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Original research article

A study on the role of Faropenem in the management of UTIs and complicated UTI as a step-down therapy: A urologist's perspective

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Abstract

Background: Urinary tract infections (UTIs) are infectious disorders that afflict both men and women. Drug-resistant bacteria are becoming more common in UTI patients. India has the world's highest rate of extended-spectrum -lactamase (ESBL)-producing microbes. Oral administration is required since it is the preferred dose form and route for patients released from the hospital. Clinicians in India frequently prescribe an alternate to intravenous carbapenems. Faropenem is an antibiotic that is taken orally and belongs to the "penems" class of - lactam antibiotics. Faropenem is increasingly popular among Indian urologists because to its broad range antibacterial action and lesser risk of resistance; nonetheless, real-world evidence is limited. Faropenem possesses wide antibacterial action against aerobic gram-positive, gram-negative, and anaerobic bacteria, as well as resistance to TEM, SHV, and CTX-M-type ESBLs. Faropenem is licenced in India for the treatment of infections of the respiratory tract, urinary tract, skin, soft tissue, and gynaecology. It is frequently used to treat invasive ESBL-producing Enterobacteriaceae infections, despite the fact that its effectiveness in these circumstances has not been shown clinically. Faropenem has little practical clinical experiences at the urologists level.

Aim and Objective: To collect practical data from Indian urologists on the usage of faropenem in the treatment of UTIs.

Materials and Methods: After asking a series of eight questions with multiple-choice and open-ended answers, Indian urologists responded on the use of Faropenem in the therapy of complex urinary tract infection

Results: The responses of 220 Urologists were analysed. The incidence of complicated urinary tract infections was 12%(10-15%) in the majority of urology clinics, whereas some reported it to be approximately 18% (15-25%). Faropenem 300 mg demonstrated better compliance among the patients. The majority of urologists (70%) thought Faropenem was a successful pharmacotherapy for the treatment of UTIs, including complex urinary tract infection as a step-down therapy (70%). The majority of participants (76%) considered Faropenem to be beneficial in their practise (out of 220 replies), and 8% had used Faropenem as an option in complex urinary tract infection. The majority of people (70%) thought it was safe to use in complicated urinary tract infections.

Conclusion: Faropenem is used to treat urinary tract infections because of its efficacy, capacity to produce reduced resistance, and safety profile. From a public health standpoint, prudent use of faropenem in the community is critical to preserving its broad spectrum of action for patients who truly require it.

Keywords: Resistance, Urinary tract infection, Extended-spectrum β – lactamase, Penems

Introduction

India has the world's highest rate of extended spectrum-lactamase (ESBL) generating microbes. Oral administration is required since it is the preferred dose form and route for patients released from the hospital. Clinicians in India frequently prescribe an alternate to intravenous carbapenems. Faropenem is an antibiotic that is taken orally and belongs to the "penems" class of-lactam antibiotics.

Penems are structurally similar to carbapenems and are a hybrid of penem (penicillin) and cepham (cephalosporin) nuclei. Faropenem possesses wide antibacterial action against aerobic gram-positive, gram-negative, and anaerobic bacteria, as well as resistance to TEM, SHV, and CTX-M-type ESBLs.

Faropenem is licenced in India for the treatment of infections of the respiratory tract, urinary tract, skin, soft tissue, and gynaecology. 2020 (Central Drugs Standard Control Organisation). It is frequently used to treat invasive ESBL-producing Enterobacteriaceae infections, despite the fact that its effectiveness in these circumstances has not been shown clinically. UTIs are among the most common infectious infections in the population, posing a significant clinical and econmical burden.

Bacteria cause over 95% of all UTIs, with E. coli accounting for the majority (30%-90%, depending on the clinical situation). UTIs can also be caused by Klebsiella, Enterobacter, Proteus, Pseudomonas, Enterococcus, Staphylococcus, and other bacteria.

