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FOSFOMYCIN: AN ASSESSMENT OF ITS POTENTIAL FOR USE IN THE TREATMENT OF MDR- ESCHERICHIA COLI IN URINARY TRACT INFECTIONS

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ABSTRACT

Antimicrobial resistance is increasing worldwide making it difficult to choose an appropriate therapy for the infections caused by the resistant pathogens. Fosfomycin, an antibiotic that was discovered about decades ago, has drawn renewed interest as an active agent against multi-drug resistant (MDR) organisms especially in the treatment of Urinary Tract Infections (UTIs) because of its unique mechanism of action and broad spectrum of activity. Available as oral and intravenous formulation, it has minimal interactions with other medications and a favourable safety profile and can be equally administered in pregnant women, elderly and those with renal and hepatic impairment. Commonly used as a single dose therapy or in combination with other antibacterial agents, fosfomycin has high treatment efficacy in UTIs caused by MDR Escherichia coli (E.Coli). Extended courses of fosfomycin can be considered in patients with poor/ no response to treatment and both the treatment regimens have been shown to be generally well tolerated. Dosage adjustment is recommended in patients with creatinine clearance less than 50ml/min/1.73m^2. The unique mechanism of action of fosfomycin limits the appearance of cross resistance and allows it to remain effective against the MDR pathogens. In addition to its excellent bactericidal activity, fosfomycin also has the potential to reduce toxicity associated with other antibacterial agents. In this review, we have discussed the potential for using fosfomycin to treat MDR E.Coli infections in UTI.

KEYWORDS: Fosfomycin, Urinary Tract Infections, Multi drug Resistant Organisms, E.Coli infections.

INTRODUCTION

One of the greatest advances in the history of medical science was the discovery of antibiotics in the 1920s which substantially reduced the morbidity and mortality of bacterial infections.[1] Antibiotic-resistant bacterial strains have emerged and proliferated as a result of the intensive, widespread, and inappropriate use of antibiotics over the past 50 years.[2] This has caused an increase in the wide spread of Multidrug resistant (MDR) organisms globally, which is particularly concerning.[3] The World Health Organization has identified antibacterial drug resistance as a significant threat to global public health. The decrease in the number of effective antibiotics together with scarcity of new antimicrobial drugs makes it hard for treating infections caused by gram negative MDR bacteria.[4]

Multi drug resistance occurs when a single bacterium is resistant to more than one antibiotic. This can occur in two distinct ways.[5] A bacterium may possess a variety of resistance genes, each of which confers resistance to a specific antibiotic. Resistance genes are frequently accumulated on tiny DNA fragments known as plasmids, which can be instantly passed from one bacterium to another. The alternative hypothesis is that many antibiotics can develop resistance to a single resistance mechanism. For example, one resistance strategy employed by bacteria is pumping the antibiotic out of the cell. These pumps can occasionally recognise a wide variety of compounds, including several antibiotic types. This is also called as cross-resistance.[5] The global emergence of MDR gram negative bacteria related to Urinary Tract Infections (UTIs) has raised concern among the healthcare practitioners which calls for re-evaluation of the neglected antibiotics or discovery of novel antibiotics.

Urinary Tract Infections (UTIs) characterized by dysuria, urinary frequency and urgency, supra pubic pain, hematuria, and/or subjective fever [6] with an estimated global incidence rate of roughly 18 episodes per 1000 person every year are one of the most prevalent health issues impacting people worldwide.[7] Studies reveal that nearly 40–50% of women experience UTIs at some point in their lives, and one third of women before the age of 24 requires antibiotic treatment for UTIs.[8] Due to variations in the structure and microflora of the male and female genitourinary systems, females have higher infection rates.[9] Antimicrobial resistance has led to the ineffectiveness of several antibiotics originally used to treat UTI.[10]

