > 0.05$). Klebsiella spp (44.3%) were also resistant to cefotaxime, ceftriaxone and cefuroxime in about half of the children. In 2 children treated with cefuroxime axetil there were pathogen changes after treatment, wherein one child

Table I. Clinical and Bacteriological Efficacy of Treatment in Children with Recurrent Cystitis

Treatment Outcome	Group I: n=33 (%)	Group II: n=32 (%)	Δ% (95% CI)
Post-Treatment Clinical Efficacy (Day 7)			
Recovery	32 (97)	29 (90.6)	8.1 (11.1 to 27.3)
Lack of Efficacy:	1 (3)	3 (9.4)	
Post-Treatment Clinical Efficacy (after 7–14 Days)			
Recovery	32 (96.9)	27 (84.4)	12.5 (7.1 to 33.5)
Lack of Efficacy:	1 (3.1)	4 (12.5)	
Relapse	0	1 (3.1)	
Post-Treatment Bacteriological Efficacy			
Eradication	31 (93.8)	22 (68.8)	27.1 (4.1 to 40.2)*
Persistence	1 (3.1)	7 (21.9)	
Superinfection	0	2 (6.2)	
Assessment is not available	1 (3)	1 (3.1)	

** – $P < 0.01$*

presented with mixed infection during bacteriological re-study. In Group I only one patient (3.1%) revealed no clinical and bacteriological efficacy of treatment due to his E.coli resistance to Furamag. In contrast, 21.9% of children in Group II had microorganism resistance to cefuroxime axetil and in 6.2% of children the pathogen isolated before treatment changed on day 7 of antimicrobial therapy (Table I).

Clinical and bacteriological efficacy. In the setting of administration of investigated antimicrobial agents, most patients in both groups achieved rapid resolution of subjective clinical signs. Statistical analysis of data showed that the majority of patients in both groups demonstrated elimination of dysuria signs on day 3 and had no significant difference (96.9% and 93.8%, respectively). More differences were found when analyzing urinary syndrome: urinary findings came within normal limits on 3-4 days in 90.9% of patients in Group I as opposed to Group II, where only 78.1% of children achieved similar results.

The results of antimicrobial therapy in patients are shown in Table 1. These are the data on clinical efficacy of antimicrobial therapy immediately after treatment and in 1–2 weeks after treatment, and the results of bacteriological efficacy after treatment. Clinical efficacy of antibacterial therapy was assessed immediately after treatment and during follow-up, and did not significantly differ, although there was a trend towards a more pronounced effect of Furamag clearly observed in the first and second weeks after treatment (difference in efficacy: 12.5%; $p > 0.05$). Analysis of bacterial efficacy demonstrated a significant difference between the studied groups. Antimicrobial therapy with Furamag led to a significantly more expressed eradication of pathogens as compared to that with cefuroxime axetil (93.8% and 63.8, respectively; $p < 0.01$). It should be noted that persistence of microorganisms was observed 7 times more frequently in Group II as compared to the group of children who received Furamag.

Anti-relapse efficacy. Within 3 months after the main phase of the study, frequency of recurrent cystitis was assessed in children of both groups.

During this follow-up period, 93.9% of examined children in Group I demonstrated significantly higher anti-relapse efficacy (no clinical manifestations of the primary disease, no changes in urine findings, no pathogen persistence or re-infection), unlike the children in Group II, where similar results were achieved only in 20 patients (62.5%). It should be noted that 1 patient (3.1%) in Group II presented with a relapse on day 6 after treatment, and 21.9% of children required substitution of cefuroxime axetil by other antibacterial drug due to the persistence of the pathogens. The average duration of recurrent episodes made up 5.2 and 7.1 days in the children of Group I and II, respectively.

Another important fact is that side effects were not reported for both drugs used in children. In our opinion, excellent tolerance of Furamag is primarily associated with magnesium carbonate, which is a part of the preparation. Magnesium carbonate prevents the conversion of furagin potassium salt to furagin, improves its absorption in the small intestine, thereby increasing bioavailability of the medicinal drug. Higher bioavailability of the medicinal drug allows for a therapeutic effect at lower doses and reduces side effects. At the same time, it should be noted that oral cefuroxime axetil enters the gastrointestinal tract in the form of a prodrug, which also reduces the likelihood of adverse gastrointestinal events [1, 2, 5].

CONCLUSIONS

Thus, a thorough sensitivity analysis of the most clinically significant causative agents of cystitis (E.coli, Enterococcus spp., Enterobacter spp., and Klebsiella spp.) detected in the Poltava region showed high rates of resistance to ampicillin, amoxicillin/clavulanate, gentamicin, which makes it inappropriate to use these medicinal drugs for empirical

treatment of cystitis in children. At the same time, increasing resistance of these cultures to cefotaxime, ceftriaxone, and cefuroxime, in our opinion, requires special attention when choosing these drugs for initial therapy of recurrent episodes of cystitis in children in our region.

Careful analysis of all detected microorganisms demonstrated significantly higher sensitivity to Furamag vs. cefuroxime, which was accompanied by a significantly higher eradication level of one of the four clinically most significant cystitis pathogens, isolated in the study. High bacteriological efficacy of Furamag (93.9%) in the treatment of recurrent cystitis in children was proved, and the elimination of major clinical manifestations of the disease was observed as early as on day 3 of therapy. There was observed 2 times greater frequency of the E. coli strains susceptible to Furamag vs. cefuroxime axetil. Eradication of Enterococcus spp. and Enterobacter spp. was significantly higher during the treatment with Furamag than with cefuroxime axetil, wherein these pathogens were resistant to the latter in 100% of cases.

Our results confirm the literature data as for high efficacy of Furamag in the treatment of cystitis in children, practical absence of resistance of primary disease pathogens and excellent tolerance. The results of 3 months' follow-up demonstrated high efficacy of Furamag in relation to recurrence prevention. Based on these data, Furamag can be recommended as first-line therapy for recurrent episodes of cystitis in the present conditions of widespread multiresistant pathogens.

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Received: 5.02.2017
Accepted: 1.06.2017