To treat infectious infections, a variety of antimicrobial medicines with distinct modes of action can be

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utilised. These agents primarily consist of protein or cell wall synthesis inhibitors, such as aminoglycosides (e.g., streptomycin), -lactams (e.g., penicillins, cephalosporins), macrolides (e.g., azithromycin), and tetracyclines (e.g., doxycycline), but also include folic acid synthesis inhibitors (e.g., sulphonamides,). Carbapenems and penems are two broad-spectrum-lactam antibiotic groups. Their antibacterial effect is obtained from binding to and inhibiting PBPs, which eventually affects the formation of peptidoglycan, a component of the bacterial cell wall. Carbapenems were initially found as natural products generated by some bacterial species, with a carbon atom at position C-1 in the -lactam ring; penems, on the other hand, do not exist naturally and are chemically synthesised, with a sulphur atom at position C-1 in the-lactam ring.

There are hundreds of -lactam antibiotics, but carbapenems offer the broadest breadth of activity and the greatest effectiveness against Gram-positive and Gram-negative bacteria. As a result, when other antibiotics fail, carbapenems are utilised as a last-line antibiotic for treating severe and/or resistant bacterial infections 9, which are frequently associated with substantial morbidity and death. However, bacterial resistance to carbapenems is rising globally. Carbapenem resistance can develop through a variety of mechanisms, the most common of which is breakdown by -lactamases, including carbapenem-specific Class A and Class D carbapenemases (such as KPC enzymes and OXA-23, respectively).

Other resistance strategies include efflux pump removal and mutations that affect the production or function of porins and PBPs. Under antibiotic selection pressure, carbapenem resistance pathways may accumulate. Resistance patterns to carbapenems, and to antibiotics in general, reflect the effect of environmental and other variables. It is critical to protect carbapenems since their use to treat non-severe illnesses when other treatment options are available may jeopardise their utility as 'last resort' treatments. Faropenem, an oral penem, is approved for the treatment of urinary tract infections (UTIs), respiratory tract infections, skin and skin structure infections, and gynaecological diseases in Japan and India.

Faropenem is marketed in Japan as 150 and 200 mg tablets, with a 600 mg daily for 7 days regimen advised for treating uncomplicated UTIs (uUTIs).The Indian Government's 2019 standard treatment guidelines do not mention faropenem for treating UTI32, despite Medindia's recommendation of 200-300 mg of faropenem twice day for UTIs, and dosage formulations available in India include 150 and 200 mg. Faropenem has little real-world clinical experiences at the urologist level. To the best of our knowledge, this is the first study to look at urologists' clinical experience and satisfaction with faropenem for the treatment of UTIs. As a result, in this survey, we attempted to collect replies and feedback on the use of Faropenem from urologists.

Aim and Objective: To obtain practical data on the use of faropenem in the treatment of UTIs from Indian urologists.

Materials and Methods

Indian urologists answered to a set of eight questions with multiple-choice and open-ended answers about the use of Faropenem in the treatment of complicated urinary tract infections. We collected responses from 391 Indian urologists across India on the use of faropenem for the therapy of Complicated Urinary Tract Infection in the current study. Each participant was given a series of eight questions with both multiple choice and open answers, and their replies were recorded.

Statistical analysis: The data was analysed using IBM SPSS ver. 20 software. To determine the frequency of each answer, a frequency distribution was used. Data is shown as a number or as a percentage. There was no additional data analysis.

Results

The replies of 220 Urologists were evaluated. In most urology clinics, the incidence of complex urinary tract infections was 12% (10-15%), however others reported it as 18% (15-25%). Faropenem 300 mg was found to improve patient compliance. Faropenem was deemed an effective pharmacotherapy by the majority of urologists (70%) for the treatment of UTIs, including complicated urinary tract infection as a step-down therapy (70%). Out of 220 responses, the majority of participants (76%) thought Faropenem was advantageous in their practise, and 8% had used Faropenem as an alternative in difficult urinary tract infection. The vast majority of respondents (70%) believed it was safe to use in severe urinary tract infections.

A total of 220 individuals responded to the current survey. The incidence of Complicated Urinary Tract Infection was 5-10% [140 (64%)] in the majority of urology clinics. Other participants reported a prevalence of 10- 20% [35 (16.6%)] to 20-30% [42 (19.43%)].

A mixed response was shown as a first and second line treatment therapy for Complicated Urinary Tract Infection. Some of these were 3rd generation cephalosporin, aminoglycoside, aminoglycoside combination with cefalosoporin, beta lactam carbapenem like faropenem, cephalosporin, ceftriaxone, combination of ceftriaxone + amikacin, and fluoroquinolone and its combination with cephalosporins.