The primary pathogen involved in UTI is Escherichia coli. However other organisms belonging to the Enterobacteriaceae family are also frequently responsible for infection.[11] Many classes of antibacterial agents which were previously active against Enterobacteriaceae, including cephalosporins, carbapenems, fluoroquinolones, aminoglycosides, sulphonamides are now resistant because of the substantial spread of MDR isolates.[12] These findings indicate that there is a medical need to discover alternatives for the treatment of MDR E.coli infections in UTI.[13] Fosfomycin, an old and forgotten antibiotic, has lately attracted the interest of clinicians across the world for the treatment of UTIs. This antibiotic could be an helpful option for the treatment of patients with these challenging infections, especially in populations at risk for infections with MDRO.[14]

FOSFOMYCIN

Fosfomycin, an antibiotic discovered more than 40 years ago has proven as an active agent against a range of MDR pathogens because of its unique mechanism of action and broad spectrum of activity. Originally described in 1969 from cultures of Streptomyces species,[15] it is a bactericidal antibiotic that works by irreversibly inhibiting an early stage in the bacterial cell wall synthesis and decreases bacterial adherence to epithelial cells in the urinary tract.[16] Studies suggest that, fosfomycin when combined with other antimicrobial drugs that act via a different mechanism of action shows synergistic effect that allows for reduced dosages and less harmful effects.[1]

Chemistry

Fosfomycin is freely soluble in water and has a low molecular weight (138g/mol).[17] The chemical structure of fosfomycin is cis-1,2-epoxypropyl phosphonic acid ($C_3H_7O_4P$) where the epoxide moiety is the main structural factor conferring fosfomycin's antibacterial activity.[17] The structure of fosfomycin is depicted in Figure 1.

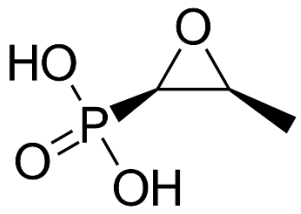

Figure 1: Chemical structure of fosfomycin.

Available formulations

Currently, fosfomycin is available in three formulations, two of which are in the oral forms- fosfomycin trometamol also known as fosfomycin tromethamine and fosfomycin calcium.[14] Fosfomycin tromethamine with chemical formula $C_3H_7O_4P.C_4H_{11}NO_3$ are available in the form of granules in packages of 2 or 3 gram.[14] It is the preferred formulation for oral administration of fosfomycin as it is more readily absorbed into the blood.[18] Fosfomycin calcium with chemical formula $C_3H_5CaO_4P$ is available as 500mg hard gelatin capsules [14] and is largely inactivated by hydrolysis in the acidic gastric environment.[12] Fosfomycin disodium is an intravenous formulation (chemical formula – $C_3H_5Na_2O_4P$) which consists of 1 to 8 grams of fosfomycin disodium with succinic acid as the only excipient.[14] The structures of the three available formulations of fosfomycin are depicted in figure 2.

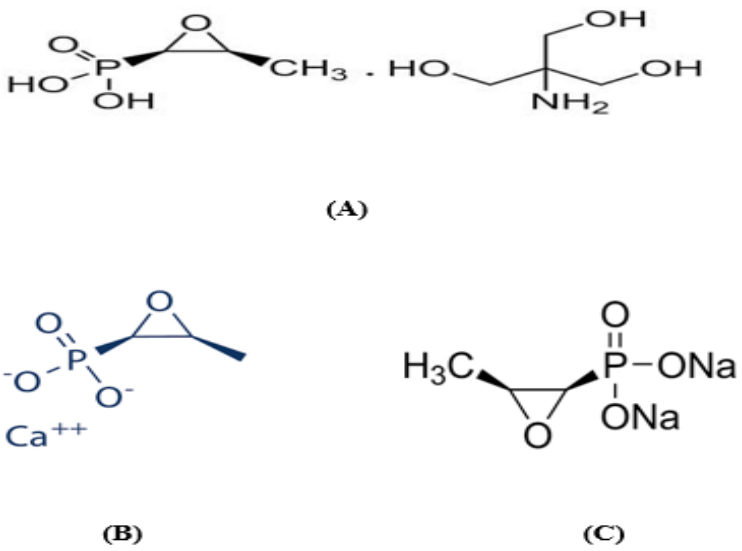

Figure 2: Chemical structures of (A) Fosfomycin tromethamine, (B) Fosfomycin calcium and (C) Fosfomycin disodium.

