The utilization patterns of vancomycin, metronidazole, ceftriaxone, and ceftazidime in the ICU ward of a public hospital of Tehran Medical University: a cross-sectional study

Mansoor Rastegarpanah[a], Sara Safaee Rad[a], Mandana Moradi[b], Fatemeh Izadpanah[c]

[a]Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, [c]Food and Drug Laboratory Research Center, Food & Drug Administration of Iran, MOHME, Tehran, [b]Department of Clinical Pharmacy, Faculty of Pharmacy, Zabol University of Medical Sciences, Zabol, Iran

Correspondence to Dr. Fatemeh Izadpanah, Food and Drug Laboratory Research Center, Food & Drug Administration of Iran, MOHME, Tehran, P.O. Box: 1457886619, Iran.
Tel: +989 122 116 375; fax: 00982166434572;
e-mail: achpharmacy@gmail.com

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Introduction
Pharmacoepidemiology is a relatively new scientific topic, and it's the concepts, methods, and implications are in line with the observations of health studies in the past few decades. It involves the postmarketing investigations, drug utilization review, and the monitoring of both adverse drug reactions and the clinical efficacy of drugs. The Anatomical Therapeutic Chemical classification system as a drug classification method and the defined daily dose (DDD) as a measurement unit have been recommended by WHO for drug utilization studies.
Patients and methods
This was a prospective cross-sectional study. It was done using the Anatomical Therapeutic Chemical/DDD system and by calculating DDD per 100 bed-days (BDs) for four antibiotics, namely, vancomycin, metronidazole, ceftriaxone, and ceftazidime, used in 78 patients admitted in the internal medicine ICU ward in a hospital of Tehran University of Medical Sciences from April to October 2018.
Results
The DDD/100 BDs for ceftazidime, ceftriaxone, metronidazole, and vancomycin was 5.96, 4.17, 9.65, and 28.02, respectively.
Conclusion
Comparing the results of the current study with those of similar studies, it was found that the DDD/100 BDs for ceftazidime, ceftriaxone, and metronidazole is within the normal range, whereas that of vancomycin was much higher than normal.

Keywords:
antibacterial agents, cross-sectional studies, drug utilization review, ICUs, treatment outcome

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Introduction

Antibiotic is a substance produced by or extracted from a microorganism, which can be used to kill or hinder the activity of other microorganisms [1]. This definition comprises all kinds of antibiotics, including synthetic antibiotics like sulfonamides and quinolones. Antibiotics are different in their chemical, physical, and pharmacological qualities; their antimicrobial spectrum; and mechanism of action [2]. Broad-spectrum antibiotics are those with activity against a variety of microorganisms, for example, tetracyclines, which are active against many gram-negative bacteria, chlamydia, mycoplasma, and rickettsia [3]. The narrow-spectrum antibiotics are those with activity against only one type of microorganism or a very limited spectrum of microorganisms, for example vancomycin, which is almost active against gram-positive cocci like staphylococci and enterococci [2]. The purpose of pharmacoepidemiological studies was initially the detection or recording of drug utilization-associated diseases to find or treat the adverse drug events [4]. However, over the recent years, its purposes have been extended to the study of drug utilization reviews (DUR), physicians' prescription habits, the efficacy of drugs, the chronic toxicity of drugs, informing the medical team of drug complications, monitoring the pharmacological treatment, assisting in drug pharmacoeconomic analysis, and collecting information regarding the new indications of a drug [4]. Overall, the purpose of pharmacoepidemiology is the discussion, explanation, control, and prediction of the effects and implications of pharmacological treatment within a specified time, place, and population [5]. The most important implication of pharmacoepidemiology is to lay the groundwork for pharmacoeconomic analyses, especially in predicting the costs of pharmacotherapy in different countries. Pharmacoepidemiological studies facilitate the

comparison of drug utilization patterns among different places and point out the problems associated with it. Excessive prescriptions and drug abuses are determined with minimal data. The drug utilization monitoring programs are then placed within the task list of drug utilization committee [6]. Pharmacoepidemiology involves the postmarketing investigations, DUR, and the monitoring of both adverse drug reactions and the clinical efficacy of drugs. The Anatomical Therapeutic Chemical (ATC) classification system as a drug classification method and the defined daily dose (DDD) as a measurement unit have been recommended by WHO for drug utilization studies [7]. The ATC/DDD system is a useful tool to analyze the medical statistics available in the different ranks of the health chain [8].

