IVYSPRING INTERNATIONAL PUBLISHER

International Journal of Medical Sciences

2011; 8(4):339-344

Research Paper

The Impact of a Nationwide Antibiotic Restriction Program on Antibiotic Usage and Resistance against Nosocomial Pathogens in Turkey

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Received: 2011.02.22; Accepted: 2011.05.16; Published: 2011.05.24

Abstract

Purpose: Antimicrobial resistance among microorganisms is a global concern. In 2003, a nationwide antibiotic restriction program (NARP) was released in Turkey. In this study we evaluated the effect of NARP on antibiotic consumption, antimicrobial resistance, and cost.

Materials and Methods: The data obtained from all of the four university hospitals, and one referral tertiary-care educational state hospital in Ankara. Antimicrobial resistance profiles of 14,233 selected microorganisms all grown in blood cultures and antibiotic consumption from 2001 to 2005 were analyzed retrospectively.

Results: A negative correlation was observed between the ceftriaxone consumption and the prevalence of ceftriaxone resistant *E.coli* and *Klebsiella* spp. (rho:-0.395, *p*:0.332 and rho:-0.627, *p*:0.037, respectively). The decreased usage of carbapenems was correlated with decreased carbapenems-resistant *Pseudomonas* spp. and *Acinetobacter* spp (rho:0.155, *p*:0.712 and rho:0.180, *p*:0.668, respectively for imipenem). Methicillin resistance rates of *S.aureus* were decreased from 44% to 41%. After two years of NARP 5,389,155.82 USD saving occurred.

Conclusion: NARP is effective in lowering the costs and antibiotic resistance.

Key words: Antibiotic consumption, antimicrobial resistance surveillance, restriction policy.

Introduction

It is obvious that antibiotics had saved many lives since they were first introduced to medical practice. However, when antibiotics are used the emergence of drug resistant microorganisms is inevitable. The emergence of resistant microorganisms becomes faster when antibiotic use is inappropriate [1]. As well as emergence of resistant microorganisms, increased mortality and morbidity, adverse drug reactions and excessive strain on already limited healthcare budgets are the results of inappropriate antibiotic consumption [2-4]. These findings provide compelling evidence of the need for more rational use of antimicrobial agents in all over the world [5-9]. In order to slow-down the development and dissemination of resistant bacteria, restrictions on antibiotic prescribing are becoming more widespread [10].

In February 2003, Turkish Ministry of Health released a nationwide regulation for antibiotic re-

striction. According to nationwide antibiotic restriction program (NARP), carbapenems, glycopeptids, piperacillin/tazobactam, ticarcillin/clavulanate were considered as restricted antibiotics that could be used only with the approval of an infectious disease specialist (IDS). Parenteral quinolones, 3(rd) and 4(th) generation cephalosporins, netilmisin, amikacin could still be prescribed by all specialists just for the first 72 h of treatment but further utilization required IDS approval.

In this multicenter study we aimed to assess the impact of the antibiotic restriction policy on the antibiotic use, financial cost and resistance patterns of leading nosocomial pathogens.

Materials and Methods

Hospital setting and antibiotic policy: NARP was initiated in Turkey in February 2003 by a central regulation of Ministry of Health and was announced nation-wide via official newspaper of the state [11]. This is a quasi-experimental study performed in four year period, which included two years before and after of the initiation of NARP in 2003. The study included the data obtained from all of the four university hospitals, and one referral tertiary-care educational state hospital in Ankara. These hospitals have a total of 6668 beds.

Microbiologic studies: Microbiology laboratory results of hospitals were evaluated retrospectively. Significant nosocomial pathogens, namely *Pseudomonas* spp., *Escherichia coli, Klebsiella* spp., *Acinetobacter* spp., *Staphylococcus aureus* obtained from at least one set of blood cultures of the inpatients were included. More than one set of the same isolates from the same patient were counted as one microorganism. All laboratories were using automatic blood culture systems (Bac-Tec® Becton-Dickinson, BacT-ALERT® BioMerieux) and performing antimicrobial resistance testing by Kirby Bauer disc diffusion method according to the recommendations of Clinical Laboratory Standart Institute (CLSI) [12]. Resistance patterns of ciprofloxacin, 3(rd) and 4(th) generation cephalosporins, (ceftazidime, ceftriaxone, cefepime), piperacillin-tazobactam, carbapenems (imipenem, meropenem), aminoglycosides (amikacin, gentamicin) against aforementioned pathogens were analysed. Bacterial idenfications were performed by conventional methods and automatic systems (API 20E® strips BioMerieux, BBL Crystal® Becton-Dickinson).

Antibiotic expenditure and cost: Aggregate amount of antibiotic consumption as total weight (gram) and number of boxes were calculated from two databases, 1) Hospital pharmacy computer databases, and 2) International Medication System (IMS). Because Turkey is an inflation country we have escalated all antibiotic prices. The cost of antibiotics was calculated as US dollars (USD).

