Original article

THE ASSESSMENT OF ANTIBIOTICS THERAPIES IN DIFFERENT GROUPS IN ACUTE CYSTITIS IN TERMS OF PHARMAECONOMICAL ASPECTS

Hilal İLBARS[1]*, Gülbin ÖZÇELİKAY[2]

[1]Turkish Ministry of Health, General Directorate of Pharmacy and Pharmaceuticals, Söğütözü-Ankara, TURKEY
[2]Ankara University Faculty of Pharmacy, Department of Pharmacy Management, 06100 Tandoğan-Ankara, TURKEY

Abstract

The urinary tract infection (UTI) is the second most common community acquired infection following the upper respiratory tract infections. In this study 160 subjects aged between 18-65 years with the diagnosis of acute cysytitis between 2005-2006 were involved and the objective was to determine the true cost of trimethoprim-sulphamethaxasol and fluoroquinolone group therapies that were given according to "Turkish Ministry of Health Diagnosis and Therapy Guideline".The aim of this study was to analyse the pharmacoeconomic aspect of the therapies that are proved to be effective, rather than their clinical effectiveness. The improvement rate of patients was 81.9 % at the end of the third day. The disapperance of symptoms in patients threated with ciprofloxacin, urociproxin, chemoprim forte and bactrim forte were 77.5 %, 72.5 %, 87.5 % and 90.0 % respectively. The side effects were noted in 10 % of patients involved in the study, candida vaginitis and allergy as being the most common ones. Therefore factors increasing cost and additional therapy costs become current issue. When the incremental cost effectiveness was calculated at the end of three day therapy, it is observed that the cost of urociproxin® is higher than the others. Pharmacoeconomic analysis models specific for our country should be developed, the diagnosis and therapy guidelines should be updated and statistical data should be well preserved, pharmacoeconomic studies of a drug should be performed before the drug will be involved in reimbursement system.

Key words: *Pharmacoeconomy, Acute cysytitis, Urinary tract infection, Pharmacoeconomic analysis*

Akut Sistitte Farklı Grup Antibiyotik Tedavilerinin Farmakoekonomik Yönden Değerlendirmesi

Üriner sistem enfeksiyonu (ÜSE), en sık görülen toplum kökenli enfeksiyonlardan üst solunum yolları enfeksiyonlarını takiben ikinci sırada yer almaktadır. 2005-2006 tarihleri arasında gerçekleştirilen bu çalışmada, akut sistit tedavisinde, "Sağlık Bakanlığı Tanı ve Tedavi Rehberi"nde belirtildiği gibi, Trimetoprim-sülfametaksazol ve florokinolonlar kullanmış 18-65 yaş grubundaki 160 kişide, ilaç kutu fiyatı farklılığı da söz konusu olan bu iki grup tedavinin gerçek maliyetinin ve farklılığının saptanması hedeflenmiştir. Araştırmadaki amaç, ilaçların klinik etkinliğinin değil, etkinliği kanıtlanmış farklı tedavilerin toplumda uygulandığı şekli ile farmakoekonomik yönden analizini yapmaktır. Çalışmamıza katılan hastaların iyileşme oranı 3. gün sonunda % 81.9 olarak belirlenmiştir. Siprofloksasin, urosiproksin®, kemoprim fort ve baktrim fort kullananların sırasıyla % 77.5, % 72.5, % 87.5, % 90.0'ının şikayetlerinin geçtiği belirlenmiştir. Araştırmaya katılanların %10'unda yan etki görülmüş olup, bunlar arasında en sık rastlanılanı kandida vajinit ve alerji olmuştur. Bu durumda ek tedavi maliyetleri gündeme gelmekte ve maliyeti arttıran diğer faktörler içinde yer almaktadır. Üç günlük tedavi sonrası artan maliyet etkinlik oranı hesaplandığında Urociproxin®'in maliyetinin daha fazla olduğu görülmektedir. Ülkemize özgü farmakoekonomik analiz modelleri geliştirmeli, tanı ve tedavi rehberlerimizi bu doğrultuda güncellemeli ve istatistiksel verilerimizi arttırmalı, bir ilacın geri ödeme listesine girebilmesi için farmakoekonomik çalışmaları zorunlu hale getirmelidir.

