Revista de Ciências Farmacêuticas Básica e Aplicada
Journal of Basic and Applied Pharmaceutical Sciences

Rev. Ciênc. Farm. Básica Apl., v. 29, n.3, p. 251-256, 2008
ISSN 1808-4532

Educational intervention program to optimize the use of antibiotics: impact on prescribing habits, consumption of antimicrobial agents and cost savings

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Recebido 29/09/2008 - Aceito 17/12/2008

ABSTRACT

Antimicrobials are among the most frequently used drugs worldwide, especially in developing countries, where there are limited data on the use of these therapeutic agents. The Pharmacy Service and the Hospital Infection Control Commission (HICC) of a medium complexity university hospital, concerned about the rational use of broad-spectrum antimicrobials, have devised a sequential intervention program to improve the use of the antibiotics ceftazidime, ciprofloxacin, imipenem and vancomycin in Intensive Care Units (ICUs). The program was developed in three successive steps lasting six months each: baseline data collection (November 2001 to April 2002), initial intervention period (May 2002 to October 2002), educational intervention program (November 2002 to April 2003). All the ICU antimicrobial prescriptions were reviewed and consumption was converted into Defined Daily Doses per 100 patient-days and tabulated to compare different periods and the respective costs. A total of 459 ICU patients were followed through. A change in the profile of antimicrobial prescriptions was observed: a reduction in the use of broad spectrum antimicrobials, reduced number of antimicrobials per patient and improvement in etiological investigation of infection. Significant reductions of ciprofloxacin (69.2%), imipenem (56.3%) and vancomycin (39.0%) consumption were observed. Total cost savings, based on the data for the four drugs, was US$31,523.58 (58.6%). The multidisciplinary educational intervention program was thus responsible for both an improvement in the use of broad-spectrum antimicrobials in the ICU and cost savings.

Keywords: antimicrobial utilization; costs; Defined Daily Dose; critical care.

INTRODUCTION

Antimicrobials are among the most frequently used classes of therapeutic agents worldwide and, on average, represent 35% of the total health care budget in developing countries (Isturiz & Carbon, 2000; Ozkurt et al., 2005). Alert to the hazards associated with untreated bacterial infections, most physicians utilize early empirical prescription of broad-spectrum antimicrobials. The overuse of antimicrobial agents increases drug costs and accelerates the emergence of drug resistance, which may result in a variety of adverse outcomes (Harbarth, 2001; Yoshikawa, 2002; Lutters et al., 2004).

The following strategies are used to promote rational antimicrobial use and limit the emergence and spread of antimicrobial-resistant organisms: education, drug-auditing practices, formulary restriction, pharmacy justification, formulary substitution, computer surveillance and multidisciplinary approaches (Rüttimann et al., 2004; Ozkurt et al., 2005). Education programs play a role of special importance in teaching hospitals, where physicians are well-informed and share opinions. Several studies have shown that guidelines and education intervention programs in hospitals reduce antimicrobial consumption costs (Bassetti et al., 2001; Berild et al., 2001; Bantar et al., 2003; Carling et al., 2003; Cook et al., 2004; Lutters et al., 2004; Rüttimann et al., 2004). The objective of this study was to determine the impact of an educational intervention program, not involving restrictive measures, designed to optimize the use of ceftazidime, ciprofloxacin, imipenem and vancomycin in the intensive care unit at a secondary-care teaching hospital.

MATERIALS AND METHODS

Setting

The study was performed at Hospital Universitário da Universidade de São Paulo (HU-USP) (*São Paulo University Hospital*), in São Paulo, Brazil. This 258-bed teaching hospital offers a medium-complexity clinical service to university students and the local population. The study was an epidemiological, observational, prospective study, performed between November 2001 and April 2003 in the 11-bed adults Intensive Care Unit (ICU).

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Program design.