Pharmacokinetics

Absorption of orally administered fosfomycin takes place partially in the small intestine mainly via two mechanisms: through a saturable carrier-mediated system associated with a phosphate transport system, and through a non-saturable process with first-order kinetics.[1] The absorption of calcium formulation is lower as compared to tromethamine formulation as the former is hydrolysed with the gastric acid. This shows that intragastric acidity and gastric emptying rate can influence the hydrolytic degradation of fosfomycin calcium.[1] Data suggests that consuming fosfomycin with food may result in reduced drug absorption.

Metoclopramide enhances gastrointestinal motility, that results in reduced serum concentrations and absorption. However, age does not seem to affect absorption.[14]

The oral bioavailability of fosfomycin tromethamine is around 40% and for fosfomycin calcium is 12%.[19] The bioavailability of both the oral forms of fosfomycin is decreased when taken along with food. However under fasting conditions, the tromethamine salt has 2-4 folds higher serum concentrations than calcium salt. Only a negligible amount of fosfomycin binds to plasma proteins. The apparent volume of distribution of fosfomycin tromethamine is 100-170L for a 70kg individual whereas it is 9-30L at steady state for fosfomycin disodium.[1]

Fosfomycin is mainly excreted in non-metabolized form in the urine.[17] Peak plasma concentrations are achieved within 3 hours following a single dose of oral fosfomycin.[20] Greater antibacterial activity of fosfomycin is observed in weakly acidic conditions (pH- 6.0). This characteristic, along with the fact that it tends to be excreted as an active molecule in urine, accounts for its most popular choice in the prevention and treatment of urinary tract infections.[17] 95% of fosfomycin is eliminated through the kidneys. The elimination half-life of fosfomycin, ranges between 4-8 hours.[21] The half-life of fosfomycin is greatly increased (up to 50 h) in patients with chronic renal failure, and this is correlated with a decreased fosfomycin recovery in urine.[19] Therefore, 11 to 60% of the drug can be detected in the urine within 24 hours post administration, depending on the patient's age, fasting status, and renal function.[22]

Pharmacodynamics

Fosfomycin acts in a time dependent manner with time above MIC (T > MIC).[23] Peak levels of fosfomycin tromethamine in the urine are attained 4 hours after a single 3-g dose.[14]

Mechanism of action

Fosfomycin is a bactericidal antibiotic that has unique mechanism of action. It interferes with cell wall synthesis in both gram negative and gram positive bacteria by inhibiting the initial step involving phosphoenol pyruvate (PEP) synthetase. Fosfomycin must reach the bacterial cytoplasm in order to show its activity. It enters the cells of fosfomycin susceptible bacteria by means of two different transport uptake system: a functional glycerol-3-phosphate transport system (GlpT) and the hexose phosphate uptake transport system (UhpT)[19] as depicted in figure 3. Once in the cytoplasm, fosfomycin acts as an analog of phosphoenol

pyruvate that inhibits UDP-N-acetylglucosamine enolpyruvyl transferase (MurA) by alkylating an active site cysteine residue (Cys 115 in the E.Coli MurA enzyme), thereby inactivating the enzyme in peptidoglycan synthesis leading to bacterial cell lysis and death.[17]