Statistical Analysis: Rates in every 6 months periods of the study period were analyzed by comparison of proportions with the chi-square test. Correlations between antibiotic resistance and consumption calculated by two-tailed Spearman's coefficient (r) for non-parametric correlations. A P value of less than 0.05 was regarded as significant. Software package STATA 9.0 (USA) was used for the analysis.

Results

In total, 14,233 microorganisms were enrolled in the study from 2001 to 2005. Of which 5371 were *E.coli*, 1323 *Klebsiella* spp., 1101 *Acinetobacter* spp., 1637 *Pseudomonas* spp., 4801 *S.aureus*. Data on bacterial resistance are summarized in table 1.

Changes in the consumption of given antimicrobials for two years before and after the initiation of NARP can be seen in table 2.

A negative correlation was observed between the ceftriaxone consumption and the prevalence of ceftriaxone resistant *E.coli* and *Klebsiella* spp. (rho:-0.395, p=0.332 and rho:-0.627, p=0.037, respectively).

Inspite of increased consumption of piperacillin-tazobactam after the NARP, the resistance rates of *E.coli* and *Klebsiella* spp. against piperacillin-tazobactam did not increase significantly (rho:0.626, p=0.096 and rho:0.357, p=0.385, respectively).

The decreased use of carbapenems was correlated with decreased rate of carbapenem-resistant *Pseudomonas* spp. and *Acinetobacter* spp (Spearman rho:0.155, p=0.712 and Spearman rho:0.180, p=0.668, respectively).

Ceftazidim utilization and resistance rate of *Pseudomonas* spp. to this agent both had downward tendency after NARP. Also methicillin resistance rates of *S.aureus* were decreased from 44% to 41% during the study period. However, this relationship was not statically significant (p=0,866).

The cost of antibiotic utilization before and after NARP for selected drugs is shown in Table 3. It was found out totally 5,389,155.82 USD saved in the budget for two years period.

Table 1. Impact of NARP* on bacterial resistance rates for the selected antibiotics

	Resistance rate (%)			
	Before NARP 2001 and 2002	After NARP 2003 and 2004	% Difference	*p* Value
E.coli /ceftriaxone	22	34.8	+12.8	NS
E.coli / PIP-TAZO **	16.8	24.3	+7.5	NS
Klebsiella/ceftriaxone	29.3	39.3	+10	NS
Klebsiella/ PIP-TAZO **	25.5	33.8	+8.3	NS
Acinetobacter/imipenem	51.3	45	-6.3	NS
Pseudomonas/ceftazidim	48.5	42.8	-5.7	NS
Staph. Aureus/methicillin	44	41	-3.0	NS

*nationwide antibiotic restriction program, **piperacillin-tazobactam

NS:not significant, p>0.05.

Table 2: Comparison of antibiotic consumption two years before and after the initiation of NARP*

Restricted Antibiotics	Antibiotic consumption (grams)		% difference
	2001+2002	2003+2004	
Meropenem	113362	85236	-24.8
Imipenem	50532	45935.2	-9.1
Ceftazidim	60074	38129	-36.5
Ceftriaxone	300955	190281	-36.8
PIP-TAZO*	270594	417114	+54.1
Cefepime	100588	121799	+21.1
Vancomycin	113362	85236	-17.8
Teicoplanin	50532	45935.2	-1.4
Total	60074	38129	**-11.3**

*nationwide antibiotic restriction program, **piperacillin-tazobactam

Table 3. Comparison of cost of antibiotics

Restricted Antibiotics	Cost (US $)		% difference
	2001+2002	2003+2004	
Meropenem	9,517,646.80	7,156,244.09	-24.8
Imipenem	3,728,250.96	3,389,099.06	-9.1
Ceftazidim	1,559,280.74	989,676.32	-36.5
Ceftriaxone	7,946,415.82	5,024,179.52	-36.8
PIP-TAZO*	2,310,030.91	3,561,111.98	+54.1
Cefepime	1,918,011.98	2,322,463.33	+21.1
Vancomycin	3,403,176.00	2,797,636.80	-17.8
Teicoplanin	17,328,037.09	17,081,283.38	-1.4
Total	**47,710,850.30**	**42,321,694.48**	**-11.3**

*piperacillin-tazobactam

Discussion

Antibiotics are among the most frequently prescribed drugs. A close association exists between resistance rate and the amount of antimicrobial agents used [1]. This indicates a serious need to control antibiotic consumption. Optimization of antibiotic usage not only prevents increase in resistance but also cuts down the healthcare costs.

Several strategies for regulating antimicrobial prescribing have been proposed, such as health care provider educational programmes, development of prescribing guidelines, monitoring resistance patterns, feedback activities, introduction of order forms, formulary replacement or institutional restrictions, and limitation of contacts between physicians and pharmaceutical representatives [13-16]. It has been reported that the requirement for approval from an IDS is the most effective control method [17, 18]. The studies on antibiotic restriction policies are generally about financial concerns and antibiotic utilization but the bacterial resistance are not usually co analysed [19]. We conducted this comprehensive multi centric study to evaluate the effect of a nationwide restriction programme on both antibiotic consumption and antimicrobial resistance rates.