Anahtar kelimeler: *Farmakoekonomi, Akut sistit, Üriner sistem enfeksiyonu, Farmakoekonomik analiz*

*Correspondence: E-mail: hilbars1970@yahoo.com; Tel: +90 533 6088416

INTRODUCTION

Urinary system infections (USI) are common diseases among those in which antibiotics are used commonly. The eligible therapy of an infectious disease is to use the cheapest antibiotics with the least toxic effects that will eradicate the infection in a sufficient time. This rule is also valid for USI (1). *E. coli* can penetrate into the epithelium cells of the kidney and can proliferate actively here and hence, TMP-SMZ, ciprofloxacines and fluoroquinolons with the best efficiency are most recommended antibiotics in USI therapies (2).

On the one hand, when the cost of antibiotics use and that of therapy methods, loss of labor and the socio-economic effects are taken into account and on the other hand when the complications caused by USI, it is obvious that it leads important problems in terms of public health (3).

Urinary system infections (USI) are an important health problem especially in women. Approximately, 10-35% of women experience urinary tract infection in any episode of their lives. In our country, it is reported that cystitis is diagnosed in 5 million women every year. Acute non-complicated cystitis constitutes 75 % of all urinary tract infections (4). Since it has been seen commonly, the approach to USI, the assessment and the therapy have been changed with time in order be effective and economical (5).

The complicated urinary system infections not originated from the public is one of the infections seen commonly in women, more 8 millions admissions to physicians every year in United States of America are done and it causes serious health expenditure (2).

Recurrent urinary tract infections constitute an important problem for all people in terms of either quality of life or cost. The antibiotics that are to be used continuously due to the recurrent infections cause an important problem in terms of either side-effects or the antibiotics resistance that may occur in the future (6).

As in case of many other infectious diseases originating from the public, the probability of the resistance development against the preferred antimicrobials increases also among the pathogens in non-complicated urinary system infections (7). As this resistance problem becomes widespread the use of antibiotics with narrow-spectrum decreases, this condition increases either the health expenditures or makes more complicated the resistance problem. The infections assessed as easily treatable such as non-complicated urinary system infections pose nowadays as serious clinical problems for clinicians (8).

It is extremely important to perform pharmaco-economic analyses of medications used in acute cystitis (4) seen frequently in the public and being a life-threatening infection with low probability of complication development.

Long-term continuity of health services, presentation of these services equally, cost analysis as a tool of better understanding and management of resource flow depend upon the extensive application of cost-effective tools and methods. Therefore, such a study has an extremely important place in health sector where the available resources are restricted and it pioneers to other groups of medications.

The health sector in our country has a rapid development process being parallel to the tendencies in the world. One of the most designating features of this process is to search for the maximum efficiency in the use of resource. This search is certainly based on the reality of the limited resources. Therefore, the efficient use of resources should always be the prior question.

Although the pharmaco-economic analyses in Turkey are newer, the pharmaco-economic studies are also very limited abroad Turkey.

Since the microorganisms and their sensitivity to antibiotics can be estimated in women with the diagnosis of acute non-complicated USI, it is claimed that short-term empiric antibiotics therapy without performing urine culture can be beneficial, reliable and eligible in terms of cost (9). However, the increasing resistance ratios are determined in many agents of disease including USI in the world and in our country. This results in failure of the therapy. The

factors affecting the development of resistance includes addition of antibacterial to consumption substance, nourishment of animals with food with antibiotics or the absorption of anti-infective to the objects used in daily life. Hygiene, accelerated resistance development cause increased cost of diagnosis and that of therapy (10).

