RESEARCH ARTICLE / ARAŞTIRMA

DOI: 10.4274/mjima.2017.7
Mediterr J Infect Microb Antimicrob 2017;6:7
Erişim: http://dx.doi.org/10.4274/mjima.2017.7

Cost Analysis of Ertapenem Therapy for Urinary Tract Infections and Assessment of Its Suitability for Outpatient Parenteral Antibiotic Therapy Programme in Turkey

Üriner Sistem Enfeksiyonlarında Ertapenem Tedavisinin Maliyet Analizi ve Türkiye'de Ayaktan Paranteral Antibiyotik Tedavi Programında Değerlendirilmesi

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Abstract

Introduction: The primary aim of this study was to evaluate whether there was a difference between outpatient parenteral antibiotic therapy (OPAT) and inpatient parenteral antibiotic therapy (IPAT) costs of ertapenem for urinary tract infections (UTI's) due to extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacilli, and to discuss suitability of ertapenem for OPAT programme of Turkey for the near future.
Materials and Methods: A total of 53 patients hospitalized with the diagnosis of UTI and treated with ertapenem were retrospectively evaluated. The cost of ertapenem treatment as IPAT was actual costs retrieved from the hospital records. The estimated cost of the same antibiotic for the same patients as an OPAT programme was then calculated and the costs were compared.
Results: The cost difference between IPAT and OPAT was ₺ **12.305 (€ 5783)**. Outpatient parenteral antibiotic therapy programme would provide an estimated 20% reduction in treatment costs. The estimated number of bed days saved, if the patients had received the treatment as OPAT, was calculated to be 583 days, which constitutes about 5% of the total number of hospitalization days.
Conclusion: Applying ertapenem therapy through OPAT programme for UTIs caused by ESBL-producing Gram-negative bacilli will decrease the financial burden of health expenditures and the number of inpatient bed days in Turkey.
Keywords: Ertapenem, extended-spectrum beta-lactamases, urinary tract infection, cost analysis, outpatient parenteral antibiotic therapy

Öz

Giriş: Bu çalışmanın ana amacı genişlemiş spektrumlu beta-laktamaz üreten Gram-olumsuz basillere bağlı gelişen üriner sistem enfeksiyonlarında ertapenemin ayaktan paranteral antibiyotik tedavisi (APAT) ve hastanede yatan hasta paranteral antibiyotik tedavisi (YPAT) olarak uygulanması arasındaki maliyet farkının değerlendirilmesi ve yakın gelecekte Türkiye'de ertapenemin APAT programına alınmasının uygunluğunun tartışılmasıdır.
Gereç ve Yöntem: Üriner sistem enfeksiyonu tanısı ile hastanede yatırılan ve ertapenem tedavisi alan 53 hasta retrospektif olarak değerlendirildi. Ertapenem tedavi maliyeti, YPAT olarak hastane kayıtlarından gerçekleşen maliyetten hesaplandı. Sonrasında aynı antibiyotiğin aynı hastalarda APAT programı şeklinde uygulanımı ile oluşacak tahmini maliyet hesaplandı ve maliyetler karşılaştırıldı.
Bulgular: Yatan hasta paranteral antibiyotik tedavisi ve APAT arasındaki maliyet farkı **12.305 ₺ (5783 €)** olarak hesaplandı. Ayaktan paranteral antibiyotik tedavisi programı tedavi maliyetlerinde yaklaşık %20 azalma sağlayacaktır. Eğer hastalar tedavilerini APAT olarak almış olsalardı tahmini kazanılacak yatak gün sayısı 583 gün olarak hesaplandı. Bu da toplam hospitalizasyon gününün %5'ini oluşturmaktaydı.
Sonuç: Türkiye'de ertapenem tedavisinin APAT programı şeklinde uygulanması sağlık harcalamalarında finansal yükü ve hasta yatak gün sayısını azaltacaktır.
Anahtar Kelimeler: Ertapenem, genişlemiş spektrumlu beta-laktamaz, üriner sistem enfeksiyonu, tedavi maliyeti, ayaktan paranteral antibiyotik tedavisi

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Received/Geliş Tarihi: 22.02.2017 **Accepted/Kabul Tarihi:** 28.08.20174

Published: 8 September 2017

Presented in: A poster version of this study was presented at the IDWeek 8-12 October 2014 in Philadelphia, PA, USA.