Participants were asked to discuss their clinical experience with faropenem in the treatment of UTIs. The

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majority of people [152 (69%)] agree that faropenem is highly effective for the treatment of UTIs. whereas [68 (30.9%)] discovered it to be really effective. Faropenem is believed to be beneficial for the treatment of UTIs by all participants. Faropenem was discovered to be an effective medicine for the management of Complicated Urinary Tract Infection and as step-down therapy [152(69%)].
Because of the lower risk of resistance, the majority of participants felt that faropenem 200 mg is an effective alternative for step-down therapy for Complicated Urinary Tract Infection. Due to its great effectiveness and fewer side effects, the majority of participants concluded that faropenem 300mg had excellent patient compliance and is an effective step-down choice for Complicated Urinary Tract Infection.

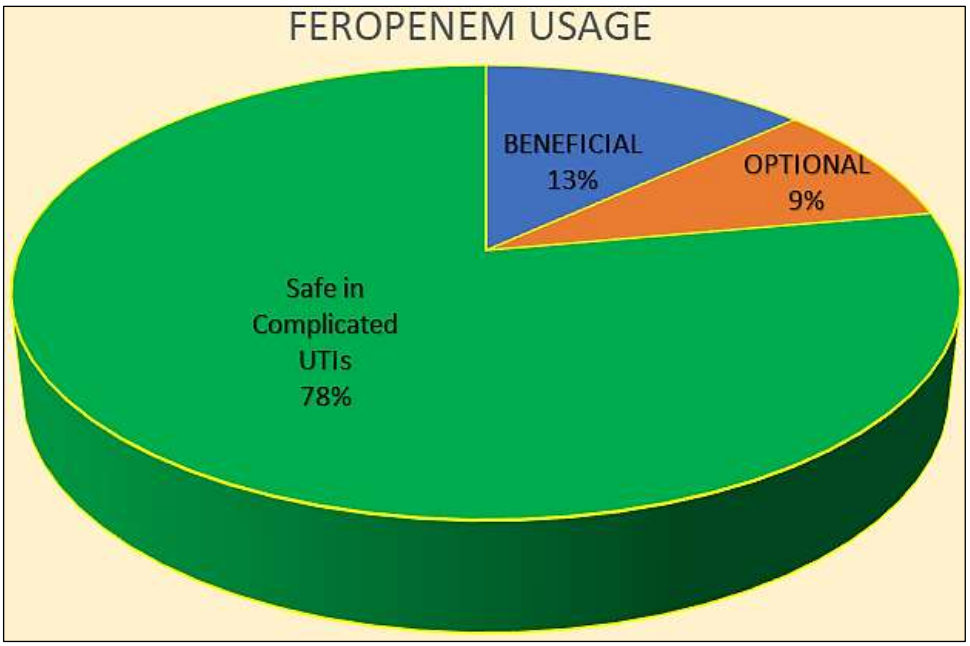

Fig 1: Pie diagram showing the Feropenem usage in UTI patients

Out of 391 replies, the majority considered faropenem to be successful [152 (69%)] and [13 (6%)] people utilised faropenem as an option in Complicated Urinary Tract Infection. There were [33 (15%) individuals who had seldom used, did not favour, or did not utilise it as a first-line therapy in the treatment of Complicated Urinary Tract Infection. However, faropenem was employed as a second-line antibiotic in the practise of [4 (2%)] individuals.

Questionnaire format

Introduction: Thank you for participating in this survey. Your insights and experiences are valuable in understanding the use of Faropenem in the treatment of complex urinary tract infections. Please answer the following questions to the best of your knowledge and experience.

Question number	Question details
Demographics	1.1. Name (Optional): _____ 1.2. Hospital/Clinic Affiliation: _____ 1.3. Years of Urology Practice: _____ 1.4. Location (City/State): _____
Clinical Experience	2.1 Have you prescribed Faropenem for the treatment of complex UTIs in your practice? ▪ Yes ▪ No
	2.2 If yes, please specify the most common types of complex UTIs for which you have prescribed Faropenem (select all that apply): ▪ Complicated pyelonephritis ▪ Catheter-associated UTIs ▪ Renal abscess ▪ Complicated urinary tract infections in elderly patients Others (please specify): _____
	2.3 According to your clinical expertise, what is the line of treatment of Complicated Urinary Tract Infection? a. First line b. Second line c. Third line