Few hospitals had a restriction policy before 2003 in Turkey. Five tertiary-care educational hospitals from which we collected data for this study had already applied a local antibiotic restriction policy and all five centres had founded infection control committees many years before the initiation of the NARP. Even in these selected centres already applying local antibiotic restriction policies the utilisation of many of the restricted antibiotics was decreased and the trend of resistance rates became downwards after implementation of NARP. The amount of money saved increased further. After two years of NARP 5,389,155.82 USD saving occurred in the selected drugs. The restriction policy has resulted in clear and immediate saving. The long term influence on medical budget may be stronger than the beginning. The financial impact of antimicrobial restriction program has been shown both in developed and developing countries [6, 17, 20-23].

The resistance rates of given microorganisms for all of the antibiotics evaluated were not increased significantly. For instance in spite of increased consumption of piperacilin-tazobactam (TZP) after NARP resistance rates did not increase significantly. This finding for TZP is in accordance with the literature [24]. This finding has revealed that restricted antimicrobials has been started to be utilized more rationale after the initiation of NARP. Also carbapenem resistance rates of *Pseudomonas* spp and *Acinetobacter* spp decreased correlating with decreased consumption of carbapenems after NARP (Spearman rho:0.155, *p*:0.712 and Spearman rho:0.180, *p*:0.668, respectively for imipenem). Falagas *et al*. reported decreased resistance rates of *Pseudomonas aeruginosa* but not of *Acinetobacter baumannii* and *E. coli* isolates by restriction policy [22]. Regal *et al*. have found imipenem resistance of *Pseudomonas aeruginosa* declined fom 20.5% to 12.3% with an 18% reduction in use [25]. A negative correlation was observed between the ceftriaxone consumption and the prevalence of ceftriaxone resistant *E.coli* and *Klebsiella* spp. (Spearman rho:-0.395, *p*:0.332 and Spearman rho:-0.627, *p*:0.037, respectively). This finding may partially be explained by a shift in antibiotic consumption toward unrestricted drugs such as second and third generation oral cephalosporines. High cephalosporine use is a well-known risk factor for emergence of ESBL producing *Enterobacteriacea* [26]. It was shown that inappropriate antibiotic use was significantly higher among unrestricted antibiotics than restricted ones in a study comparing antibiotic utilisation before and after NARP in a single centre from Turkey revealed 125.3% increase in the use of 2nd and 3rd generation oral cephalosporins [27]. Furthermore this finding was confirmed by other studies from different parts of world [21, 22]. The shift toward unrestricted antibiotics changes the antimicrobial resistance patterns of certain pathogens. Since parenteral forms of ciprofloxacin and levofloxacin were not restricted for the first three days of therapy by NARP, the consumption of these quinolones was unsurprisingly high. Besides that the use of oral quinolones for maintenance may contribute to the significant increase in prevalence of quinolone resistant *E.coli* strains [28, 29].

There are several limitations of our study. First, we were not able to investigate whether restrictive use of antibiotics in these five tertiary-care settings was associated with a change in frequency of deaths or nursing expenses. Second, we investigated only the restricted antibiotics because of this we do not know the consumption rate of the antibiotics which can be prescribed by all physicians. Third, the study period after NARP may not be long enough to see the changes in antimicrobial resistance. It should be kept in mind that there is a time lag between antibiotic use and possible changes in antibiotic resistance. Austin *et al*. showed that the time scale for emergence of resistance under constant selective pressure is much shorter than decay time after cessation or decline in the level of drug use [30]. Enne *et al*. showed that a huge decrease in sulphonamide prescribing in the UK did not have an effect on the prevalence of resistance

to this drug in *E.coli* within a useful time [31]. Although this study comprises two years after the initiation of restriction policy there is still a need for continuous surveillance studies to observe the full impact of the NARP. Fourth, we calculated antibiotic consumption in grams instead of using "daily defined dose" (DDD) to evaluate the consumption because of some concerns. The DDD is a technical unit which is the assumed average maintenance dose per day for the drug's main indication in adults and is assigned by the WHO collaborating centre [32]. Expression of data for antibiotic consumption in DDDs might not adequately address differences in dosage and for specific classes of antibiotics between centres. Also, DDDs do not take into account different doses for children. Hence the use of DDDs for adults to express children's consumption might lead to under presentation of this segment of users in total. All five hospitals in this study have their own paediatric disease wards with 839 beds totally.

In conclusion, although our study has aforementioned limitations and the antibiotic restriction is a controversial issue from many points of view (ethical, pharmaceutical, patient benefit etc.), this is the first multi centric study from Turkey which evaluates the effect of NARP on both antibiotic consumption and antimicrobial resistance rates and indicates that NARP in Turkey was effective in lowering the costs and antibiotic resistance.

Acknowledgements

The authors thank to Özay Akan, Yeşim Çetinkaya Şardan, Gülşen Hasçelik, Deniz Gür, Fırdevs Aktaş, Dilek Arman, Nedim Sultan, Bülent Beşirbellioğlu and Esra Karakoç for their kindness in data collection.

Conflict of Interest

The authors have declared that no conflict of interest exists.

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