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Full Length Research Paper

Antimicrobial consumption at a university hospital in Turkey

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Excessive antibiotic use is a challenging topic because of the total annual expenditure and the high resistance against antimicrobials in Turkey. A point-prevalence study was performed to evaluate the daily antibiotic consumption and the cost. Data were collected by infectious diseases consultants on 30 January, 2009 and 28 January 2010. Anatomical therapeutic chemical classification and the defined daily dose (DDD) methodology were used to calculate antibiotic consumption. On a specific day in 2009, 191 of 418 patients (45.6%) received antibiotics and on the specific day in 2010, 167 of 316 patients (52.8%) received antibiotics as well. With respect to the years antimicrobials were given empirically (41.9 and 38.3%, respectively). The percentage of antibiotics used appropriately was 70.2 and 71.3%, in 2009 and 2010 respectively. The mean total antibiotic consumption was 64.5 DDD/100 bed-days in 2009 and 70.46 DDD/100 bed-days in 2010. The most frequently used substance class was cephalosporins (16.75 and 24.14 DDD/100 bed-days, respectively). The cost of all used antibacterials during the study period in 2009 was 5,713.7 € for all patients (29.9 € per infected patient). In the study period of 2010, the total cost was 4,240.13 € (25.39 € per infected patient). The cost of all used antimycotics for the combined study periods of 2009 and 2010 was 623.74 and 920.62 €, respectively. Hospitals should follow and evaluate their antibiotics use as DDDs so they could compare their antibiotics use with hospitals from other countries.

Key words: Antimicrobial consumption index, antimicrobial use, cost, defined daily dose, surveillance

INTRODUCTION

The surveillance of antimicrobial consumption is one of the most important issues that must be considered to improve the quality of antimicrobial use (Papova et al., 1997). Antimicrobial agents are among the most costly categories of drug expenditures in hospitals. They account for up to 20 to 30% of the total cost of drugs (Pestotnik et al., 1996; Vlahovic-Palcevski et al., 2004). The total annual expenditure of antimicrobials in Turkey in 2002 was 24% of all drug expenditures (Hosoglu et al., 2005). However, it is accepted that the majority of this consumption is irrational. Irrational antibiotic use has been considered a common problem in Turkey. Despite its importance, there is very little available information about hospital antibiotic consumption in Turkey (Hosoglu et al., 2005).

The recommended standard unit for measuring antibiotic consumption in hospitals is defined as daily dose (DDD) per 100 bed-days. The use of this standart unit of measurement is based on the promotion made by the World Health Organization (WHO) (WHO, 2010). The WHO-assigned DDD is the assumed average maintenance dose per day for a drug used for its main indication. Definitions of DDD are updated on a yearly basis. Expressing antibiotic use by using the 'DDD per 100 bed-days' unit is thought to allow hospitals to compare their antibiotic use with that of other hospitals,

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regardless of differences in formulary composition, antibiotic potency, and hospital census (Kuster et al., 2008; Muller et al., 2006).

The objective of this study is to evaluate the expenditure and pattern of antibiotic consumption in a university hospital in Turkey.

MATERIALS AND METHODS

Setting

Pamukkale University Hospital is a 352-bed tertiary-care training hospital. Four intensive care units (ICU) (Anesthesiology and Reanimation ICU, Neurosurgery ICU, Cardiovascular Surgery ICU, and Newborn ICU) and 25 other units are assigned to different departments.

Data collection

In this study, data were collected from 'medical' (cardiology, endocrinology, gastroenterology, haematology, oncology, nephrology, infectious diseases, neurology, paediatrics, physical therapy and rehabilitation, pulmonology, psychiatry, dermatology, and rheumatology); 'surgical' (general surgery, cardiovascular surgery, gynaecology and obstetrics, neurosurgery, orthopaedics, paediatric surgery, otolaryngology head and neck surgery, plastic surgery, thoracic surgery, ophthalmology, and urology), and 'intensive care unit (ICU)' (paediatric ICU, anaesthesiology and reanimation ICU, cardiovascular ICU, and neurosurgery ICU). On the days of the study, none of the patients in the psychiatry, dermatology, rheumatology, or ophthalmology departments were using antibiotics. A modified point-prevalence study design was used. All wards were surveyed once on the study day. Data on the use of antimicrobial agents in the hospital were collected by infectious diseases consultants on 30 January, 2009, and 28 January, 2010. All patients who received antimicrobials, for any reason, were included in this study. The data were collected for each department from the patients' charts, using a standard form. For each patient receiving anti-infectives, the demographic data, results of microbiological tests, diagnosis, name, and dosage of the anti-infectives were recorded on the form. After a week, the incomplete data were also recorded in the patients' charts.