This study was done using the ATC/DDD system to review the drug utilization patterns of four antibiotics, namely, vancomycin, metronidazole, ceftriaxone, and ceftazidime, in the internal medicine ICU ward of Tehran Dr Shariati Hospital in 2018.

Patients and methods

This was a prospective cross-sectional DUR study, which was done using the ATC/DDD system in the internal medicine ICU ward of a hospital in Tehran University of Medical Sciences from April to October 2018. A total of eight fixed active internal medicine ICU beds were involved during the study. The medical cases of 78 patients admitted in the internal medicine ICU ward were reviewed over the 6 months of study, and the data regarding the drugs used, the pharmaceutical forms, and the dosage were extracted. As the necessity of a standard method, which could be comparable in different places and times, the international ATC/DDD system was used in this study. A standard questionnaire was designed to record the extracted data from patients' medical cases. The method of use in this study was the ATC/DDD system, and the scale unit was the DDD. The drugs studied in the current study are categorized as group J of ATC classification. Using the used dosages and calculating the DDDs, the total DDD for each drug was calculated. Then, using the bed-days (BDs) for each ward, DDDs for each 100 BDs were calculated. SPSS, version 18.0 for Windows (SPSS Inc., Chicago, Illinois, USA) and EXCEL were used to analyze the data. Finally, the results were compared with the national and international standards. This study was approved by the institutional review board of Tehran University of Medical Sciences, and permission was obtained from Shariati Hospital for data collection.

We have obtained consent to publish from the participant.

Results

The number of antibiotic administrations are shown totally and by month in Tables 1 and 2, respectively. The utilized doses of antibiotics (per grams) are shown totally and by month in Tables 3 and 4, respectively.

The occupied bed-days data

The number of occupied BDs in the internal medicine ICU ward of Dr Shariati Hospital in different months during the study is shown in Table 5.

Table 1 The number of antibiotic administrations during the study

Numbers	ATC code	Drug name	Administrations
1	JO1D	Ceftriaxone	21
2	JO1D	Ceftazidime	25
3	JO1X	Vancomycin	63
4	JO1X	Metronidazole	20

ATC, Anatomical Therapeutic Chemical.

Table 3 The utilized dose (g) of antibiotics during the study

Numbers	ATC code	Drug name	Dose (g)
1	JO1D	Ceftriaxone	90
2	JO1D	Ceftazidime	257
3	JO1X	Vancomycin	603.75
4	JO1X	Metronidazole	156

ATC, Anatomical Therapeutic Chemical.

Table 2 The number of antibiotic administrations by month during the study

Numbers	Month	Drug name			
		Ceftriaxone	Ceftazidime	Vancomycin	Metronidazole
1	April	3	3	9	2
2	May	4	5	12	4
3	June	5	3	14	2
4	July	3	7	9	5
5	August	2	5	10	2
6	September	4	2	9	5

Table 4 The utilized dose (g) of antibiotics by month during the study

Numbers	Month	Drug name			
		Ceftriaxone	Ceftazidime	Vancomycin	Metronidazole
1	April	13	5/44	108	24
2	May	17	39	75/109	26
3	June	15	5/48	101	26
4	July	16	46	96	29
5	August	15	40	94	23
6	September	14	39	95	28

Table 5 The occupied bed-days of the internal medicine ICU ward by month

Numbers	Month	Occupied bed-days
1	April	178
2	May	179
3	June	182
4	July	177
5	August	183
6	September	178
7	October	1077

The calculation of defined daily dose/100 bed-days

The DDD/100 BDs was calculated using the data in Tables 3 and 5. The results are shown in Table 6 and Fig. 1 by month for each drug.