One of the most important parameters among all of these factors affecting the resistance development is the improper antibiotics use (10). All microorganisms causing to infection in public are affected by the extravagant and immoderate use of antibiotics. It is known that the infections caused by the resistant bacteria lead higher therapy expenses and increase the mortality and morbidity (11). The pharmacologic surveillance studies consisting of the data of antibiotics consumption analysis are indispensable in following and scrutinizing the bacterial resistance (12). The aim of this research is not to analyze the clinical efficiency of the medications but to analyze different therapies with proven efficiency in terms of administration in public and in terms of pharmaco-economic aspect.

EXPERIMENTAL

This is a case control interference study.

The frequency of acute cystitis in public is 17.8 % (13). Accordingly, in the calculation of overall sampling size; it was found that population: 5000; prevalence: 80 %; alpha: 5 % and sampling size: 160.

While computing the minimum patient number, the difference was found by taking the standard deviation of the difference between the lower and the higher cost, alpha=0.05, beta=0.20 (power:80 %).

In order to fit to normal distribution and to use parametric tests, since it is suggested that losses can occurs during follow-up and to maintain the number of individuals as 30 in each group, 40 patients were included in each group.

In this study, to detect the actual cost of these two group therapies where the difference in price on the label exists and to detect the difference in people using Trimetoprim-sülfametaxasole (TMP-SMZ) (Bactrim Forte®), TMP-SMZ (Kemoprim Forte®), Ciprofloxacin (Urociproxin® 250 mg) and Ciprofloxacin (Cipro® 250 mg) in acute cystitis treatment as indicated in the "Guidance of Diagnosis and Therapy of Ministry of Health".

After being informed by the physician, informed consent was signed by the participants to about the acceptance of the patients to participate to the study.

Four different medications were given randomly to the patients after signing the informed consent. The use of medication was determined as daily use of one tablet twice according to the Guidance of Diagnosis and Therapy of Ministry of Health in 2003.

Then, the cases were followed in the 1st, 2nd, 3rd, 7th, and 14th days in phone visits. In this follow-up, the continuity of medication use in eligible way was aimed and controls were done. During the follow-up, questions about the therapy processes were asked, information about whether the complaints were reduced, about the success of the therapy, about the recurrence of the infection were asked. During the therapy it was asked to the patients whether complaints related to medications, side effects and any unexpected effect occurred or not.

As indicated in the Guidance of Diagnosis and Therapy of Ministry of Health in 2003, the response to therapy was assessed as follows:

-To express that dysuria, pollakuria complaints were completely disappeared in 48 to 72 hours; recovery,

-Reduction of the signs in the same time but no loss of signs; partial recovery, Continuation, exacerbation of the signs and the addition of sensitivity in costovertebral angle and fewer to the complaints; no recovery are not cured.

Data were analyzed with SPSS for Windows version 12.0 statistics software (license number:55345-26752-51345-33006-86803-93573-71895-65752-87). The statistical significance level was assessed as 0.05.

Since to conduct the study in the first step according to the diagnosis and therapy guidance was found eligible, all patients included to the study were selected from Altındağ Dr. Sait Yazıcı Primary Health Care Facilities and from Dikmen Mürsel Uluç. Primary Health Care Facilities.

The 18 to 65 years old patients having complaints such as frequent voiding and burning while voiding however, that do not have higher fewer and sensitivity in costovertebral angle and/or diagnosed as acute cystitis by the physician which referred to Altındağ Dr. Sait Yazıcı and Dikmen Dr. Mürsel Uluç Primary Health Care Facilities were included.

The pregnant patients, those receiving another antibiotics therapy and those out of the range of 18 to 65 years-old were excluded from the study.

As a result of the study, the assessed parameters are side-effects and medication prices on the label.

RESULTS

People that are 18 to 65 years old were included to the study and totally 160 people were examined. Although no statistically significant difference was found in our study between groups included to the research in terms of age, it was seen that acute cystitis was more common in the range of 24 to 47 years old with the ratio of 67.4 %.

5 % of the subjects participating to the research were male and 95% of them were female. When the distribution of the patients was examined in terms of gender, it was found that female patients were dominant. This evidence supports that acute cystitis is seen more frequently in women in the public.

