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Clinical application analysis of phosphomycin aminotriol granules in urinary system infections

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Abstract: *Urinary tract infections are prevalent infectious diseases in clinical settings. The increasing irrational use of antimicrobial drugs has contributed to a gradual rise in the resistance of pathogens causing UTIs. The introduction of new phosphomycin oral formulations, characterized by high concentrations and prolonged duration in body fluids, minimal side effects, and relatively low resistance of relevant infecting strains, has made them a common choice for UTI treatment. However, improper use may still lead to bacterial resistance issues. This study extracts and analyzes data from UTI patients treated in our hospital during three months in 2022, focusing on the medication patterns in antimicrobial therapy. Specific issues related to the inappropriate and non-standard use of phosphomycin aminotriol granules are identified, including instances of non-indicated use, prolonged treatment duration for uncomplicated lower urinary tract infections beyond guideline recommendations, and the importance of administering the medication before meals or after gastric emptying. These issues are delineated to facilitate targeted clinical improvements.*

Keywords: *Phosphomycin amdinotriol granules; Urinary tract infection; Clinical application analysis*

1. Introduction

Urinary tract infections (UTIs) are common infectious diseases in clinical practice. With the increasing misuse of antimicrobial drugs, especially the overuse of fluoroquinolones, the drug of pathogens causing urinary tract infections has gradually increased[1].phosphomycin, discovered by a Spanish scientist in 1969 from the culture fluid of actinomycetes isolated from soil, is an antibiotic derived from the fermentation of soil bacteria. It belongs to the phosphonic acid class and is a broad-spectrum bactericidal antibiotic.phosphomycin exhibits high antibacterial activity against various Gram-positive (G+) and Gram-negative (G-) bacteria, including some drug-resistant strains such as MRSA, Gram-negative bacteria producing extended-spectrum beta-lactamases (ESBLs), and vancomycin-resistant Enterococcus (VRE)[2]. It serves as a rapid bactericidal agent used for the treatment of acute uncomplicated lower urinary tract infections caused by susceptible bacteria, such as acute cystitis, acute exacerbation of chronic cystitis, acute urethrocystitis syndrome, nonspecific urethritis, and asymptomatic bacteriuria during pregnancy. Additionally, it is employed for the prevention of urinary tract infections during surgical procedures and infections caused by diagnostic procedures involving the urinary tract.

Whilephosphomycin-class preparations have been used earlier, the high risk of allergy tophosphomycin injections and their low bioavailability limited their early clinical application, primarily used for simple urinary tract infections[3]. In recent years, novelphosphomycin-class preparations have been more widely used. These preparations, when taken orally, exhibit high concentrations in body fluids, have a long maintenance time, fewer side effects, and lower drug resistance of relevant infection strains. They have become a routine medication for urinary tract infections abroad[4]. To explore the rational application ofphosphomycin in urinary tract infections, this paper analyzes the clinical application ofphosphomycin amdinocaine in sporadic urinary system infections in our hospital, aiming to guide clinicians in the more standardized and reasonable use ofphosphomycin preparations.

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2. Use ofphosphomycin methanesulfonate in patients with sporadic urinary tract infections

This study involves the extraction of data from patients treated for UTIs in our hospital during the first three months of 2022, considering both outpatient and inpatient cases. The focus of the analysis is on the antimicrobial treatment of these patients, with a specific emphasis on scrutinizing the inappropriate and non-standard use of phosphomycin aminotriol granules. The aim is to identify and delineate issues related to the improper use of this medication.

2.1 Outpatient data research

In April, August, and December of 2022, all urology outpatient records totaled 5157, with 1785 involving the use of antimicrobial drugs, accounting for 34.61% of the total. Among these, 697 records involved the use ofphosphomycin, constituting 39.05% of cases using antimicrobial drugs. A detailed analysis of the 697 records usingphosphomycin revealed 385 cases with irrational prescriptions, representing 55.24% of the total. Among these, inappropriate indications accounted for 61.82%, and improper dosage and administration accounted for 9.15%. Additionally, due to unclear diagnostic information (only diagnosing urinary tract infection without specifying upper or lower urinary tract involvement) and incomplete medical records, 171 cases could not be evaluated for prescription rationality, constituting 24.53%. Therefore, the proportion of irrational prescriptions may be even higher.