The cost estimation of utilized antibiotics (per rial) during the study is shown in Table 7.

The quality evaluation of antibiotics utilization based on drug administration protocols

According to the quality evaluation of antibiotics administrations, 17.4% of administrations were not in line with the defined drug administered protocols.

Discussion

Nowadays, antibiotics comprise the greatest proportion of administered medications. Every year, ~235 billion units of various antibiotics are consumed all over the world [9,10]. Antibiotic resistance is one of the major health issues of countries. This can endanger in particular those with an uncomplicated infection, who could have been treated under the supervision of a physician by a simple antibiotic, while owing to the previous unnecessary consumption of such antibiotics, had left them ineffective [9,11].

Keeping in mind the indispensability of antibiotics in the treatment of various infections, it is predictable that through the increase in the rate of microorganisms' resistance to the different mechanisms of antibiotics, the human and animal populations will be exposed to circumstances when most of the common antibiotics will lose their effectiveness. Hence, studies on the antibiotic utilization patterns and monitoring of microorganisms' resistance toward antibiotics will be essential [12].

Studies on the different aspects of antibiotics utilization patterns on an international and national scale in terms of the ethnicity and race and so forth at a country, state, and city level increased the precision of such utilization patterns dramatically [13]. To perform fundamental and practical studies, the hospitals and the different wards within them should be the bases of scheduled continuous studies, as many such have been done both in different parts of Iran and globally [14].

These studies can not only contribute to a decrease in the antibiotic resistance rate but also can correct the wrong utilization patterns and indicate the excess utilization of antibiotics, as well as can reduce the burden of therapeutic costs and hence, the need for production or import of drugs.

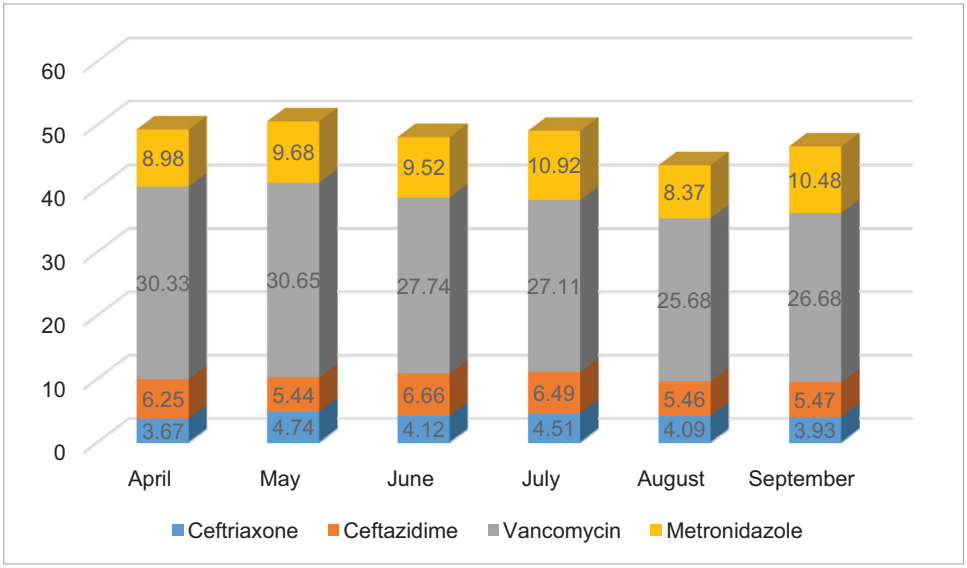
A principal rule of using ATC/DDD methodology in DUR studies is the possibility to compare the utilization patterns internationally and study them over a prolonged period. To compare the data of different countries and different times, it is necessary to know the ATC codes and DDD values used in each study. As only a very few studies report their DDD values, drawing comparisons is not so feasible [15,16]. Nevertheless, this methodology is still more valid than other systems used to compare drug utilization in different levels.