The higher frequency of acute cystitis is in January, June and October in our study supports the fact that this disease occurs more commonly in those months (4, 14).

The investigation of report use in order to assess the effect of acute cystitis to loss of labor was seen only in one patient working as an employee in a state office. This evidence is acceptable when the majority of the patients were house wives.

When most commonly seen symptoms and evidences were considered in patients with non-complicated USI, in our study; complaints such as dysuria and pollakiuria were observed in all participants. While the subjects with complaints of either dysuria or pollakiuria were 72.5 % of those included into the study, recovery was seen in 81.9 % of them. While those referring with pollakiuria were 5 % of the total, it was observed that no recovery was observed in 25 % of them.

In our study, people were selected randomly without bias in a fashion that they will be included into groups, it was demonstrated that gender, profession and to presence of complaints previously had no effects except medication.

Recurrent cystitis is seen in 20 % of the women with acute cystitis. During these episodes, the agent should be determined with urine culture and it should be discriminated whether this is due to the relapse (infection with the same organism) or due to the recurrence (infection with different organism). The multiple infections caused by the same microorganisms are defined as complicated as USI and require long-term use of antibiotics and more advanced diagnostic tests. However, the majority of the recurrent USIs are non-complicated infections caused by different microorganisms (15).

Side effects were seen in 10 % of the subjects included into the research. When candida vaginitis is considered among the side effects seen in the subjects included into the study, the cost of the necessary laboratory tests according to the guidance of diagnosis and therapy with

the physician visits in the second step and the cost of therapy being the cheapest options that will provide the application of the first-preference therapy are accounted as additional cost.

The additional therapy options used in the treatment of allergy being seen beside these side effects are also another factor increasing the cost.

43.8 % of the subject included into the research in which side effects were seen used TMP-SMZ (Bactrim forte®), 31.3 % of them used TMP-SMZ (Kemoprim forte®), 12.5 % of the used ciprofloxacine (Urociproxin®), 12.5 % of them used ciprofloxacine (Cipro®). In that case, the highest probability of side effects was detected most commonly in those using (Bactrim forte ®).

In our study also, the subjects used TMP-SMZ and ciprofloxacine for three days and the recovery rate was determined as 81.9 %. The fact that acute cystitis will be recovered after the three-day therapy has been determined in the Guidance of Diagnosis and Therapy, recovery was observed in the 81.9 % of the subjects 3 days later.

No statistically significant difference was observed in the comparison of the complaint groups of the subjects included into the study with the state of recovery (p>0.05).

No statistically significant difference was found in terms of recovery state according to the medication prices applied in the third day when the therapy was assessed (p>0.05; Table 1).

Table 1. The comparative distribution of the recovery state at the third day with the price of medication.

Medications	Prices	Recovery State					
		Recovered			Not recovered		
		No	Percentage of row	Percentage of column	No	Percentage of row	Percentage of column
(Ciprofloxacin) Cipro®	4.50	9	22.50	31.00	31	77.50	23.70
(Ciprofloxacin) Urociproxin®	7.41	11	27.50	37.90	29	72.50	22.10
(TMP-SMZ) Kemoprim forte®	7.55	5	12.50	17.20	35	87.50	26.70
(TMP-SMZ) Bactrim forte®	12.20	4	10.00	13.80	36	90.00	27.50

Chi-square=5.517; p=0.138

When ICER values after therapy for 3 days and when (Cipro®) and (Urociproxin®) were compared, it is seen that the cost of (Urociproxin®) is higher (Table 2).

The recurrence ratio was determined as 0.8 % during the follow-up in 7th and 14th days and this evidence supports the efficiency of the selected antimicrobial agents.

The cost based on tablet of TMZ-SMZ and medications containing ciprofloxacin such as (Bactrim forte®), (Kemoprim forte®), (Urociproxin®) and (Cipro®) totally for three days is respectively 3.66 YTL, 2.28 YTL, 7.41 YTL and 1.92 YTL. Therefore it is seen that the most expensive medication is (Urociproxin®) during the therapy for three days (Table 3).

