IRAQI Academic Scientific Journals
العراقية المجلات الأكاديمية العلمية
University of Kut Journal
ISSN (E): 2616 - 7808 II ISSN (P): 2414 - 7419
www.kutcollegejournal.alkutcollege.edu.iq
k.u.c.j.sci@alkutcollege.edu.iq
Special Issue for the Researches of the 6th Int. Sci. Conf. for Creativity for 16 -17 April 2025

Comparison effect of Meropenem and Levofloxacin on activity of urease produced by Proteus mirabilis in patients with multi-drug resistant urinary tract infection in Karbala province, Iraq

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Abstract

In both community and health care settings, Proteus mirabilis and the rest species of the Enterobacteriaceae family are prominent pathogens for a variety of illnesses .In recent years, the incidence of isolation of Multidrug-Resistant bacteria (MDR) has grown, impacting hospitalized patients' prognosis and survival. meropenem is a β-lactam antibiotic used intravenously to treat a broad range of bacterial illnesses; Meningitis, intra-abdominal infection, pneumonia, sepsis, and anthrax are only a few of them, while levofloxacin which is a quinolone antibiotic used to treat bacterial infections such as acute sinusitis, lung infection, Helicobacter pylori (in conjunction with other antibiotics), genitourinary infection and gut infections.

Evaluation of the effect of treatment with meropenem and levofloxacin on activity of ureases enzyme produced by meropenem /levofloxacin resistant Proteus mirabilis among UTIs patients. Samples were collected from 100 patients outpatients aged between 25-80 years old males with a history of recurrent Urinary Tract Infection(UTI) caused by Proteus mirabilis. Among them, 50 patients were take meropenem for ten days, and the rest of the patients received levofloxacin for the same period. General Urin Examination (GUE) was done before and after therapy to estimate the level of urease activity as a virulence factor for Proteus mirabilis. There was a significant reduction in urease activity when meropenem was used for treatment compared to Levofloxacin.Using meropenem is superior in a patient with resistant UTI caused by Proteus mirabilis upon levofloxacin.

Keywords: Proteus mirabilis, Meropenem, Levofloxacin, Urease, UTIs

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Paper Info.
Published: Oct. 2025

مقارنة بين تأثير meropenem و levofloxacin على نشاط إنزيم اليوريز الذي تنتجه *Proteus mirabilis* في المرضى الذين يعانون من عدوى المسالك البولية المقاومة للأدوية المتعددة في محافظة كربلاء العراق

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المستخلص

في كل من المجتمع وأماكن الرعاية الصحية على حد سواء، تعتبر بكتيريا *Proteus mirabilis* وبقية أنواع عائلة البكتيريا المعوية من مسببات الأمراض البارزة لمجموعة متنوعة من الأمراض، وفي السنوات الأخيرة، ازدادت حالات عزل البكتيريا المقاومة للأدوية المتعددة ((MDR، مما أثر على تشخيص المرضى في المستشفيات وبقائهم على قيد الحياة. meropenem هو مضاد حيوي من نوع بيتا لاكتام يستخدم عن طريق الوريد لعلاج مجموعة واسعة من الأمراض البكتيرية، التهاب السحايا والعدوى داخل البطن والالتهاب الرئوي والإنتان والجمرة الخبيثة ليست سوى عدد قليل منها، في حين أن levofloxacin وهو مضاد حيوي من quinolone يستخدم لعلاج الالتهابات البكتيرية مثل التهاب الجيوب الأنفية الحاد والتهاب الرئة وعدوى الرئة وبكتيريا (Helicobacter pylori بالاشتراك مع مضادات حيوية أخرى) وعدوى الجهاز البولي التناسلي والتهابات الأمعاء. تقييم تأثير العلاج meropenem و levofloxacin على نشاط إنزيم اليوريز التي ينتجها meropenem /levofloxacin المقاوم لـ Proteus mirabilis بين مرضى التهابات المسالك البولية. جمعت العينات من 100 مريض خارجي تتراوح أعمارهم بين 25-80 سنة من الذكور الذين لديهم تاريخ من عدوى المسالك البولية المتكررة التي تسببها Proteus mirabilis من بين هؤلاء المرضى، تناول 50

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معلومات البحث
تأريخ النشر: تشرين الاول 2025

مريضًا منهم دواء meropenem لمدة عشرة أيام، وتلقى بقية المرضى دواء levofloxacin لنفس الفترة. تم إجراء الفحص العام للبول GUE قبل وبعد العلاج لتقدير مستوى نشاط اليوريز كعامل ضراوة Proteus mirabilis . كان هناك انخفاض كبير في نشاط إنزيم اليوريز عند استخدام meropenem للعلاج مقارنة بـ levofloxacin ، استخدام meropenem أفضل في مريض مصاب بالتهاب المسالك البولية المقاوم الناجم عن Proteus mirabilis على levofloxacin.