Introduction

In recent years, urinary tract infections (UTIs) due to extended-spectrum beta-lactamase (ESBL)-producing bacteria show an increased incidence both among out-patients and hospitalized group of patients in Turkey as well as around the world. Extended-spectrum beta-lactamase-producing bacteria show increasing levels of resistance to aminoglycosides and quinolones as well as most beta-lactam antibiotics. Because of the ESBL-producing bacterial infections, the rates of hospitalization, morbidity and mortality increase and this condition causes an increasing cost of treatment and socio-economic losses. Carbapenems may be the only treatment option in at least some of the cases[1,2].

Decision for an appropriate antibiotherapy should be made according to isolated organism, results of the antibiotic susceptibility test and the potential pharmacokinetic and pharmacodynamic features of the drug. Outpatient parenteral antibiotic therapy (OPAT) is generally used to refer to the provision of parenteral antimicrobial therapy in at least 2 doses on different days without intervening hospitalization[3]. Outpatient parenteral antibiotic therapy practice will decrease the costs of staffing and maintenance services compared to hospitalization. Consequently, this will allow vacancy of beds for other patients who need hospitalization[4]. Among carbapenems, ertapenem is a good alternative with its pharmacokinetic features and bactericidal activity. Additionally, it can be administered daily as a single intramuscular, subcutaneous, or intravenous injection and, therefore, it is suitable for OPAT[5-7]. Various studies in different countries have shown that OPAT was efficient, reliable and cost-effective[8-11]. However, ertapenem has not yet been approved for OPAT programme in Turkey.

The primary aim of this study was to evaluate whether there is a difference between OPAT and inpatient parenteral antibiotic therapy (IPAT) costs of ertapenem for UTIs due to ESBL-producing Gram-negative bacilli, and to discuss suitability of ertapenem for OPAT programme of Turkey for the near future.

Materials and Methods

This study was conducted in a tertiary-care training and research hospital between July 2008 and August 2010. Files of hospitalized patients with the diagnosis of UTI in the Department of Infectious Diseases and Clinical Microbiology were retrospectively reviewed. The diagnosis of UTI was established according to the presence of isolates positive for ESBL production ($\geq 10^5$ CFU/mL) and presence of one of the followings: fever (>38 °C) and UTI symptoms (e.g., dysuria, pollakiuria, urinary urgency, urinary incontinence, abdominal pain, suprapubic tenderness, etc.)[2]. The demographic characteristics, clinical findings, risk factors for UTI and the duration of treatment were analysed. Adult patients (over 17 years old), symptomatic patients and those who were unresponsive and/or could not use fosfomycin, nitrofurantoin and/or other antibiotic treatments were included in the study. Patients with clinical and/or radiological evidence of upper UTI and sepsis were excluded. Sepsis was defined by using the final report of the 2001 International Sepsis Definitions Conference[12]. UTI was not stratified according to its origin (community-acquired or nosocomial.). The isolates were identified by conventional methods, and antibiotic susceptibility tests were performed by the Kirby-Bauer disc diffusion method according to the Clinical and Laboratory Standards Institute standards. Extended-spectrum beta-lactamase production was tested by the double disk diffusion method[13].

The cost of ertapenem treatment as IPAT was retrieved from the actual hospital records. The estimated cost of the OPAT was calculated with following assumptions:

1) Same duration of antibiotic treatment given as IPAT; and,
2) Same antibiotic treatment used as IPAT given to the same patient.