In 2002, the Hospital Infection Control Commission (HICC) designed a sequential intervention program to optimize the use of 4 broad-spectrum antimicrobials in the Intensive Care Unit (ICU): ceftazidime, ciprofloxacin, imipenem and vancomycin. The program was divided into three successive steps, over 6-month periods, as follows: period 1 (baseline; November 2001 to April 2002) - broad spectrum antimicrobial use estimated by an infectious diseases physician and a pharmacist, both members of HICC; period 2 (initial intervention period; May 2002 to October 2002) - case discussions with responsible physicians and recommendations for more appropriate antimicrobial therapy, the importance of a culture-based treatment being systematically recorded in orders; period 3 (educational intervention program; November 2002 to April 2003) - effective implementation of educational intervention with physicians' compliance.

There were no restrictions on the antimicrobials provided by the Pharmacy Service and no direct interventions on the part of HICC in prescriptions, to maintain physician autonomy. To determine the real impact of the antimicrobial control program, no specific actions were taken by the HICC to control and prevent nosocomial infections (beyond the standard precautions already being undertaken before the study), during the 18-month period of the study.

Data collection

Data were collected from in-patient charts in Adults ICU and the signature of a head nurse indicating the hour, recorded on the prescription, confirmed the administration of the drug. The data were expressed monthly in Defined Daily Doses (DDD) per 100 patient-days for parenteral formulations (Table 1). Data on month-by-month bed utilization in each hospital unit, used in the calculation of the number of patient-days, were obtained from the Medical and Statistical Archives Service.

The consumption of all the antimicrobials during the study was calculated per month and expressed in terms of weight (grams), DDD/100 patient-days and US dollars (April 2006); the purchasing prices used were those in April 2003.

Table 1 - Defined Daily Dose (DDD)

Antimicrobial	DDD (g)
Ceftazidime	4.0
Ciprofloxacin	0.5
Imipenem	2.0
Vancomycin	2.0

Statistical analysis

Having determined the monthly consumption of each antimicrobial and having calculated the corresponding DDD per 100 patient-days, the averages of the data surveyed in each period of six month were compared (November 2001 to April 2002, May 2002 to October 2002 and November 2002 to April 2003), to detect variations among the three consecutive periods, named 1, 2 and 3. In the analysis of the ratios between months, the confidence interval and γ^2 tests were used. The probability of a type I error (α) was taken as 0.05 (5.0%).

Ethical aspects

The investigation was approved by the Research Ethics Committee / Institutional Review Board of the hospital.

RESULTS

All data that related to the prescriptions for patients hospitalized in the ICU between November 2001 and April 2003, to whom at least one antimicrobial drug was given, were compiled. A follow-up was maintained of 459 patients, uniformly distributed across genders and hospitalization periods: 113, 171 and 175, for the first, second and third periods, respectively. The majority was between 55 and 84 years old, and the commonest types of primary infection were respiratory (51%), followed by systemic (14%) and then surgical wound infection (10%).

The total antimicrobial consumption during the study period was 3,113.63 DDD/100 patient-days and the antimicrobials on which the intervention focused, ceftazidime, ciprofloxacin, imipenem and vancomycin, represented 40.33% of overall consumption. In period 1 (November 2001 to April 2002), while the patterns of antimicrobial utilization were established, these four antimicrobials were those most consumed in the ICU, accounting for 53.8% of consumption (Table 2).

Between May and October 2002 (period 2), the ICU physicians began to adapt to controlled use of antimicrobials and the four in question were still among the most heavily consumed drugs, but at a lower rate than before (Table 3). Vancomycin consumption was reduced by 41.3%, a statistically significant decrease ($p<0.05$). There were also reductions in ceftazidime, ciprofloxacin and imipenem consumption (by 17.5%, 59.2% and 55.7%, respectively), but no statistical significance was shown. In the third period (November 2002 to April 2003), in the education intervention phase, the consumption of ciprofloxacin was reduced by 24.6% and that of imipenem by 21.5%, with no significant change in the average consumption between the second and third periods (Table 4).

Table 2 - Antimicrobial consumption, in DDD/100 patient-days (November 2001 to April 2002).