الكلمات المفتاحية: Proteus mirabilis، meropenem، levofloxacin ، اليوريز، التهابات المسالك البولية

Introduction

It is well known that the Gram negative bacterium, *Proteus mirabilis*, is most commonly a urinary tract pathogen causing urinary tract infections (UTIs), particularly in individuals undergoing long-term catheterization [1]. This bacterium is characterized by their resistant to some antibacterial agents in addition to the swarming motility in a pattern called the spectacular bulls'-eye pattern [2]. The current study considers P. mirabilis focusing on UTIs, especially those caused by resistant P. mirabilis. It was noted that swimming and swarming are both facilitated by flagella [3]. The control of this complicated process was explored in addition to many other virulence factors, including urease and stone formation, fimbriae, and other features enabling the bacteria to enter and colonize the human urinary system [4].

The swarming phenomenon is pathognomonic for *P.mirabilis* and is distinguishing this species from other members of the genus in addition to the production of urease [5]. Furthermore, *P.mirabilis* is characterized by other features such as lactose non-fermenter, indole non-producer, and damage to hydrogen sulfide production. It is proved that *P.mirabilis* belongs to Enterobacteriaceae, which is the same family as that of the *E. coli* [6].

Proteus mirabilis causes around one to ten percent of all UTIs, depending on the study's geographic region, samples taken, and the patient characteristics analyzed. This species was responsible for 4% of over 3,000 UTI cases in a recent important research in North America [7]. In the United States, UTIs accounted for 11 million medical visits in 2006. P.mirabilis is more frequently isolated from patients with complicated UTIs (as in the case of spinal cord injury or anatomical abnormalities). P.mirabilis was also isolated from catheterized patients with UTI samples, accounting for 10-44 percent of long-term catheter-associated UTIs in the United States at a cost of $43-256 million per year [8].

The optical S-(-) isomer of ofloxacin is levofloxacin, an oral fluoroquinolone antibacterial drug [9]. It has double the potency of ofloxacin in vitro. like those of other fluoroquinolones, levofloxacin's mode of action is to block the enzyme DNA gyrase of the bacteria, has modest efficacy against anaerobes, and is active on most aerobic bacteria [10]. After oral delivery, the bioavailability of levofloxacin in the targeted sites of infection is quick and extensive. Oral levofloxacin has shown antibacterial effectiveness in clinical studies in Japan, including infections of the respiratory passages, genitourinary infections, obstetric and gynecological infections. Levofloxacin exhibited equal effectiveness and fewer side effects than ofloxacin [11].

Meropenem has demonstrated both in-vivo and in-vitro effectiveness in treating a broad spectrum of severe illnesses in different age groups similar to existing treatment choices [12]. It was shown that

meropenem causes its bactericidal effect by corrupting cell wall production via binding covalently to penicillin-binding proteins [13]. Another study in 2018 revealed that the effectiveness of meropenem is almost equivalent to antibiotic combinations such as tobramycin and clindamycin; cilastatin and imipenem; and metronidazole with cefotaxime in case of intra-abdominal infections. While in the case of meningitis, it is comparable with ceftriaxone or cefotaxime. For the treatment of the lower respiratory tract, the efficacy of meropenem is comparable to that of imipenem/cilastatin and ceftazidime plus/minus aminoglycoside [14].

Furthermore, meropenem has shown to have satisfactory response rates in dermatologic, obstetric, and gynecological infections or septicemia and the case of febrile immune-compromised patients [15]. Meropenem has a potent ratio of minimum bactericidal activity (MBC) to minimum inhibitory concentration (MIC) for a wide range of sensitive bacteria (which is one or two). On the other hand, carbapenems affect Gram negative microbes and cause a post-antibiotic effect, and meropenem's impact was frequently more prominent than imipenem's in the same bacteria [16].