Then the actual IPAT cost was compared with estimated OPAT cost. The total actual hospitalization cost was retrieved from the hospital registration system in a cost breakdown format. Using the total cost, calculations were made to include only the cost components attributed to the treatment of UTI. Following cost components were taken into consideration in order to calculate the cost of IPAT including bed fees, escort fees, and intravenous access, intravenous injection, intravenous cannula, isotonic solution, ertapenem (1 gram per day) and, urine analysis (UA) charges. For calculation of costs of OPAT, it was assumed that actual costs of the following cost components had to be included: ertapenem 1 gram vial, intramuscular injection (for which the cost is the same with intravenous injection) and UA fees. The difference between the two costs was then calculated. Costs of tests in common both for outpatients and inpatients, such as complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), urea, creatinine, UA, urine culture, and urinary tract ultrasound examinations, were excluded from the calculation for cost analysis. Similarly, laboratory examinations, consultations and treatments for other comorbid diseases during hospitalization were also excluded. Saved inpatient bed days were calculated using the total number of patients in our clinic and the inpatient bed days during the study period.

Cost Analysis Method

The activity-based cost analysis method was used in this study. All the cost calculations were based on actual costs retrieved from the hospital records of the Department of Finance. The costs were calculated from the Republic of Turkey Social Security Institute perspective. In this study, cost figures were converted to a hard currency in order to eliminate inflationary impacts and to

show the value of the costs. All the calculations were made using the prices in Turkish Liras (₺) in 2008-2010 and the Central Bank of Turkey exchange rates were used for converting to Euros (€). The average ₺ to € currency exchange rate was 0.47 for the given period (Central Bank of Turkey foreign currency exchange rates archive: Web site: http: // www.tcmb.gov.tr / wps / wcm / connect / TCMB + TR / TCMB + TR / Main + Menu / Istatistikler / Doviz + Kurlari / Gosterge + Niteligindeki + Merkez + Bankasi + Kurlarii, Access date: 12.10.2014). All costs were presented with mean values and standard deviations.

Ethical Declaration

Ethics Committee of İzmir Katip Çelebi University Atatürk Training and Research Hospital (Ethics Committee Approval Number: 53, Date: 19th October 2012) approved the study.

Results

Clinical Data

Fifty-three patients were included in the study. Most (n=36; 67.9%) were females. The mean age was 55.1±19.0 years (range: 20-86). The most common symptoms were dysuria (85%), pollakiuria (25%) and urinary urgency (19%). The frequency of urinary incontinence and abdominal pain was <10%. Fever was not detected in any patient. Risk factors of UTI were uro-genital interventions and pathologies (transurethral prostate surgery, bladder cancer surgery, urolithiasis operation, benign prostatic hypertrophy, ureterocele, etc.) in 38% and diabetes mellitus in 32% of patients. Diabetes mellitus was more frequent in females and uro-genital interventions and diseases were more frequent in male patients. No risk factor was found in 21% of patients (Figure 1). Only 9% of patients had a history of recurrent UTIs. Laboratory test results were as follows: mean ESR: 42.5±33.8 (range: 6-123) mm/h; CRP: 5.4±11.3 (range: 0.06-56) mg/dL, and white blood cell count: 7284.1±2367.6 (range: 3060-12.000) cells/mm^3. *Escherichia coli* were the most common bacteria (92%) isolated from urinary cultures. Other etiologic agents were *Klebsiella pneumoniae* (4%), *Citrobacter freundii* (2%) and *Enterobacter cloacae* (2%). Although all the isolates were susceptible to imipenem and ertapenem, the rates of resistance to other antibiotics were as follows: piperacillin/tazobactam: 11%, gentamicin: 59%, trimethoprim-sulfamethoxazole 84%, ciprofloxacin: 97%, and ampicillin/sulbactam 100%. During the study period, nitrofurantoin and fosfomycin were not included in the antibiotic susceptibility test. Duration of ertapenem treatment ranged from 5 to 18 days (mean: 10.7±2.5). No serious side effect leading to drug discontinuation was observed during ertapenem treatment. Clinical improvement and microbiological eradication were achieved at the end of the treatment in all patients.