Presence of an infectious disease was diagnosed according to signs and symptoms and non-microbiological and microbiological laboratory findings, and defined as proven infection. The Centers for Diseases Control (CDC) criteria and National Nosocomial Infections Surveillance System (NNIS) methodology were used for the diagnosis of nosocomial infections (NI) (Garner et al., 1988; NNIS, 2004). Fever of unknown origin (FUO) was diagnosed according to Petersdorf and Beeson criteria (Petersdorf and Beeson, 1961). An infectious diseases physician evaluated the appropriateness of the antimicrobial prescriptions. The appropriateness of the antibiotic therapy was determined using the criteria described by Kunin and Jones and by The Sanford Guide to Antimicrobial Therapy (Kunin et al., 1973; Jones et al., 1977; Sanford et al., 2009, 2010).

The surgical antimicrobial prophylaxis administration and the accuracy of the antimicrobial prophylaxis management were analysed in accordance with the international guidelines on the types of antibiotics prescribed as well as on the dose, administration time and duration of the prophylaxis relative to the time of surgery (ASHP, 1999; Dellinger et al., 1994). The guidelines recommend that an intravenous single dose of an inexpensive, non-toxic, and limited-spectrum antibiotic be administered within 30 to 60 min before the first incision. Cefazolin and cefuroxime have been accepted by the WHO as the only appropriate choices for non-allergic individuals. The only situations in which vancomycin is appropriate for surgical prophylaxis are major surgical procedures that involve the implantation of prosthetic materials or devices at institutions that have a high rate of infections caused by MRSA or MRSE. Vancomycin is also appropriate in patients who have a life-threatening allergy to β-lactam antimicrobials. Repeated dosage is recommended when surgery is prolonged beyond two times the half-life of the administered antibiotic.

The Anatomical Therapeutic Chemical (ATC) classification system and DDD are recommended by the WHO as a measuring units for drug utilisation studies (WHO, 2010). DDDs are standardised doses provided as part of the ATC drug classification system maintained by the WHO Collaborating Centre for Drug Statistics Methodology (WHO, 2010). Antimicrobial and antimycotic utilisation was measured in DDDs per 100 bed-days. This index is called the antimicrobial consumption index (ACI). ACI is calculated by taking the total (inpatient) DDD for a hospital and dividing that number by the total number of bed-days for the hospital. The total is multiplied by 100 to obtain the ACI in DDD/100 bed-days.

In the current study, DDDs for anti-infective agents were listed for systemic use [Group 'J01' and 'J02' (antibiotics for systemic use and antimycotics for systemic use)] according to the ATC–DDD Index 2010 (WHO, 2010). The costs of antimicrobials were calculated by using daily pharmacy prices in Turkish currency (Turkish Lira=TL). The total costs were expressed as Euro (€) by taking 1 €=2,112.80 TL in 2009 and 1 €=2,091.80 TL in 2010.

Two-year averages were calculated by using the data for the periods 2009 and 2010, and the changes in antibiotic prescription between these two periods were expressed as percentage.

RESULTS

In 2009, the mean age (±SD) of the patients was 46.9 ± 24.6 years, and men accounted for 52.4% of the group. In 2010, the mean age (±SD) of the patients was 47.98 ± 23.5 years, and men accounted for 51.5% of the group. During this period, NI rates were 17.9% in 2009 and 13.3% in 2010. In 2009, 191 of 418 patients (45.6%) received anti-infectives. In 2010, 167 of 316 patients (52.8%) received anti-infectives. The indications of antimicrobial therapy were evaluated. With respect to the years, antimicrobials were given empirically (41.9 and 38.3%, respectively), for surgical antimicrobial prophylaxis (38.2% and 46.1%, respectively), for medical prophylaxis (6.8 and 4.8%, respectively), and according to microbiological data (13.2 and 10.8%, respectively).

The percentages of antibiotics used appropriately were 70.2% in 2009 and 71.3% in 2010. Antibiotics were used inappropriately more frequently in surgical wards (56.6 and 43.4%, respectively) than in medical wards (11.25 and 1.8%, respectively) and in ICU (28.6 and 16 %, respectively). The timing of the prophylaxis was found appropriate in all procedures; however, the duration was optimal only in 24.7 and 27.9%, respectively, in all cases.