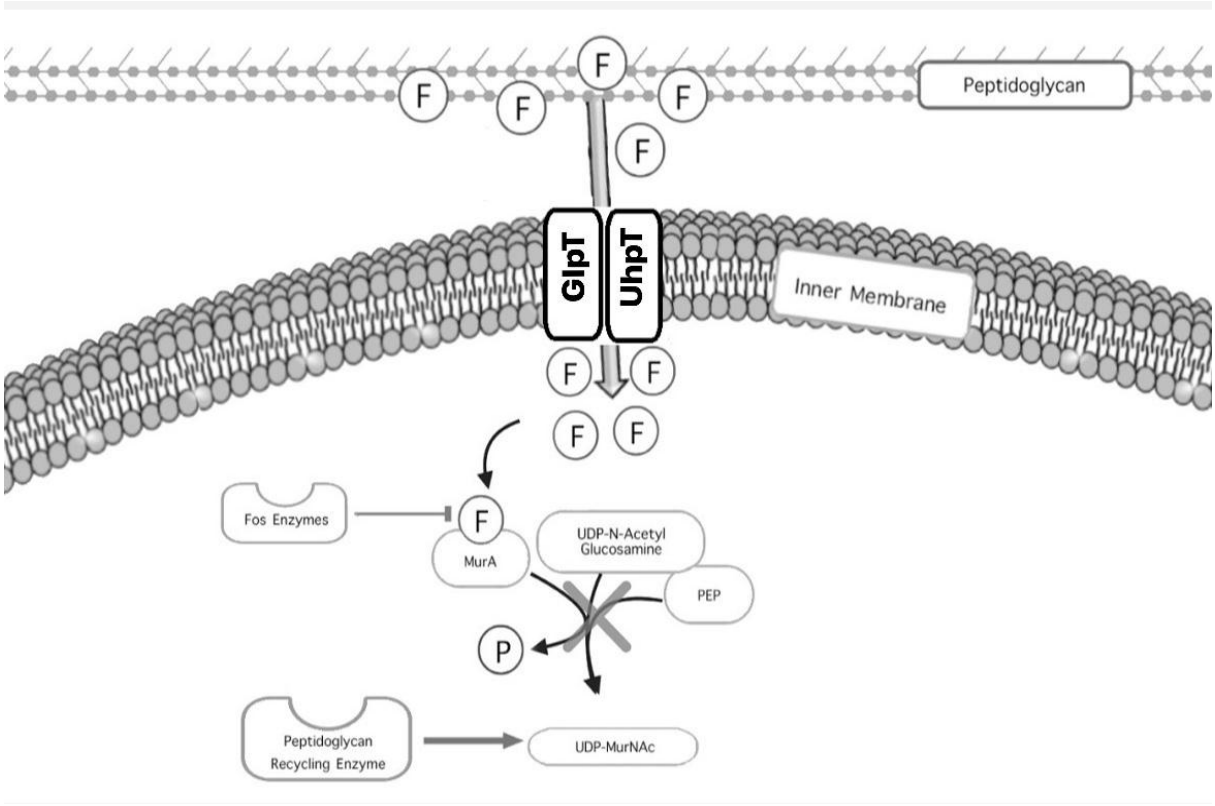

Figure 3: Mechanism of action of Fosfomycin.

In addition, fosfomycin also decreases penicillin binding proteins. It also reduces bacterial adherence to uroepithelial cells.[17]

Antibacterial activity

Since, fosfomycin has a unique mechanism of action, it displays broad spectrum activity against a wide range of both gram positive and gram negative bacteria including the urinary pathogens E.coli, Proteus mirabilis, Enterobacter species, Citrobacter species, Klebisella pneumoniae and Salmonella typhii.[18,24] Based on various in vitro data available from different countries, the susceptibility of fosfomycin ranges between 98-100% [25,26] which are generally higher than those seen with co-trimoxazole, ciprofloxacin or nitrofurantoin.[27]

Resistance

Even though resistance to fosfomycin can develop during the course of treatment, it is rarely seen in E.coli (less than 1%) than in Klebisella species or Pseudomonas especially in UTI.[28,29] Resistance to the fosfomycin susceptible bacteria occurs through different

mechanisms primarily via mutations in the uptake systems that is in the chromosomal genes encoding the GlpT and UhpT pathways.[17] Other less commonly mechanisms include modification, inactivation or over expression of the MurA enzyme, fosfomycin kinases (fomA and fomB) or via fosfomycin modifying enzymes such as fosA, fosB and fosX.[28] However, fosfomycin's unique mechanism of action appears to prevent cross-resistance and allows it to remain effective against MDR pathogens.