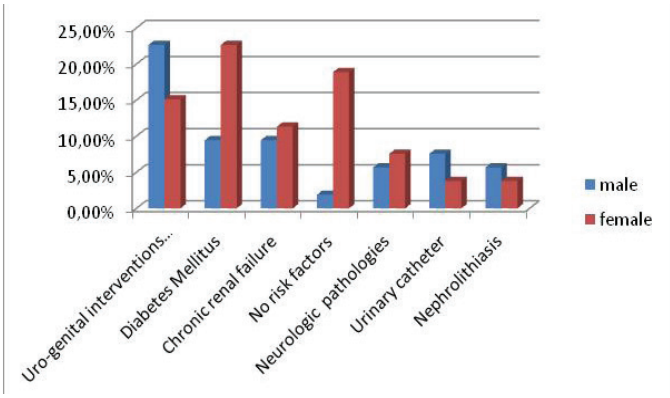

Figure 1. Risk factors of patients (%) for urinary tract infection

Cost Analysis

The total inpatient cost of 53 patients was ₺74.084 (€ 34819); the calculated cost of IPAT was ₺62.447 (€ 29350). The difference [₺11.637 (€ 5469)] was due to comorbid disorders, additional examinations, or treatment consultation fees. The total estimated cost of OPAT (if the patients were to receive the same agent as OPAT) was found to be ₺50.142 (€ 23566). The cost difference between IPAT and OPAT was ₺12.305 (€ 5783) and it was 20% less than IPAT cost. Treatment costs for IPAT and OPAT by age and gender per patient are shown in Table 1. The number of productive-age patients (ages 20-65) was almost twice the number of patients older than 65 years. Detailed cost components for IPAT and OPAT per patient are presented in Table 2. During the study period, 1.089 patients were hospitalized for 11.124 days in the clinic where this study was conducted. The estimated number of bed days saved, if the patients had received the treatment as OPAT, was calculated to be 583 days, which constitutes about 5% of the total number of hospitalization days.

Discussion

This study showed that implementation of ertapenem therapy as an OPAT protocol for UTIs caused by ESBL-producing bacteria would decrease the financial burden of healthcare expenditures in Turkey.

In different parts of the world, as well as in Turkey, a significant increase has been observed in the burden of both complicated and non-complicated community- or hospital-acquired UTIs due to ESBL-producing *E. coli*. Treatment of these patients is more complicated and expensive[14-18].

In a recent study, which examined risk factors for ESBL-production in uropathogenic *E. coli* isolated from community-acquired UTIs from four different geographical regions, it was observed that the production of ESBL was at alarming rates, especially in patients with complicated UTIs (17.4%). The main risk factors were more than three UTI episodes in the preceding year, usage of beta-lactam antibiotics in the preceding 3 months, and prostatic

disease[19]. In a study carried out in a tertiary training hospital in Switzerland, the analysis of risk factors of UTI occurring due to community-acquired ESBL-producing *E. coli* were older age, female gender, diabetes mellitus, recurrent UTI, invasive urological procedures, and prior use of antibiotics such as aminopenicillins, cephalosporins or fluoroquinolones[14]. In our study, uro-genital interventions or diseases and diabetes mellitus were found to be the most important risk factors. Failing to detect any risk factors in 21% of patients might be due to not being able to get a detailed history about the prior use of antibiotics.

The rate of antibiotic resistance and ESBL production increased in recent years both in Turkey and all over the world. This causes difficulties in treating patients with UTIs. More patients need hospitalization. Treatments are getting more complicated. Morbidity and mortality rates and treatment costs have increased. In a study from our country, which compared community-onset healthcare-associated and hospital-acquired UTIs caused by ESBL-producing *E. coli*, no resistance was found to carbapenems or fosfomycin. The rate of sensitivity to nitrofurantoin, amikacin, trimethoprim sulfamethoxazole and quinolons was 97.6%, 89%, 29.4% and 17.9%, respectively. In both groups, similar rates of antibiotic resistance were found[20]. In our study, the rate of sensitivity to carbapenems was similar but the rate of sensitivity to other antibiotics was much lower.