Antimicrobial	Medium ± SD	Total consumption n	%
Ceftazidime	23.19 ± 9.26	139.12	12.86
Ciprofloxacin	23.61 ± 13.20	141.64	13.10
Imipenem	21.22 ± 8.40	127.29	11.77
Vancomycin	28.90 ± 5.72	173.42	16.03
Total	180.26 ± 35.65	1081.56	100.00

SD: standard deviation

Table 3 - Antimicrobial consumption, in DDD/100 patient-days (May 2002 to October 2002).

Antimicrobial	Medium ± SD	Total consumption n	%
Ceftazidime	19.12 ± 6.07	114.74	11.43
Ciprofloxacin	9.64 ± 5.32	57.84	5.76
Imipenem	11.81 ± 4.23	70.85	7.06
Vancomycin	16.97 ± 4.60	101.82	10.15
Total	167.25 ± 25.52	1003.50	100.00

SD: standard deviation

Table 4 - Antimicrobial consumption, in DDD/100 patient-days (November 2002 to April 2003).

Antimicrobial	Medium ± SD	Total consumption n	%
Ceftazidime	20.63 ± 7.65	123.75	12.03
Ciprofloxacin	7.27 ± 3.85	43.60	4.24
Imipenem	9.28 ± 3.69	55.65	5.41
Vancomycin	17.62 ± 4.57	105.75	10.28
Total	171.43 ± 27.67	1028.57	100.00

SD: standard deviation

Comparing the first (baseline) and the third period (education intervention program), there was a statistically significant reduction in consumption of three out of the four antimicrobials under study: ciprofloxacin (69.2%), imipenem (56.3%) and vancomycin (39.0%). The four antimicrobials represented 32.2% of the total antimicrobial consumption in the third period, compared to 53.8% in first (Tables 2 and 4).

The reduced consumption of the four antimicrobials (ceftazidime, ciprofloxacin, imipenem and vancomycin) changed the antimicrobial prescription patterns in the ICU (Table 5). The percentage of patients who received only one antimicrobial rose from 6.2% in the first period (baseline) to 15.8% in the third (education intervention) and the proportion who received 5 or more antimicrobials fell (29.6% in period 1 to 18.8% in period 3).

Total costs associated with the use of the four antimicrobials in the three periods and the percentages of total consumption are displayed in Table 6. Comparing the baseline period and the intervention phase, a reduction of U$1,570.25 (74.0%), U$24,363.39 (64.5%) and U$4,860.09 (47.9%) was observed in ciprofloxacin, imipenem and vancomycin costs. Total costs associated with the use of antimicrobials in the ICU were U$159,502.35, comprising U$68,709.41, U$ 53,361.52 and U$37,449.03 for the first, second and third periods, respectively (Table 6). Total costs related to the use of the four antimicrobials were U$53,755.57, U$27,804.21 and U$22,231.99 for the three periods, respectively. These data show a U$25,951.36 (48.3%) reduction in the cost of using these four drugs during the second period and a further U$5,572.22 (20.0%) during the last, adding up to U$31,523.58 (58.6%) for the whole period.

DISCUSSION

Antimicrobial resistance of bacteria has become a worldwide problem, because of which ineffective or expensive drugs are sometimes selective, prolonging

Table 5 - Numbers of patients for whom each antimicrobial was prescribed in each period.

Antimicrobial	November 2001 to April 2002		May 2002 to October 2002		November 2002 to April 2003	
	N	%	N	%	N	%
Ceftazidime	61	54.0	51	29.8	81	46.3
Ciprofloxacin	36	31.8	26	15.2	26	14.9
Imipenem	44	38.9	38	22.2	37	21.1
Vancomycin	67	59.3	63	36.8	72	41.1
Total	113	100.0	171	100.0	175	100.0

Table 6 - Total cost involved in the use of antimicrobials in the ICU.