2.2 Inpatient data research

In April, August, and December of 2022, urological surgery inpatient records involving the use ofphosphomycin numbered 124. Of these, 26.61% had reasonable medication records. Among them, cases wherephosphomycin was used as part of combination therapy for multidrug-resistant bacterial infections constituted 7.26% of the total. However, 73.39% of inpatient records were deemed unreasonable. Inappropriate indications accounted for 81.32%, and improper dosage and administration accounted for 11.11%.

3. Analysis of irregular use of phosphomycin in patients with urinary tract infections

① Usage without appropriate indication: In both outpatient and inpatient settings, a notable issue in the inappropriate use ofphosphomycin is the frequent absence of a clear indication for its administration. While the drug's instructions and relevant guidelines recommend its use for uncomplicated lower urinary tract infections such as cystitis and urethritis, instances were observed wherephosphomycin was prescribed for conditions that do not align with its approved indications. Examples include prostatic hyperplasia, epididymitis, reproductive urinary tract infections, complicated urinary tract infections with stones or obstruction, pyelonephritis, and other upper urinary tract infections. Due to the pharmacokinetic characteristics ofphosphomycin, its use is not recommended for these types of infections.

② Issues in dosage and administration: Phosphomycin presents some concerns regarding dosage and administration. In the treatment of uncomplicated lower urinary tract infections, the recommended dosage for phosphomycin is 3g orally, once daily, for 1-3 days. Since phosphomycin is not metabolized in the body when taken orally and is excreted in its unchanged form through urine, it leads to a high urinary drug concentration. Guidelines for the treatment of uncomplicated lower urinary tract infections recommend using phosphomycin for 1-3 days. However, the analysis of patient records revealed an average treatment duration of approximately 3 days, with some cases showing an extension beyond this period. In outpatient prescriptions, instances where the treatment course exceeded 3 days accounted for 17.22% of phosphomycin prescriptions. Dosage administration timing considerations: It is important to note the timing of phosphomycin administration. Phosphomycin should be taken before meals or after gastric emptying. The reason is that food intake can affect the absorption of active phosphomycin compounds, leading to a reduction in both blood and urinary concentrations. Co-administration with food decreases concentrations by approximately 33% compared to fasting. Additionally, it is advisable to take phosphomycin before bedtime after urination to extend the time the drug remains effective in the urine. To ensure the effectiveness of phosphomycin, patients should receive relevant instructions regarding medication timing. However, according to the investigation, only 16.13% of all prescriptions provided patients with such guidance. Therefore, there is a need to strengthen patient education on medication use to promote the rational use of phosphomycin.

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4. Discussion

4.1 Characteristics of phosphomycin and recommendations in the treatment of urinary tract infections according to guidelines

Colistin acts by irreversibly binding to bacterial lipopolysaccharide, inhibiting the synthesis of uridine diphosphate-N-acetylglucosamine enolpyruvyl transferase, and consequently early inhibition of bacterial cell wall synthesis. It is rapidly absorbed, exhibits strong permeability, and has a broad distribution in various tissues including the kidneys, bladder wall, prostate, lungs, cerebrospinal fluid, and heart valve, reaching effective antibacterial concentrations. Phosphomycin achieves high concentrations in the urine, being 5-20 times higher than blood concentrations[5, 6]. Upon oral administration, phosphomycin is absorbed by the gastrointestinal tract (30-40%), with a half-life of 5.7 hours. It does not undergo degradation in the body and is excreted primarily unchanged in urine (30-40%), with an additional 18% excreted in feces. Taking phosphomycin with meals can slow down renal clearance, and the peak plasma concentration (Cmax) after a 3-gram oral dose on an empty stomach is approximately 26.1 (±9.1) μg/ml within 2 hours. Co-administration with high-fat food results in Cmax averaging 17.6 (±4.4) μg/ml within 4 hours, representing a reduction of about 33% compared to fasting conditions. These pharmacokinetic characteristics contribute to phosphomycin's effectiveness in treating urinary tract infections, particularly those caused by susceptible bacteria. Guidelines recommend phosphomycin for uncomplicated lower urinary tract infections such as cystitis and urethritis. However, the observed trends in prescription patterns suggest areas of concern related to appropriateness, indicating a need for closer adherence to recommended indications and dosages.