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	Any other
	2.4 What proportion of your patients present with Complicated Urinary Tract Infection? a. 5-10% b. 10-20% c. 20-30% d. >30%
Efficacy and Outcomes	3.1 In your experience, how effective has Faropenem been in treating complex UTIs? ▪ Very Effective ▪ Somewhat Effective ▪ Neutral ▪ Somewhat Ineffective ▪ Very Ineffective
	3.2 Have you observed any adverse effects or complications associated with the use of Faropenem in treating complex UTIs? If yes, please describe: Open-ended response: _____
	3.3 According to your clinical expertise, what are the indications where faropenem has an advantage over other antibiotics? a. Complicated Urinary Tract Infection b. Complicated Urinary Tract Infection for resistant infections c. Complicated Urinary Tract Infection for step down therapy d. Complicated Urinary Tract Infection for hospital acquired infections e. Pyelonephritis f. Prostatitis g. Post-operative care h. Abscess Any other
	3.4 As per your clinical experience management of UTIs with faropenem is? a. Extremely effective b. Very effective c. Moderately effective d. Slightly effective Not at all effective
	3.5 How do you perceive faropenem in your practice?
	3.6 How efficacious is Faropenem as compared to other available options?
	3.7 How is the safety profile of Faropenem?
	3.8 In your opinion what is the place of faropenem in UTIs management?
Treatment Regimen	4.1 What is your typical dosage and duration of Faropenem treatment for complex UTIs? Open-ended response: _____
	4.2 Do you combine Faropenem with other antibiotics or therapies when treating complex UTIs? ▪ Yes ▪ No
	4.3 If yes, please specify the antibiotics or therapies you commonly combine with Faropenem: Open-ended response: _____
Challenges and Considerations	5.1 What challenges, if any, do you face when prescribing Faropenem for complex UTIs? Open-ended response: _____ 5.2 Are there specific patient populations or clinical scenarios where you find Faropenem to be particularly effective or ineffective? Please provide details: Open-ended response: _____
Future Perspectives	6.1 In your opinion, how can the use of Faropenem in the therapy of complex UTIs be optimized or improved? Open-ended response: _____
Additional Comments	7.1 Do you have any additional comments or insights related to the use of Faropenem in treating complex UTIs that you would like to share? Open-ended response: _____
Consent and Contact Information (Optional)	8.1 Would you be interested in participating in follow-up interviews or discussions regarding your experiences with Faropenem in complex UTI therapy? ▪ Yes ▪ No 8.2 If yes, please provide your contact information (email or phone number): Contact Information: _____ Thank you for taking the time to complete this survey. Your input is invaluable in enhancing our understanding of Faropenem's role in treating complex urinary tract infections.

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In response to the question, "How efficacious is faropenem in comparison to other available options?", the majority of participants [187 (85%)] believed that faropenem is highly efficacious in the management of Complicated Urinary Tract Infection, while [13(6.14%)] participants believed that faropenem is equally efficacious as the other available options. However, [18 (8%)] of the participants lacked clinical expertise with faropenem.
In regard to safety concerns about faropenem use, the majority [154(70%)] of participants thought it was safe, 51 (23%) thought it had an outstanding safety profile, while just 40 (10.2%) thought it was unsafe and caused acidity or gastritis.