Patients and method

This study was done between April and November of 2021 in Karbala province, Iraq. The acceptance was taken from the patients to perform urine culture and sensitivity test for subsequent getting colony samples for rapid urease kit test. With, these 100 outpatients aged between 25-80 years old males with a history of recurrent UTI caused by bacteria *Proteus mirabilis* of 50 patients were take meropenem for ten days, and 50 patients took levofloxacin for ten days. Urine samples before and after treatment were taken for all; urine culture was performed for all before and after treatment.

Colorimetric Quanti-Chrom™ Urease Assay Kit (Urease Activity Assay Kit allows the detection of urease activity quickly and easily. The kit detects ammonia using a modified Berthelot technique, which has been detected at 670 nm) was performed for all the samples. The results were analyzed statistically by using paired t-test for each antibiotics before and after treatment using SPSS program V.22.

Results

This study revealed that using meropenem was associated with a significant reduction of urease activity as compared to control groups (before treatment), as shown in table (1), or using levofloxacin treated group as shown in table (2). While levofloxacin was associated with a reduction in urease activity compared to the non-treated group but still statistically not significant, as shown in table (1).

Table (1): comparison of using meropenem or levofloxacin on urease activity (expressed as mean±SD) with the untreated group

Antibiotic	Urease activity (µU) before using antibiotic	Urease activity (µU) after using antibiotic	P value
Meropenem	**50±10.886**	**14.8±5.541**	**<0.001***
Levofloxacin	**44.4± 7.570**	**36± 13.856**	**0.103**

* significant at $P < 0.05$

Table (2): comparison of using meropenem or on urease activity (expressed as mean±SD) as compared to levofloxacin treated group.

Group	Urease activity (µU) after using meropenem	Urease activity (µU) after using levofloxacin	P-value
Treated group	**14.8±5.541**	**36± 13.856**	**0.0128***

* significant at P < 0.05

Discussion

Anatomical or functional abnormalities in the urinary system, as well as the presence of a catheter, are the primary risk factors for *P. mirabilis* infection, the first is impossible to avoid [2]. The presence of a catheter is linked to a daily risk of bacterial infection of 3-10% [17].

Catheterization should be avoided wherever feasible, and if it cannot be avoided, the length of time spent catheterized should be kept to a minimum [18]. If the local recurrence rate is less than 10%-20%, a 3-day course of double-strength trimethoprim-sulfamethoxazole is currently recommended for acute uncomplicated cystitis [19]. On the other hand, this organism exhibits a wide range of local resistance rates, ranging from 16 to 83 percent, for which using other drugs was necessary to eradicate the recurrent infection by *P. mirabilis*. In many studies, it was shown that resistance for levofloxacin was increased [20].

Fluoroquinolone-resistant extended-spectrum-beta-lactamase(ESBL)-producing *E. coli* and *P.mirabilis* strains have been detected worldwide, causing infections. It has also been shown that 18-56 percent of ESBL-producing *E.coli* and *P.mirabilis* strains are fluoroquinolone-resistant and that fluoroquinolone resistance is tightly linked to ESBL production [21]. In another study, Oral antibiotic co-resistance was shown to be high among ESBL phenotypes, raising concerns about fluoroquinolones and co-trimexazole for treating resistant UTIs outside of the hospital. On the other hand, intravenous carbapenems continue to work against resistant UTI infections [22,23].New carbapenem-based oral alternatives would fill a gap in treating resistant urinary tract infections [24,25].

Antimicrobial susceptibility, antibiotic resistance gene prevalence, and molecular typing of *P. mirabilis* isolates obtained from three hospitals in northern Taiwan were investigated [26].Except for cefazolin and tigecycline, the obtained isolates of *P. mirabilis* were sensitive to most antibiotics (including meropenem). Many resistance genes were found in the isolates, with TEM genes most prevalent. At least one of the extended-spectrum-beta-lactamase (ESBL) or Amp C genes was linked to resistance to third- or fourth-generation cephalosporins and fluoroquinolones. Both cefepime and ceftazidime resistance appeared to be predicted by the presence of the VEB-1 gene [24].

Conclusions

Using meropenem is superior in a patient with resistant UTI caused by *Proteus mirabilis* upon levofloxacin.

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