Urinary tract infections are predominantly caused by Gram-negative bacteria, with only a small percentage attributed to Staphylococcus aureus, Enterococcus, and fungi. Both domestic and international guidelines recommend fosfomycin and phosphomycin as first-line antibiotics for lower urinary tract infections. For instance, the "Guidelines for the Diagnosis and Treatment of Urinary Tract Infections and Male Reproductive Tract Infections" by the European Association of Urology recommends single-dose oral fosfomycin and includes phosphomycin, fosfomycin, and SMZ/TMP as recommended treatments for uncomplicated cystitis in women. In the context of recurrent urinary tract infections, fosfomycin is considered a key first-line drug for acute cystitis, and phosphomycin is deemed effective[7]. In the "2022 AUGS Best Practice Statement: Management of Recurrent Uncomplicated Female Urinary Tract Infections" , it is emphasized that for the treatment of urinary tract infections, first-line antibiotics recommended for adult women include nitrofurantoin, SMZ/TMP (Sulfamethoxazole/Trimethoprim), and fosfomycin. In the case of acute cystitis in individuals with recurrent urinary tract infections, nitrofurantoin is identified as a key first-line drug, and fosfomycin is effective[8]. The 2016 guidelines from the Spanish Society of Clinical Microbiology and Infectious Diseases state that due to minimal resistance and a low propensity for collateral damage, fosfomycin (single dose of 3 grams) and fosfomycin (5-7 days) are preferred for treating uncomplicated cystitis. Fluoroquinolones are effective but have a high propensity for collateral damage. Beta-lactam antibiotics, including amoxicillin-clavulanate, cefuroxime, cefprozil, and cefaclor, are suitable alternatives when other recommended drugs cannot be used[9]. In the UK's 2020 SIGN National Guidelines, empirical treatment for uncomplicated cystitis is directed at Escherichia coli. In a meta-analysis comparing the efficacy of phosphomycin with other antibiotics for treating cystitis, phosphomycin demonstrated similar efficacy and fewer adverse events than fluoroquinolones, TMP/SMX, beta-lactams, and fosfomycin. In the 2023 edition of the "National Antimicrobial Treatment Guidelines" in China, phosphomycin is recommended as the first-line treatment for acute uncomplicated lower urinary tract infections (cystitis, urethritis), recurrent urinary tract infections in women, and urinary tract infections during pregnancy.

In summary, for acute uncomplicated lower urinary tract infections such as cystitis and urethritis, phosphomycin is a well-established first-line treatment. It also serves as a first-line option for women with recurrent urinary tract infections and pregnant individuals, according to both international and Chinese guidelines. The effectiveness of phosphomycin, along with its favorable resistance profile, makes it a valuable option in the management of urinary tract infections.

4.2 Significance of fosfomycin in the treatment of multidrug-resistant bacteria

In recent years, the global situation of bacterial resistance has become critical, particularly concerning multidrug-resistant Gram-negative bacteria. There is currently a shortage of new antimicrobial drugs for short-term therapeutic use. Phosphomycin, due to its unique mechanism of

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action, pharmacokinetic characteristics, and low occurrence of cross-resistance, has gradually become one of the focal points of antimicrobial drug research. The continuous growth of drug-resistant bacteria poses a serious threat to human life and health, and the options available for antimicrobial drugs are extremely limited. Phosphomycin, owing to its distinctive physicochemical properties and mechanism of action, exhibits broad-spectrum antibacterial activity. Abundant in vitro data show that it still maintains high sensitivity against clinically prevalent drug-resistant bacteria. An increasing number of clinical studies have reported on the safety and effectiveness of phosphomycin in combination therapy for drug-resistant infections and severe cases, especially in critically ill patients with impaired organ function. Phosphomycin remains one of their limited choices for a safe and effective drug[10]. Although the current optimistic clinical research results demonstrate the potential clinical application of phosphomycin, well-designed clinical studies are still lacking. Despite its long history of use, phosphomycin still warrants further research, and more clinical studies are anticipated to provide a definitive evaluation of its clinical efficacy.