In a study in which clinical and microbiological outcomes of ertapenem in OPAT for complicated UTIs was investigated, microbiological and clinical cure rates were 67% and 92%, retrospectively. In this study, it was demostrated that ertapenem

Table 1. Distribution of treatment costs for inpatient parenteral antibiotic therapy and outpatient parenteral antibiotic therapy by age and gender per patient

Variables	Male			Female			Grand total
	Age groups			Age groups			
	20-65	>65	Total	20-65	>65	Total	
Number of patient	11	6	17	24	12	36	53
Average treatment days	10.6±2.4	12.1±3.8	11.2±2.1	10.5±2.2	10.5±2.5	10.5±2.3	10.7±2.5
Total cost of treatment (₺)	1636.9±551.8	1680.3±630.7	1652.2±561.3	1174.4±306.8	1483.8±449.4	1277.5±383	1397.7±476.7
Cost of IPAT (₺)	1289.6±331.4	1272.6±252.3	1283.6±297.6	1056.2±280.5	1273.2±363.6	1128.5±322.5	1178.2±320.3
Calculated cost of OPAT (₺)	1049.8±315.6	989.5±227.9	1028.5±281.7	842.9±282.5	1035.7±341.3	907.1±312.3	946.1±305.5
Cost difference IPAT vs OPAT (₺)	239.8±92.8	283.1±102.7	255.1±95.5	213.3±44.9	237.5±80.5	221.3±59.1	232.2±73.6
Cost difference IPAT vs. OPAT (%)	19±1	22±1	20.5±1	21±1	19±1	21±1	20±1

OPAT: Outpatient parenteral antibiotic therapy, IPAT: Inpatient parenteral antibiotic therapy

Table 2. Cost components of inpatient parenteral antibiotic therapy and outpatient parenteral antibiotic therapy (per patient)

Features	IPAT treatment cost (₺)	OPAT treatment cost (₺)	Cost difference (IPAT-OPAT) (₺)
Cost components			
Bed fees	189.0±66.6	0	189.0±66.6
Escort fees	5.2±21.8	0	5.2±21.8
Intravenous access	14.5±3.9	0	14.5±3.9
Intravenous cannula	1.5±0.4	0	1.5±0.4
Isotonic solution	22.0±5.6	0	22.0±5.6
Intravenous/Intramuscular injection	24.0±6.1	24.0±6.1	0
UA	1.5±0.5	1.5±0.5	0
Ertapenem	920.6±299.6	920.6±299.6	0
Total treatment cost (₺, per patient)	1178.2±320.3	946.1±305.5	232.2±73.6

OPAT: Outpatient parenteral antibiotic therapy, IPAT: Inpatient parenteral antibiotic therapy, UA: Urine analysis

was a good alternative to broader-spectrum carbapenems for the treatment of complicated UTIs. As well as being safe and effective, it has adventages of having a narrower spectrum and once daily dosing[21]. In another study, clinical efficacy of ertapenem in the treatment of recurrent cystitis caused by ESBL-producing *E. coli* in female outpatients was retrospectively reviewed and ertapenem treatment was found to be effective and well-tolerated[22].In our study, clinical and microbiological cure was sustained in all patients receiving ertapenem therapy and no side effect was observed. This shows that ertapenem therapy is efficient and safe in OPAT and it is estimated that use of ertapenem in OPAT may increase patient satisfaction.