Discussion

Faropenem has strong antibacterial action against E. coli and *Klebsiella* spp. with ESBLs, which are the main causal organisms of Complicated Urinary Tract Infections. Its therapeutic value will be determined by the minimal effective concentration attained in the urinary system, which is the site of the majority of community infections caused by ESBL manufacturers.
Recurrent or complicated urinary tract infection is one of the most prevalent conditions seen in urology clinics. This might be because to an increase in the occurrence of Complicated Urinary Tract Infection. This was also noted in the current study, where the prevalence of Complicated Urinary Tract Infection was 5-10% in the majority of urology clinics, however some participants reported a frequency between 10-20% and 20-30%, which is concerning. In the current study, a mixed response was obtained for first and second line treatment therapy for Complicated Urinary Tract Infection. 3rd generation cephalosporin, aminoglycoside, combination of aminoglycoside with cefalosoporin, beta lactam carbapenem like faropenem, cephalosporin, ceftriaxone, combination of ceftriaxone with amikacin and fluoroquinolone and its combination with cephalosporins were the most commonly used pharmacotherapy. This demonstrates that no particle medicine is utilised to treat Complicated Urinary Tract Infection.
However, when participants were asked to discuss their clinical experience with faropenem care of UTIs. The majority of people (69%) say faropenem is very effective for the treatment of UTIs, while 33.6% believe it is highly effective. Faropenem was thought to be useful for the treatment of UTIs by all participants. Gandra *et al*. found that faropenem use has surged by 154% since its approval in 2010 (from 7.4 million standard units in 2010 to 18.9 million standard units in 2014). Gandra, S. (2016) it was also discovered that meropenem consumption grew between 2010 and 2014, although faropenem consumption outpaced overall carbapenem consumption in India. Gandra, S. (2016).
Complicated urinary tract infections (cUTI) are a common reason for hospitalisation, and they are extremely prone to progress to sepsis or septic shock.
Faropenem is a successful medicine for the management of Complicated Urinary Tract Infection and as a step-down therapy (66.4%), according to the urologist's scope of faropenem in Complicated Urinary Tract Infection. This demonstrates a rise in urologists' belief in faropenem in the treatment of Complicated Urinary Tract Infection.
Cephalosporin-resistant Enterobacteriaceae resistance and prevalence are evolving and rising in nature. Faropenem is effective against ESBL producers, which are increasingly causing community-onset infections.
The same was emphasised by replies from current trial participants, who believe that faropenem 200 mg is a feasible alternative step-down therapy for Complicated Urinary Tract Infection due to lower resistance risks. In terms of -Iactamase stability, a recent study comparing faropenem to cephalosporins and imipenem corroborated this. Faropenem and the other cephalosporins tested positive for severe resistance to penicillinase generated by S. aureus and E. coli. Cephalosporinase from E. coli and P. vulgaris, on the other hand, severely degraded cephaloridine, cefaclor, and cefotiam, although faropenem remained stable.
The majority of participants stated that faropenem 300 mg extended release had great patient compliance and is an appropriate step-down choice for Complicated Urinary Tract Infection because to its high effectiveness and fewer adverse effects. The availability of extended release tablets may have contributed to the rise in compliance with 300 mg faropenem. Faropenem's advantages may possibly be attributed to its chiral tetrahydrofuran substituent at position C2, which improves chemical stability.
Though few clinical trials have found faropenem 300 mg twice daily to be less effective than co-trimoxazole in acute uncomplicated urinary tract infections, a small Japanese trial found faropenem 300 mg three times daily to be equivalent to levofloxacin given as a 100 mg three times daily regimen in Complicated Urinary Tract Infection. Faropenem has broad-spectrum antibacterial action *in vitro* against a wide range of gram-positive and gram-negative aerobes and anaerobes and is resistant to hydrolysis by almost all -lactamases, including extended-spectrum -lactamases and Amp C -lactamases.
In response to the question, "How efficacious is faropenem in comparison to other available options?", the majority of participants [187 (85%)] believed that faropenem is highly efficacious in the management of Complicated Urinary Tract Infection, while [13(6.14%)] participants believed that faropenem is equally efficacious as the other available options. However, [18 (8%)] of the participants lacked clinical expertise with faropenem. In response to safety concerns about faropenem use, the majority [270(69%)]

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of participants thought it was safe, 90 (23.0%) thought it had an outstanding safety profile, while just 40 (10.2%) thought it was unsafe and caused acidity or gastritis.
Faropenem is believed to be similarly effective as other accessible choices by 5.8% of participants. However, 5.1% of participants lacked clinical expertise with faropenem.
In regard to safety concerns about faropenem use, the majority [154(70%)] of participants thought it was safe, 51 (23%) thought it had an outstanding safety profile, while just 40 (10.2%) thought it was unsafe and caused acidity or gastritis. Faropenem's safety may be attributed to the presence of a chiral tetrahydrofuran group at position C2, which has offered improved stability and fewer CNS effects when compared to imipenem.

Conclusion

Faropenem is used to treat urinary tract infections because of its efficacy, capacity to produce reduced resistance, and safety profile. From a public health standpoint, prudent use of faropenem in the community is critical to preserving its broad spectrum of action for patients who truly require it.

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