In 2009, 37.6% of patients in the medical unit, 47.5% of patients in the surgical unit, and 90.3 % of patients in the ICU received anti-infectives. In 2010, 31% of patients in the medical unit, 80% of patients in the surgical unit, and 78% of patients in the ICU received anti-infectives. The mean total anti-infective consumption rate was 64.5 DDD/100 bed-days in 2009 and 70.46 DDD/100 bed-

Table 1. Consumption of antiinfectives as a total and by ATC group a hospital in Turkey, 2009 and 2010.

Antiinfectives group	ATC code	DDD per 100 bed-days			Percentage of total use	
		Absolute change (%)				
		2009	2010	2009-2010	2009	2010
Combinations of penicillins, including ß-lactamase inhibitors	J01CR	15.75	14.34	-1.41 (-8.95)	24.42	20.35
Cephalosporins, first-generation	J01DB	5.26	11.49	6.23 (118.4)	8.16	16.3
Cephalosporins, second-generation	J01DC	4.07	5.69	1.62 (39.8)	6.31	8.08
Cephalosporins, third-generation	J01DD	7.42	6.96	-0.46 (-6.2)	11.5	9.88
Carbapenems	J01DH	11.72	7.1	-4.62 (-39.4)	18.17	10.08
Aminoglycosides	J01GB	1.8	0.53	-1.27 (-70.6)	2.79	0.75
Imidazoles	J01XD	4.22	5.7	1.48 (35.1)	6.54	8.09
Glycopeptides	J01XA	7.72	4.75	-2.97 (38.5)	11.97	6.74
Fluoroquinolones	J01MA	3.25	5.44	2.19 (67.4)	5.04	7.72
Others antibacterials		2.34	4.53	2.19 (93.6)	3.63	6.43
Antimycotics for systemic use	J02A	0.95	3.93	2.98 (313.7)	1.47	5.58
Antibacterials and antimycotics for systemic use(total)		64.5	70.46	5.96	100	100

*ACI: antimicrobial consumption index (DDD per 100 bed-days).

Table 2. DDDs and ACI* of antiinfectives as a total by clinical units in the survey, 2009 and 2010.

Antiinfectives group	Medical units				Intensive care units				Surgical units			
	2009		2010		2009		2010		2009		2010	
	DDDs	ACI	DDDs	ACI	DDDs	ACI	DDDs	ACI	DDDs	ACI	DDDs	ACI
Combinations of penicillins, including ß-lactamase inhibitors	28.05	13.36	24.4	14	2.9	9.4	0.64	2	34.9	20	24.3	22.12
Cephalosporins	19.5	9.28	17.2	9.9	5.2	17	8.7	27	45.3	26	50.1	45.55
Carbapenems	16	7.62	10	5.8	17	55	5.05	16	16	9.1	7.2	6.55
Aminoglycosides	0.5	0.23	0.6	0.4	2	6.5	0.4	1.3	5	2.8	0.66	0.6
Imidazoles	4	1.91	4.4	2.5	1	3.2	2.3	7.2	12.6	7.1	11.3	10.26
Glycopeptides	11.75	5.6	9	5.2	9	29	1	3.1	11.5	6.5	5.5	5
Fluoroquinolones	9.4	4.47	9.8	5.6	2.6	8.4	2	6.3	1.6	0.9	5.4	4.9
Others antibacterials	5.16	2.46	1	0.6	2	6.5	6	19	2.66	1.5	3.3	3
Antimycotics for systemic use	2	0.95	6.43	3.7	2	6.5	6	19	0	0	0	0
Total	96.36	45.88	82.8	47.58	43.7	140.97	32.1	100.28	130	73.2	108	97.98

days in 2010 (absolute change, 5.96). Cephalosporins, combinations of penicillins (including ß-lactamase inhibitors), carbapenems, and glycopeptides had the highest consumption rates during the study periods (Table 1). When we examined the consumption changes in the various classes of antibiotics DDD/100 bed-days, first-generation cephalosporin consumption was the greatest (showing absolute change of 6.23) (Table 1).

The daily cost of all analysed antibacterials in the 2009 and 2010 study periods were 5,713.7 € (29.9 € per infected patient) and 4,240.13 € (25.39 € per infected patient), respectively. The daily costs of all used antimycotics in the 2009 and 2010 study periods were 623.74 € (103.94 € per infected patient) and 920.62 € (92.06 € per infected patient), respectively.

Using the standard index of DDDs per 100 bed-days, antibiotic consumption was 45.88 and 47.58 in the medical units, 73.2 and 97.98 in the surgical units, and 140.97 and 100.28 in the ICUs in 2009 and 2010, respectively. In 2009 and 2010, the ICUs showed the highest consumption of antibacterials. Consumption in the surgical units increased by 33.85% while in the

medical units consumption increased by 3.7%. On the other hand, antibiotic consumption decreased in the ICUs by 28.86%. In both years, in the DDD/100 bed-days ranking, the most frequently used substance classes were cephalosporins, penicillins and penicillins-ß-lactamase inhibitors, and carbapenems (Table 2).