Antimicrobial	Period 1	%	Period 2	%	Period 3	%
Ceftazidime	U$3.704.51	5.4	U$2.944.67	5.5	U$2.974.46	7.9
Ciprofloxacin	U$2.123.24	3.0	U$769.08	1.4	U$552.98	1.5
Imipenem	U$37.777.80	55.0	U$18.559.94	34.8	U$13.414.41	35.8
Vancomycin	U$10.150.02	14.8	U$5.530.52	10.4	U$5.290.14	14.1
SUBTOTAL	U$53.755.57	78.2	U$27.804.21	52.1	U$22.231.99	59.3
TOTAL	U$68.709.41	100.0	U$53.361.52	100.0	U$37.449.03	100.00

hospitalization and leading to higher mortality. There is an urgent need to use these drugs more rationally. Education, drug-auditing practices, formulary restriction or substitution, pharmacy justification, computer surveillance and multidisciplinary approaches are strategies that can be used to promote the rational use of antibiotics and limit the emergence and spread of resistant organisms.

The present study was carried out in three consecutive periods. During period 1 (baseline), major problems were detected in the use and prescription patterns of antimicrobials in the HU-USP ICU. It was observed that four antimicrobials (ceftazidime, ciprofloxacin imipenem and vancomycin) were responsible for 53.8% of the antimicrobial consumption, in patient-days (Table 2), and 78.2% of the total costs of antimicrobials in the ICU (Table 6), so the intervention program focused on improving their use. There were also: a low rate of etiological diagnosis, an association of two antipseudomonas drugs in empirical treatment of nosocomial pneumonia (ceftazidime and ciprofloxacin, or ceftazidime and imipenem), early change of the antimicrobial and antimicrobial change without a prior bacterial culture.

The empirical use of broad-spectrum antimicrobials should be governed by the distribution of pathogens and the pattern of sensitivity in the institution and/or ICU, and reassessed on identification of the infecting organism and after performing an antibiogram. Preference should then be given to narrow-spectrum antimicrobials, reducing the unnecessary use of broad-spectrum agents and helping to reduce the development of resistance (Kollef, 2004; Kang et al., 2005).

In the first six months of the educational intervention (May 2002 to October 2002), when the IHCC began making recommendations on orders, physician staff resistance was observed, and there was intense debate as to the antimicrobial indications and review of the literature, especially in regard to combined empirical therapy (two antipseudomonal drugs).

There is evidence that neither traditional education (in class) nor passive distribution of information is effective in changing physician behavior (Bauchner et al., 2001; Schatter et al., 2001). However, group discussions, case studies, recommendations, guidelines, opinion of leaders (specialists) and economic incentives can be more effective (Schatter et al., 2001). Curry (2000) believes that the probability of success in encouraging the adoption of therapeutic standards is increased if an intervention is based on system revisions and meta-analysis or on evidence-based medicine that is simple and consonant with local clinical practice and presents explicit and measurable objectives (Bauchner et al., 2001).

Face-to-face intervention and a careful approach by the staff that perform the intervention are important factors, in view of the reasons presented by doctors for not adhering to the changes, some of which were: loss of physician autonomy, preparation of cost reductions by persons that ignore clinical practice, impracticality, unreliable information, no reliable information, difficulty of assessment and the fact that treatment may be radically different from what is normally employed, etc (Greco & Eisenberg, 1993; Curry, 2000; Elovainio et al., 2000; Garfield & Garfield, 2000).

Despite initial resistance to the program, consumption of the four antimicrobials fell in period 2 and, when periods 1 (baseline) and 3 (intervention) were compared, only ceftazidime did not show any statistically significant reduction in consumption. The change in antimicrobial utilization patterns in the ICU was confirmed

by the smaller number of patients receiving broad spectrum antimicrobials (Table 4) and the reduced number of antimicrobials used per patient. These changes probably resulted from the improved selection of antimicrobials and a culture-based treatment, as well as a longer treatment time before broad-spectrum antimicrobials were used or decreased treatment time and elimination of the combined use of ceftazidime and ciprofloxacin or imipenem to treat *Pseudomonas aeruginosa* infections.

Reduced consumption and, especially, rational use of broad-spectrum antibiotics are recommended as ways to retard the development of bacterial multi-resistance and offer a better chance of providing the correct initial antimicrobial therapy. A decrease in imipenem consumption suggests that the reduction in the use of antimicrobials was not found to aggravate the patients´ clinical evolution, because the empirical use of carbapenems is indicated in the event of therapeutic failure of narrow-spectrum antimicrobials (Ibrahim et al., 2000; Kollef, 2004; Kang et al., 2005).