Table 2. ICER values, differences between costs and differences of recovery ratios according to medications (After therapy for 3 days).

ICER Values				
Medications	*Cipro*	*Kemoprim*	*Bactrim*	*Urociproxin*
Cipro	--	0.04	0.14	-1.10
Kemoprim	0.04	--	0.55	-0.34
Bactrim	0.14	0.55	--	-0.21
Urociproxin	-1.10	-0.34	-0.21	--

Table 3. The prices of the medications used in the research on the label (in 2005 as YTL) and the amount of tablets in the package of medication and the cost after three-day therapy and the cost of one tablet.

Medication	Price of 1 box	Number of tablet in 1 box	Cost of 1 Tablet	Cost of therapy (for 3 days)
(TMP-SMZ) Bactrim forte®	12.20	20	0.61	3.66
(TMP-SMZ) Kemoprim forte®	7.55	20	0.38	2.28
(Ciprofloxacin) Urociproxin®	7.41	6	1.24	7.41
(Ciprofloxacin) Cipro®	4.50	14	0.32	1.92

DISCUSSION

When it is suggested that 6 tablets of the medications will be used in the research for 3 days during the treatment of the acute cystitis it has been seen that only (Urociproxin) has form with 6 tablets. However, when the cost of one tablet was calculated, the cost of (Urociproxin) was found as higher with 1.24 compared to other medications. Although the medications are not sold as one tablet in our country, it was determined that the cost of (Urociproxin) is higher than the other drugs.

The medication expenditures constitute an important part of the health expenditures and bigger part of the health expenditures are increasingly financed by the public institutions.

According to the data of 2006, while the expenditure ratio for medications in health expenditures is 25 % in our country, this ratio was given as 12 % in USA, and as 9 % in Denmark (16).

While the mean of the ratio of the health expenditures in GDP is 8.8 % in some OECD countries according to data in 2006, it is 7.7 % in our country. Also, expenditure for medications per capita in our country is less than one third of that of OECD countries (6).

However, some of the factors that should be noticed and that manage the expenditures of medication are as follows; the frequent occurrence of the diseases that can be diagnosed and that can be treated, the trend to more elderly population, use of therapies with higher cost, the increase in the number of the used medications per patient, the introduction of new drugs to treatment and the inflation (17).

One of the reasons of finding the ratio of the expenditures for drugs as higher is that other health expenditures cannot be computed completely.

Different models developed in different countries cannot be applied to our country, because in different health systems that is in different people;

-Demographic structure and epidemiology can be different.

-Unit price may be different.

-Therapies in use may be different.

-Applied therapy protocols may be different.

-The therapy places may be different.

-The priorities of the health institutions and those of health professionals may be different.

-Different definitions in different countries may imply different meanings.

In acute cystitis the use of TMP-SMZ and that of ciprofloxacins were ensured according to the guidance of diagnosis and therapy during therapy for three days. Since the tablet numbers in the box in medications used in the therapy was different and since no statistical significance exists in terms of efficiency in therapy, the use of the preparations that consists the tablet numbers during the therapy will be beneficial.

In the next studies therapy costs of the side effects should also be taken into account. In order to include the cost of side effects, vigilance system related to feed back about side effects should be made more effective and map of antibiotics resistance should be constructed.

When economical assessment is in question, collaboration with all institutions providing health services should be established.

The goal of the pharmacoeconomics is to find more effective and proper therapy (18). While the physician and the patient want to use more effective therapies spending the minimal time, the state and the insurance institutions that make the expenditures of health have the tendency to use therapies with the least cost. The objective should be to make therapy more effective instead of lowering the expenditures of health. However, the cost of health may be reduced with an effective therapy.