The daily costs of all analysed antibacterials during the 2009 and 2010 study periods were 2,346.2 € (29.7 € per infected patient) and 1,670.97 € (30.95 € per infected patient) in the medical units; 1,237.6 € (44.2 € per infected patient) and 989.43 € (41.97 € per infected patient) in the ICU; and 2,130.02 € (26.03 € per infected patient) and 1,579.74 € (17.93 € per infected patient) in the surgical units, respectively. The daily costs of all antimycotics used were 310.3 € (103.44 € per infected patient) and 890.5 € (149.9 € per infected patient) in the medical units and 310.3 € (103.44 € per infected patient) and 21.02 € (5.3 € per infected patient) in the ICU during the 2009 and 2010 study periods, respectively. Antimycotics were not used in the surgical units during the 2009 and 2010 study periods.

DISCUSSION

In hospitals, antimicrobial use varies broadly, which may be partially explained by differences in patient and hospital characteristics, antibiotic policies, physicians, education, and health care systems (Kuster et al., 2008). Over the last 30 years, many surveys have defined the worldwide extent of the problem of antimicrobial misuse (Vlahovic-Palcevski et al., 2000). The inappropriate use of antimicrobial agents in hospitals has resulted in the emergence of resistant microorganisms, increased costs, and unnecessary exposure of patients to drugs (Vlahovic-Palcevski et al., 2004; 2007). Anti-infective drugs are the drugs used most often (22% of all drugs) in Turkey (Usluer et al., 2005).

To the best of our knowledge, this is the first study in Turkey that covers all departments of a hospital to calculate antibiotic consumption using the ATC / DDD methodology.

Enhanced antimicrobial surveillance is a key strategy that can be used to monitor the amount of antimicrobial use (Karabay and Hosoglu, 2008). Antimicrobial consumption indexes have been measured according to the descriptions of the WHO for anti-infectives for systemic use. For individual hospitals, prescribing is better reported according to internal activity, for which WHO recommends DDDs per 100 (or per 1,000) bed-days (Berrington, 2010).

The use of the ATC classification system and the DDD as measuring unit are recommended by the WHO for drug utilisation studies (WHO, 2010). The system is now widely used internationally, and the number of users is gradually increasing (WHO, 2010). DDDs have been used to compare hospitals, as well as countries.

Antibiotic use calculated per admissions and per bed-day complement one another. DDD 100 bed-days has been used to compare both out-of-hospital and hospital antibiotic use internationally, and such data have been useful, both for benchmarking and for illuminating the relation-ship between antibiotic use and resistance at a national level (Berrington, 2010).

The rate of antibiotic use among inpatients increased from 45.6 to 52.8% in our hospital. In different studies, antimicrobial prescription frequency was found to be between 14 and 65% in hospitalised patients (Pestotnik et al., 1996; Vlahovic-Palcevski et al., 2007; Usluer et al., 2005; Ozkurt et al., 2005; Mora et al., 2002).

In our study, NI rates were between 13.3 and 17.9%. The prevalence of NI in Europe has been estimated to be between 3.5 and 10% (Vlahovic-Palcevski et al., 2007; Berrington, 2010).

Antimicrobial drugs represent a great part of the total yearly drug expenditures. Similarly, the cost of antimicrobials is a serious problem for the insurance systems in Turkey. In this study, the daily expenses of antibacterial drugs were 5,713.70 € in 2009 and 4,240.13 € in 2010 (cost per infected person was calculated as 29.90 € and 25.39 €, respectively). The daily expenses for antimycotics were 623.74 € in 2009 and 920.62 € in 2010 (cost per infected person was calculated as 103.94 € and 192.06 €, respectively). The total costs of anti-infectives (antibacterials and antimycotics) per infected person were calculated as 33.18 € and 30.90 € in this study. On the other hand, the decrease in the cost of anti-infectives could be related to a decrease in drug prices in Turkey (for example, in 2010, the price of teicoplanin 0.4 gr decreased from 41.74 € to 32.84 €, and the price of cefoperazone 1gr decreased from 12.73 € to 7.51 €).