The cumulative total savings related to the use of ciprofloxacin, imipenem and vancomycin was U$31,260.38 (45.5%). The most significant percent reduction was observed in the use of ciprofloxacin (74.0%), although this represents a cost savings of only U$1,570.25. Additionally, the imipenem and vancomycin reductions were responsible for savings of U$24,363.39 (64.5%) and U$4,860.09 (47.9%), respectively. The total reductions in the cost of the four antimicrobials were 78.2%, 52.1% and 59.3% in the first, second and third periods, respectively.

Overall cost savings reached 58.6%, in agreement with other studies that have demonstrated the positive impact of programs to promote rational antimicrobial use: an educational program in a geriatric university hospital in Geneva was responsible for a reduction of 54% in antimicrobial-related costs (Lutters et al., 2004); in an Italian hospital, after implementation of an antibiotic control program, the usage of and expenditure on the restricted group antibiotics decreased by 78.5% and 53.5%, respectively, resulting in an overall savings of 342,927 Euros (Bassetti et al., 2001); in an Argentinian hospital, a program involving education and prescription control resulted in savings of US$913,236, after two years (Bantar et al., 2003). In Turkey, a restrictive policy resulted in more appropriate antimicrobial use and U$332,000 per year (18.5%) in savings (Ozkurt et al., 2005).

The above results show that the educational intervention program achieved the proposed objectives. Three out of four antimicrobials showed significantly reduced consumption rates, based on improved antimicrobial prescription patterns: (a) lower broad-spectrum antimicrobial consumption; (b) fewer antimicrobials per patient and (c) improvement in etiological investigation of infection. The program had a positive impact on the hospital, with costs savings and more rigorous nosocomial infection control.

ACKNOWLEDGEMENTS

Financial support: University Hospital – University of São Paulo.

RESUMO

Programa de intervenção educativa para otimizar o uso de antibióticos – impacto nos hábitos de prescrição, consumo de antimicrobianos e economia de recursos

Antimicrobianos estão entre os medicamentos mais freqüentemente utilizados em todo o mundo, principalmente nos países em desenvolvimento, onde há dados limitados sobre o uso desses agentes terapêuticos. O Serviço de Farmácia e a Comissão de Controle de Infecção Hospitalar (CCIH) de um hospital escola de média complexidade, preocupados com o uso racional dos antimicrobianos de amplo espectro, elaborou um programa de intervenção seqüencial para otimizar o uso de ceftazidima, ciprofloxacina, imipenem e vancomicina na Unidade de Terapia Intensiva (UTI). As sucessivas etapas foram desenvolvidas durante períodos de seis meses: (Novembro de 2001 a Abril de 2002), o período inicial de intervenção (Maio de 2002 a Outubro de 2002) e programa de intervenção educativa (Novembro de 2002 a Abril de 2003). Todas as prescrições de antimicrobianos da UTI foram revisadas e o consumo convertido em Dose Diária Definida por 100 pacientes-dia realizando a comparação entre o consumo durante os períodos bem como o custo. Os 459 pacientes internados na UTI foram acompanhados e uma mudança no perfil das prescrições de antimicrobianos foi observada como: redução do uso de antimicrobianos de amplo espectro, número menor de antimicrobianos por paciente e melhora na investigação da etiologia da infecção. Observou-se redução estatisticamente significativa do consumo de ciprofloxacino (69,2%), imipenem (56,3%) e vancomicina (39,0%). A economia total considerando o uso dos quatro antimicrobianos foi de US$ U$31.523,58 (58,6%). Conclui-se que o programa de intervenção educativa multidisciplinar foi responsável por melhorar o uso de antimicrobianos de amplo espectro na UTI e na redução dos gastos com antimicrobianos.

Palavras-chave: utilização de antimicrobianos; custos; Dose Diária Definida; unidades de terapia intensiva.

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