Dosing of fosfomycin in UTI

The ability of fosfomycin to decrease adhesion of E.Coli onto the bladder wall and high concentrations achieved in urine, appeals it for the treatment of UTI.[14] Multiple-dose regimens with fosfomycin tromethamine have been shown to be an effective treatment option for complicated, uncomplicated and/or recurrent UTI as well as MDR bacterial infections.[30] However, currently it is recommended as a single dose as it is readily absorbed and maintains a therapeutic concentration in the urine for one to three days.[19] Studies suggest that a regimen of single 3 gram doses administered at two days interval provides safe and well tolerated option for treating uncomplicated UTIs in women and complicated lower UTIs, especially UTIs caused by E.Coli infections.[1] Comparative clinical trials suggest that a single 3-g dose of fosfomycin tromethamine is just as therapeutically efficacious as 7 to 10 day treatment regimens of common UTI medications including nitrofurantoin, norfloxacin, and trimethoprim/sulfamethoxazole.[19] In paediatric patients, evidence suggest a regimen of 1 to 2 grams of fosfomycin as compared to the usual 3 gram adult dose.[14] Fosfomycin tromethamine is classified as pregnancy category B by FDA (i.e, animal reproduction studies have failed to demonstrate a risk to the foetus, and there are no adequate and well controlled studies in pregnant women). Although it can cross the placental barrier, it is quite safe during pregnancy and is well tolerated.[31] It has been recommended as a first line bactericidal agent for UTI in pregnant women in certain countries.

Depending upon the severity of disease, different dosing regimens for intravenous fosfomycin are recommended. However, administration could be a limitation in patients with heart failure or those receiving haemodialysis as intravenous formulation is associated with high sodium intake.[32] In patients with normal renal function, the intravenous dosage ranges from 12 to 16 gram daily dose administered in 2-4 infusions.[19] For both of the oral formulations of fosfomycin, no dosage adjustment is necessary in patients with hepatic or renal failure or for elderly patients with creatinine clearance (CrCl) >50ml/min/1.73m2.[14]

However, doses should be reduced if CrCl is less than 50ml/min as renal impairment significantly reduces excretion of fosfomycin. If CrCl is 40-20 ml/min , then recommended dose of intravenous fosfomycin is 4g every 12 hour, and 4g every 24 hour if CrCl is in between 20-10ml/min. If CrCl is <10ml/min, then the dose should be limited to 4g every 48 hours.[33] On the basis of these observations, a dose individualization based on CrCl is necessary to avoid under dosing or over dosing in order to reduce the chance of therapeutic failure or toxicity.

Adverse Drug Reactions

Oral Fosfomycin is generally well tolerated and free of serious adverse effects. Only 5% of patients have reported side effects, the most commonly being gastrointestinal symptoms such as diarrhoea, nausea, abdominal pain and dyspepsia.[19,34] All these symptoms are transient, mild and self-limiting. Other commonly observed side effects include back pain, weakness, vaginitis, rhinitis, pharyngitis, hyper-eosinophilia, neutropenia and local phlebitis.[19] Hypernatremia and hypokalemia were the most commonly reported adverse effects with intravenous fosfomycin. Thus potassium supplements should be co-administered and their levels should be regularly monitored in patients receiving fosfomycin.[14] 1g of intravenous fosfomycin brings about 14.4mEq of sodium, which can cause heart insufficiency in certain patients. Therefore, intravenous fosfomycin is not recommended in patients above 80 years old and those with chronic heart or kidney insufficiency.[35] Co-administration with metoclopramide and probenecid should be avoided as it can decrease urinary concentrations of fosfomycin.[36]

Why Fosfomycin over other drugs in UTI caused by MDR E.Coli?