Today, indications for OPAT programs, which are successfully used, differ among countries[23,24]. In a study which analyzed the cost of OPAT in adult patients in a tertiary training hospital in Canada between 1995 and 1998, different parenteral antibiotics were administered for different types of infections, such as bone and joint, skin and soft tissue, endocarditis and others. This study showed that OPAT programme provided an economically attractive alternative to continued hospitalization for selected adult patients with infections requiring parenteral antimicrobial treatment. Also from the hospital perspective, the cost of therapy through the OPAT programme was approximately 13% of the cost estimated if the patient was to continue to be managed in hospital settings[23]. In another study from UK, clinical efficacy and cost-effectiveness of OPAT in 334 episodes (skin and soft tissue infections, cardiovascular infections, central nervous system infections, genito-urinary infections, etc.) between 2006 and 2008 was evaluated. It was found that OPAT cost was 41% of equivalent inpatient cost for an infectious diseases unit and, over the 2-year period, the total number of bed days saved through OPAT activity was 4034. As a result, they concluded that OPAT was safe and clinically effective, with low rates of complications/readmissions and high levels of patient satisfaction, and also OPAT was found to be cost-effective when compared with equivalent inpatient care[24]. In these two studies, OPAT programme was found more cost-effective than in our study. This can be attributed to longer duration of OPAT needed for the treatment of infections such as bone and joint infections, endocarditis, skin and soft tissue infections, central nevous system infections (mean duration: 23 days) in these studies. Another reason might be differences in health-care expenditures for inpatients between countries. In another retrospective study of patients treated for UTIs caused by ESBL-producing organisms through OPAT over a 4-year period, 24 OPAT episodes involving 11 patients were reviewed. Six patients had an underlying urological abnormality and all patients were treated with parenteral ertapenem. There were no adverse effects related to ertapenem requiring cessation of a course earlier than planned. The mean duration of the OPAT episodes was 9.9 days and a total of 238 inpatient bed days were avoided. As a result, they concluded that ertapenem administration through OPAT may help decrease the costs associated with ESBL infections by reducing the number of inpatient bed days[8].

In our study, all patients were treated with ertapenem and the mean duration of the treatment was 10.7±2.5 days and there were no serious side effects during the treatment. At the end of the treatment, clinical improvement and microbiological eradication were achieved in all patients, and ertapenem therapy was found to be safe and effective. It was predicted that if ertapenem therapy had been applied as OPAT programme, there would have been an estimated 20% savings of the existent inpatient cost. During this 2-year period, the total number of bed days that could have been saved through OPAT was 583 (5% of the total number of bed days). Most of the patients were in economically productive age groups and the changes in opportunity costs due to missed work days were not included in our study, hence the difference in costs between two treatment options might be underestimated.

The findings of this study should be evaluated within its limitations. This is a retrospective study. A limited number of patients were evaluated in this study. This study shows data from a tertiary-care training hospital in Turkey, thus, it demonstrates only local data which can limit generalisability of the findings. The patients were not stratified according to whether the infection was community-acquired or nosocomial. During the study period, nitrofurantoin and fosfomycin could not be included in the antibiotic susceptibility test. Opportunity costs were not evaluated in this study, therefore, the actual cost differences might be higher than our estimates. Multicenter studies about cost analysis of ertapenem therapy for UTIs and assesment of its suitability for OPAT programme are needed in Turkey.

Conclusion

In conclusion, the widespread and rapid dissemination of ESBL-producing microorganisms seems to be an emerging issue worldwide and in Turkey. Consequently, treatment of these infections, which are causing high treatment costs as well as growing financial burden on health services, is becoming more difficult. In our country, due to the increasing incidence of UTIs caused by ESBL-producing bacteria, applying ertapenem treatment with OPAT programmes for this indication will decrease the financial burden of these infections. In addition, this programme might reduce the number of inpatient bed days required for successful treatment and increase patient satisfaction. Use of ertapenem in an OPAT programme is not available in our country. This is the first study in Turkey analysing the cost of ertapenem used in an OPAT programme.

Acknowledgements

Special thanks to Çiçek Kopraman for the contribution to this study through analyzing the cost calculations (Deputy Managing Director of a leading dairy company operating in Turkey; Bachelor's Degree in Business Administration).

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of İzmir Katip Çelebi University Atatürk Training and Research Hospital (Ethics Committee Approval Number: 53, Date: 19th October 2012).**Informed Consent:** The consent form is not needed for this submission.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Medical Practices: B.Ö., N.T., Z.K., N.S., Concept: B.Ö., N.T., Design: B.Ö., N.T., F.K., Data Collection or Processing: Z.K., N.S., Analysis or interpretation: M.K.S., Literature Search: N.S., T.D., Z.K., Writing: B.Ö., N.T., F.K., T.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This study was undertaken as part of our routine clinical activity and did not receive additional funding.

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