The "Antibiotic Resistance; Prevention and Control" (ARPAC) Project showed that the range of antibiotic use was 129 DDD/100 occupied bed-days (median = 55) in European hospitals (MacKenzie et al., 2005). Antibiotic use increased by 7.2%, and ACI use increased by 9.24%, in our hospital from 2009 to 2010. In the present study, ACI increased from 64.5 DDD/100 bed days in 2009 to 70.46 DDD/100 bed days in 2010. The DDD/100 bed-days findings of this study were similar to that of South and West Europe, but were higher than North, Southeast, and Central/East Europe (MacKenzie et al., 2005). Surveys carried out in the university hospitals of different countries showed ACI as 39 to 85.6 DDD/100 bed days (Vlahovic-Palcevski et al., 2000; Vaccheri et al., 2008).

Inappropriate antimicrobial usage is a worldwide problem. In Turkey, an antibiotic restriction policy was applied in 2003 to reduce the expenditure of antibiotics, based on a directive from the Ministry of Health. According to this policy, certain intravenous and expensive broad-spectrum antibiotics were restricted by legal regulation, and their use required approval from an infectious disease specialist. Previous reports on hospitals applying an antibiotic policy had shown that the

rate of the appropriate use of antibiotics increased after intervention (Ozkurt et al., 2005; Tunger et al., 2009). According to surveillance studies in Turkey, the percentages of appropriate antibiotic use were reported to be between 45.7 and 91.4% (Usluer et al., 2005; Ozkurt et al., 2005, 2009). In some studies conducted in other countries, the percentages of appropriate antibiotic use were reported to be between 45 and 89 % (Mora et al., 2002; Apisarnthanarak et al., 2006; Raveh et al., 2001). In the present study, the percentages of appropriate antibiotic usage within the study days in 2009 and 2010 were 70.2 and 71.3%, respectively. The problem is more serious in ICUs and in surgical departments than in medical departments (Usluer et al., 2005). Antimicrobial prescription ratios have been reported as higher in ICUs than in other hospital departments (Usluer et al., 2005; Hartmann et al., 2004). Antibiotic prophylaxis in surgery is one of the matters of discussion regarding hospital use of antimicrobial agents, as surgical procedures often are associated with unnecessary prescriptions of antibiotics (Vaccheri et al., 2008). Antibiotics were used inappropriately more frequently in the surgical wards (56.6 and 43.4%, respectively) than in the medical wards (11.25 and 1.8%, respectively) and ICUs (28.6 and 16%, respectively) in our hospital. In our study, the timing of the prophylaxis was found appropriate in all procedures, but the duration was optimal only in 24.7 and 27.9% of all cases, respectively. In a study conducted in our hospital 2002 and Yalcin et al. (2007) found that, although the timing of the prophylaxis was appropriate in all procedures, the duration was optimal only in 29.0% of all cases. There was no change in the duration of surgical prophylaxis for about eight years in our hospital. A national guideline for the surgical prophylaxis would be useful for improving the local consensus regarding guidelines and for increasing the quality of antibiotic use. There are surgical prophylaxis guidelines in some Turkish hospitals, but currently there is no national guideline. Unfortunately, our hospital does not have any local guidelines on surgical antibiotic prophylaxis. To ensure the correct and restrictive use of antibiotics, the development of hospital guidelines for rational antibiotic use is now being included in our hospital's infection control program.

The antibiotic consumption rate is higher in Turkey than in many European countries, such as Sweden, Denmark, Germany, and Hungary (Muller et al., 2007). Penicillin consumption is higher in Turkey and, compared with other European countries, cephalosporin, fluoroquinolone, and macrolide consumption rates are also very high (Karabay and Hosoglu, 2008). The increasing use of fluoroquinolones and cephalosporins is alarming, given that they may increase the risk of the emergence of resistant microorganisms (Sener et al., 2007). In the ARPAC Project, it was found that in all hospitals, penicillin beta-lactams were used most often, followed by non-penicillin beta-lactams and quinolones (MacKenzie, 2005). In our study, cephalosporins were the most frequently used antibiotics, followed by penicillins with beta-lactam inhibitors, carbapenems, imidazole derivatives, and fluoroquinolones.

There are some limitations in our study. One of the limitations is its single-centre nature. The second limitation of our study is that antimicrobial resistance rates were not investigated. Another limitation is that the study contains data for only one day of each year. Combining this point prevalence 'detail' study with a 'broad-brush' survey of antibiotic consumption over a longer time period. Nevertheless, this study, using a simple and inexpensive point-prevalence method, revealed several differences in antimicrobial drug prescription among the various units of the hospital. Point-prevalence studies are often used to provide baseline information regarding antibiotic consumption in hospital settings.

In conclusion, hospitals should use the DDDs to make international comparisons of their antibiotic use. Hospital antibiotic use could be collected and reviewed routinely to determine the antimicrobial consumption trend.

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