



## EFFECTIVE USE OF FOSFOMYCIN IN THE TREATMENT OF URINARY TRACT INFECTIONS

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### Abstract

Urinary tract infection (UTI) is one of the most common urological diseases and presents a problem of rational antibiotic therapy due to growing antibiotic resistance. Fosfomycin is one of the old low-molecular-weight broad-spectrum bactericidal antibiotics with activity against uropathogens, in particular *Escherichia coli* and others. Modern data indicate that after a single dose of fosfomycin, sufficient concentrations in the prostate tissue are achieved. Thus, the accumulation of new scientific data on the mechanisms of action and resistance of fosfomycin increases the possibilities of its practical application.

**Keywords:** Fosfomycin, resistance, urinary tract infections, cystitis, prostatitis

### Introduction

#### Relevance

Urinary tract infection (UTI) is one of the most common urological diseases and presents a problem of rational antibiotic therapy due to growing antibiotic resistance. Fosfomycin is one of the broad-spectrum bactericidal antibiotics with activity against gram-negative and gram-positive flora. Modern data indicate that in the treatment of prostatitis, after a single dose of fosfomycin, sufficient concentrations in the prostate tissue are achieved. Recent reviews in 2019 and 2022 presented the results of studies on the use of fosfomycin for the prevention of infectious complications after transurethral prostate biopsy, as well as in patients with chronic bacterial prostatitis whose pathogens are resistant to other antibiotics.

Many factors contributed to the preservation of the antibacterial activity of fosfomycin, including the use of a single dose, limited use for UTIs only, very high and sustained concentrations in the urine that quickly kill bacteria, reducing the possibility of mutant selection. In addition to its antimicrobial properties, fosfomycin has an immunomodulatory effect by altering the function of lymphocytes, monocytes





and neutrophils. It affects the acute inflammatory cytokine response. Fosfomycin is considered as a potentially useful antibiotic for the treatment of prostatitis.

**Goals and objectives.** Ensuring the effective use of fosfomycin in UTIs.

**Materials and methods.** Analysis of literature data and clinical observations on the use of Fosfomycin.

### **Results of the Study**

Fosfomycin is a synthetically obtained bactericidal antibiotic with a broad spectrum of action, the bactericidal activity of which extends to gram-negative and gram-positive bacteria. The drug inhibits the synthesis of the microbial wall during mitosis, blocking the enzyme transpeptidase and leading to the death of bacteria [1].

Preservation of the antibacterial activity of fosfomycin is achieved by the fact that it is used in a single dose, used only for the treatment of urinary tract infections, very high concentrations of the drug are created in the urine, which reduces the possibility of bacterial resistance. In addition to its antimicrobial effect, fosfomycin has an immunomodulatory effect by changing the function of lymphocytes, monocytes and neutrophils. It inhibits the acute inflammatory cytokine response.

In 2020 studies, fosfomycin compared efficacy with other antibacterial preparations such as  $\beta$ -lactams/cephalosporins, quinolones, sulfonamides, nitrofurantoin in a wide range of patients – with uncomplicated UTI or asymptomatic bacteriuria – and did not reveal differences in the incidence of clinical and microbiological cure with the comparison groups. A number of other studies in patients with UTI or a complicated course have also shown high sensitivity of uropathogens to fosfomycin and the efficacy of treatment with multiple doses (2–3 doses with an interval of 48–72 hours) [3,5].

Fosfomycin is considered as an effective antibiotic for the treatment of prostatitis. According to the latest data, there are results of the use of fosfomycin for the prevention of postoperative infectious complications, as well as in patients with chronic bacterial infections, the causative agents of which are resistant to other antibiotics. Thus, new scientific data on the clinical pharmacology of fosfomycin increase the possibilities of its practical application.

Uncomplicated urinary tract infection (NIMP) is a common disease that requires rational antibiotic therapy. One of the modern problems of medicine in the field of bacterial infections is the development of antibiotic resistance to widely used drugs,





which creates difficulties in treatment and leads to an increase in complicated disease courses [2,7].