China bacterial resistance monitoring study gram-positive bacteria report (2021-2022): insights on phosphomycin sensitivity: The Gram-positive bacteria report from the china bacterial resistance monitoring study for 2021-2022 provides valuable information on the sensitivity of various strains to phosphomycin. The sensitivity rate to phosphomycin is reported to be greater than 85%. This highlights the robust efficacy of phosphomycin against Staphylococcus aureus, including methicillin-resistant strains. The resistance rates for faecal streptococci and faecal-like streptococci are recorded at 4.5% and 22.4%, respectively. This suggests notable effectiveness of phosphomycin against these strains. Phosphomycin exhibits a sensitivity rate of over 90% against MDR E. coli. This high in vitro sensitivity indicates that phosphomycin maintains considerable activity against enzymes like extended-spectrum beta-lactamases (ESBLs) and metallo-beta-lactamases, showcasing its efficacy. Research indicates that oral phosphomycin and intravenous ertapenem demonstrate comparable clinical efficacy in UTIs caused by ESBL-producing Enterobacteriaceae. This suggests that phosphomycin is a viable oral option for treating infections caused by these bacteria. Both domestic and international guidelines and expert consensus recommend phosphomycin as a selectable combination drug for urinary tract infections caused by CRE. This underscores the potential role of phosphomycin in addressing infections caused by these highly resistant strains. Phosphomycin demonstrates high sensitivity to Pseudomonas aeruginosa, and its precise penetration of biofilms is noted. This emphasizes the significant therapeutic implications of phosphomycin in the treatment of infections caused by P. aeruginosa. These findings underscore the broad-spectrum effectiveness of phosphomycin against a variety of resistant strains, making it a valuable option in combating bacterial infections, especially in urinary tract infections.

5. Conclusion

Phosphomycin, with its unique mechanism of action, demonstrates synergistic effects when used in combination with other antibiotics. It boasts minimal side effects, good tolerance, and, notably, strong antimicrobial activity against uropathogens, with high urinary drug concentrations and prolonged duration of action. Multiple clinical guidelines recommend its use for urinary tract infections, albeit restricted to uncomplicated lower urinary tract infections. However, its clinical efficacy is suboptimal in complex urinary tract infections and acute uncomplicated upper urinary tract infections due to the influence of pharmacokinetics. Therefore, careful consideration of indications and standardized dosing is crucial in clinical practice to prevent misuse of phosphomycin.

The genus of multidrug-resistant bacteria, especially those of Enterobacteriaceae, poses significant threats. Additionally, the long development cycles of novel antibacterial drugs often fail to meet the urgent demands. Hence, rational utilization of existing antibacterial drugs and exploration of new combination strategies are crucial. Clinical monitoring has consistently shown that many multidrug-resistant Enterobacteriaceae bacteria maintain high sensitivity to phosphomycin. Both in vitro and in vivo studies have demonstrated that phosphomycin in combination with most antibacterial drugs exhibits good synergistic effects and possesses excellent capabilities in combating multidrug-resistant Enterobacteriaceae bacteria. This suggests that phosphomycin has a broader application scope in clinical settings. Current clinical research, however, is limited by factors such as narrow inclusion criteria, small sample sizes, and non-specific clinical observations. Therefore, there is a need for multicenter, large-sample, prospective, and randomized controlled clinical studies to precisely evaluate the therapeutic effects of phosphomycin in combination with other antibacterial drugs against infections caused by multidrug-resistant Enterobacteriaceae.

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Phosphomycin maintains potent antibacterial activity against both Gram-positive and Gram-negative bacteria, including some drug-resistant strains. In the current challenging scenario of urinary tract infections caused by ESBL-producing Escherichia coli, appropriate use of phosphomycin in selected cases can reduce exposure to carbapenems and β-lactam/β-lactamase inhibitor antibiotics, thereby mitigating the development of resistance. Thus, the rational use of phosphomycin should be emphasized to delay the further development of multidrug-resistant bacteria, ensuring its valuable clinical application.

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