Fosfomycin is a good option in the treatment of UTIs caused by MDR E.Coli because of its broad spectrum of activity, low risk for allergic reactions, single dose administration, fine safety profile and its use in unique patient populations (ie, pregnancy, elderly, hepatic and renal impairment). Because of the in vitro activity of fosfomycin against the majority of E.Coli isolates, it could prevent admission for treatment of MDR UTIs or decrease length of hospital stay by substitution of oral for intravenous therapy.[11] According to datas, the overall success rates in patients treated with fosfomycin (64%) for UTIs were higher than for piperacillin - tazobactum (42%).[37] In addition to the increased antibacterial efficacy, fosfomycin also reduces the potential toxicity associated with other drugs such as nephrotoxicity and ototoxicity with aminoglycosides, neurotoxicity and nephrotoxicity with

colistin and increased mortality associated with tigecycline. In another study, clinical resolution of infections treated with fosfomycin occurred in nearly 80% of the treated patients.[17] Nitrofurantoin which is commonly prescribed for UTIs caused by MDR E.Coli, is not recommended in the third trimester of pregnancy whereas fosfomycin appears to be safe in pregnant women.[38] Also, fosofmycin has minimal interactions with other medications, with relatively good safety profile and has lesser reported adverse effects. Studies with clinical outcomes after administration of fosfomycin v/s a comparator drug for UTIs caused by MDR E.Coli are represented in Table 1. Clinical cure is defined as resolution of UTI symptoms whereas microbiological cure is defined as the complete eradication of the urinary pathogen as documented by urine culture after the completion of treatment.[39,40]

Table 1: Clinical outcomes after administration of fosfomycin v/s a comparator drug in the treatment of UTI.

FIRST AUTHOR [REFERENCE]	FOSFOMYCIN TREATMENT (F)	COMPARATIVE DRUG (C)	CLINICAL CURE		MICROBIOLOGICAL CURE	
			F	C	F	C
Sojo-Dorado J et al.[13]	4g IV every 6 hours	Ceftriaxone 1g IV every 24 hours	96.7%	90.1%	82.8%	85.5%
Kaye KS et al.[35]	6g IV every 8 hours for 7-14 days	Piperacillin – Tazobactum 4.5g IV every 8 hours for 7-14 days	92%	90%	54%	36%
Ceran N et al.[41]	3g single dose P/O	Ciprofloxacin 500mg P/O every 12 hours for 5 days	83%	81%	83%	78%
Palou J et al.[42]	3g , 2 doses P/O	Ciprofloxacin 250mg P/O every 12 hours for 3 days	86.5%	82.1%	62.2%	59%
Krcmery S et al.[43]	3g single dose P/O	Ceftibuten OD P/O 400mg for 3days	95.2%	90%	NA	NA

CONCLUSION

Antibacterial drug resistance is one of the most serious threats to global public health, particularly given the shortage of effective antibiotics. The increasing rates of resistance in the urinary pathogens to the antibiotics which were used to treat UTIs has proposed interest in identifying newer and better treatment options or re-evaluating existing agents for the treatment of MDR organisms. One such agent is fosfomycin which is a safe and effective antibiotic for UTIs caused by MDR E.Coli. Because of its broad spectrum of activity, it offers a viable treatment option for UTIs, given its currently overall low reported resistance rates in the clinical settings (0% to 6.7%) [6] Fosfomycin administered as a single dose oral therapy or in combination with other antibacterial drugs can be safely prescribed in pregnancy, elderly and those with hepatic and renal impairment. Oral fosfomycin is well tolerated with minimal

adverse effects whereas mild hypokalaemia is commonly observed with the intravenous formulation. In fact, a single dose therapy with oral fosfomycin has similar efficacy to a three or seven day course with fluoroquinolones, cephalosporins and amoxicillin- clavulanate in the treatment of UTIs across all patient groups. Overall, fosfomycin is projected to stay and be further harnessed as an important component of the treatment strategy against MDR organisms over the coming years.

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