For many years, the most common uropathogen (>90%) causing urinary tract infection has been *Escherichia coli*, and treatment has focused on eradicating this pathogen using shorter regimens of an effective antibiotic. Antibiotic resistance to previously used drugs, such as trimethoprim and ampicillin, now often exceeds 30-50%, while fosfomycin, despite many years of use, remains highly effective. The latter is mainly used to treat NIMPs in the oral dosage form of tromethamine or calcium salt and today arouses the interest of clinicians around the world [4,8]. Fosfomycin is administered in a single dose, which reaches a very high concentration of the antibiotic in MP, successfully killing the most common uropathogens, including those with developed resistance [6].

Fosfomycin has been used for the treatment of UTIs for a long time, due to the growth of resistance to other antibacterial drugs, it is considered a rational agent for the treatment of infections caused by multidrug-resistant pathogens [10,12]. Many factors contributed to the preservation of the antibacterial activity of fosfomycin, including the use of a single dose, limited use only for urinary tract infections, very high and stable concentrations in the urine, which quickly kill bacteria, reducing the possibility of mutant selection [13]. In addition to the antibacterial effect, fosfomycin has an immunomodulatory effect, changing the function of lymphocytes, monocytes and neutrophils. It suppresses the production of pro-inflammatory cytokines (tumor necrosis factor  $\alpha$ , interleukins  $1\alpha$ ,  $1\beta$ ), leukotriene B<sub>4</sub> and increases the production of anti-inflammatory cytokines (interleukin-10) and has an effect on the activity of B-lymphocytes. The drug enhances the phagocytic capacity of neutrophils, leading to an increase in the bactericidal effect of neutrophils compared to other antimicrobials [9, 11].

Most of the clinical data on the efficacy of fosfomycin relate to the treatment or prevention of lower urinary tract infections – cystitis. It is recommended to use fosfomycin for the treatment of patients with uncomplicated cystitis. The first meta-analysis of 27 randomized clinical trials using a single dose of 3 g of fosfomycin in non-pregnant women and pregnant women with cystitis did not reveal any differences with comparator antibiotics (quinolones,  $\beta$ -lactams, aminoglycosides, nitrofurantoin, sulfonamides) either in clinical or microbiological cure [7].

In recent years, the greatest interest has been directed to comparing the effectiveness of treatment of acute uncomplicated cystitis in women between a short 1-day dose of fosfomycin and a 5-day course of nitrofurantoin. No significant differences were found in achieving clinical and microbiological cure within 4 weeks of treatment, nor





were there any differences in the incidence of adverse events with fosfomycin compared to nitrofurantoin. It is concluded that a single dose of fosfomycin represents a potentially effective and safe treatment option for NRIPs in women during pregnancy.

Fosfomycin is effective at a glomerular filtration rate of less than 60 ml/min. in the treatment of cystitis.

The etiological factors in prostatitis and UTIs are similar in bacterial flora, including multidrug-resistant gram-negative enterobacteriaceae, and represent a growing clinical problem, especially in relation to resistance to fluoroquinolones, which are widely used to treat bacterial prostatitis. In addition, the treatment of bacterial prostatitis is complicated due to the anatomical features of the prostate gland, which complicate the effectiveness of antibiotic therapy.

Acute bacterial prostatitis is often caused by an ascending UTI and is associated with the most common infecting microorganisms – *E. coli*, *P. mirabilis*, *P. aeruginosa*, *Klebsiella* spp., *Enterococcus* spp. and *Serratia* resistance to fluoroquinolones, while no cases of resistance have been identified in the fosfomycin group. Fosfomycin is not the drug of choice for the treatment of acute or CKD, but it may be a rational drug for the treatment of outpatients who are allergic to other antibiotics and have low levels of resistance.

Recent reviews in 2019 and 2022 presented a series of clinical cases in patients with CKD who received long-term courses of fosfomycin after unsuccessful treatment with fluoroquinolones and cotrimoxazole [4,6]. Fosfomycin is used in a single dose, which reaches a very high concentration of the antibiotic in the urine and bladder, sufficient to eliminate most common uropathogens, including multidrug-resistant ones.

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