CONCLUSION

Pharmacoeconomic models specific to our country should be developed, our guidance of diagnosis and therapy should be updated in that aspect and our statistical data should be increased and pharmacoeconomic studies should be made mandatory in order to include a medication into the repayment list. It is necessary to make obligatory the pharmaco-economics lectures for the health professionals in the graduate and postgraduate programs for this purpose.

REFERENCES

1. Eraksoy H, Özsüt H, Hastane dışı üriner sistem enfeksiyonlarında ampirik antibiyotik tedavisi, Ankara: İnfeksiyon Hastalıkları Derneği Yayınları 2, 241-252, 1994.
2. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE, Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women, Clin Infect Dis 29(4), 745-758, 1999.
3. McIsaac WJ, Low DE, Biringer A, Pimlott N, Evans M, Glazier R, The impact of empirical management of acute cystitis on unnecessary antibiotic use, Arch Intern Med 162(5), 600-605, 2002.
4. Topçu WA, Söyletir G, Doğanay M, İnfeksiyon Hastalıkları ve Mikrobiyolojisi, Cilt 1, pp. 1059, Nobel Kitapevi, İstanbul 2002.
5. Naber KG, Bergman B, Bishop MC, Bjerklund-Johansen TE, Botto H, Lobel B, Jinenez Cruz F, Selvaggi FP, Urinary Tract Infection (UTI) Working Group of the Health Care Office (HCO) of the European Association of Urology (EAU). EAU guidelines for the management of urinary and male genital tract infections, Urinary Tract Infection (UTI) Working Group of the Health Care Office (HCO) of the European Association of Urology (EAU). Eur Urol 40(5), 576-588, 2001.
6. Boy D, Well M, Kinzig-Schippers M, Sörgel F, Ankel-Fuchs D, Naber KG, Urinary bactericidal activity, urinary excretion and plasma concentrations of gatifloxacin (400 mg) versus ciprofloxacin (500 mg) in healthy volunteers after a single oral dose, Int J Antimicrob Agents 23(Suppl 1), 6-16, 2004.
7. Gupta K, Scholes D, Stamm WE, Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women, JAMA 281(8), 736-738, 1999.
8. Gupta K, Hooton TM, Stamm WE, Increasing antimicrobial resistance and the management of uncomplicated community-acquired urinary tract infections, Ann Intern Med 135(1), 41-50, 2001.
9. Akata F, Üriner sistem enfeksiyonlarında uygun antibiyotik kullanımı, Klinik Dergisi 14, 114-123, 2001.
10. Erdem H, Bakır M, Toplumdan edinilmiş patojenlerde antibiyotik ve direnç ilişkisi, Klinik Dergisi 15, 8-11, 2002.
11. Holmberg SD, Solomon SL, Blake PA, Health and economic impacts of antimicrobial resistance, Rev Infect Dis 9(6), 1065-1078, 1987.
12. Bremón AR, Ruiz-Tovar M, Gorricho BP, de Torres PD, Rodríguez RL, Non-hospital consumption of antibiotics in Spain: 1987-1997, J Antimicrob Chemother 45(3), 395-400, 2000.
13. Canbaz S, Peksen Y, Tevfik Sunter A, Leblebicioglu H, Sunbul M, Antibiotic prescribing and urinary tract infection, Int J Antimicrob Agents 20(6), 407-411, 2002.
14. Foxman B, Epidemiology of urinary tract infections: incidence, morbidity, and economic costs, Dis Mon 49(2), 53-70, 2003.
15. Johnson JR, Vincent LM, Wang K, Roberts PL, Stamm, WE, Renal ultrasonographic correlates of acute pyelonephritis, Clin Infect Dis 14(1), 15-22, 1992.
16. OECD. Erişim: [http://www.oecd.org]. Erişim tarihi: 21.08.2006
17. McDonald R, Haycox A, Walley T, The impact of health economics on healthcare delivery: the health economists' perspective, Pharmacoeconomics 19(8), 803-9, 2001.
18. Bootman JL, Townsed JR, McGhan FW, Principles of Pharmacoeconomics. 2nd rev. ed. USA: Harvey Whitney Books Company, 1998.