In this study, the utilization patterns of four antibiotics, namely, vancomycin, metronidazole, ceftriaxone, and ceftazidime, were determined based on data from the internal medicine ICU ward of Dr Shariati Hospital. As shown in Table 1, it was demonstrated that vancomycin had the greatest number of utilization with 63 administrations during the study, followed by ceftazidime, ceftriaxone, and metronidazole, in order, which showed values of 25, 21, and 20,

Table 6 The calculated defined daily dose per 100 bed-days by month

Numbers	Month	Drug name			
		Ceftriaxone	Ceftazidime	Vancomycin	Metronidazole
1	April	67.3	25.6	33.30	98.8
2	May	74.4	44.5	65.30	68.9
3	June	12.4	66.6	74.27	52.9
4	July	51.4	49.6	11.27	92.10
5	August	09.4	46.5	68.25	37.8
6	September	93.3	47.5	68.26	48.10
7	October	17.4	96.5	02.28	65.9

Figure 1



The calculated defined daily dose per 100 bed-days (BDs) (DDDs/100 BDs) by month. DDD, defined daily dose.

Table 7 The cost estimation of antibiotics utilized during the study per rial

Numbers	Drug name	Cost (rial)	Percent
1	Ceftriaxone	2 430 000	2.9
2	Ceftazidime	9 105 000	10.8
3	Vancomycin	60 375 000	72
4	Metronidazole	11 856 000	14.3
5	Total	83 766 000	100

respectively. The highest utilized dose of antibiotics was also for vancomycin with 603.7 g over 6 months of study, whereas ceftazidime, ceftriaxone, and metronidazole showed utilized doses of 257, 156, and 90 g, in order, respectively. As vancomycin is an antibiotic with no similarity with other antibiotics available in market and can be used orally, by injection, and as ophthalmologic drops in patients with infections resistant to other antibiotics or in case of beta-lactam allergy, its highest rate of utilization can be explained for by its higher rate of use for severe or highly resistant infections and its use for empiric treatments without performing any culture and antibiogram test. However, this has led to the increase in microorganism resistance toward such antibiotic [17,18].

In this study, the DDDs/100 BDs ratios were determined. Despite multiple studies performed in Iran on the utilization pattern of antibiotics in the hospitals and different wards within them, the findings were focused more on the total amount of utilized antibiotics; thus, to our knowledge, no distinct data regarding the utilization of studied antibiotics in the internal medicine ICU wards of other hospitals were found. Therefore, the results of this study were solely compared with the results of similar studies in other countries.

The DDDs/100 BDs ratio of the current study for vancomycin was 28.02, which was higher than those of other countries, which had indicated ratios of 9.8 (1998–2000), 4.9 for educational, and 3.7 for noneducational (2001–2002) hospitals of Germany; 10.6 for southwest (1999) and 1.6 for east France (2001); 6.9 for educational and 3.5 for

noneducational hospitals of Switzerland (2008); 9.9 for India (2008); 0.01 for Turkey (2001–2006); 10.1 for Netherland (2005); and 19.18 for Italy (2004) hospitals [19–25].

Furthermore, the DDDs/100 BDs ratio of this study for ceftriaxone was 4.17, which in comparison with those of other studies is roughly at an average level, with reported ratios of other studies as 3.3 for southwest (1999) and 0.81 for east France, 1.9 for educational and 3.1 for noneducational hospitals of Switzerland (2008), 2.9 for Indonesia (2003), 2.9 for India (2008), 1.9 for Spain (1992), 4.2 for Turkey (2001–2006), 3.1 for the Netherland (2005), 0.54 for Germany (1991–1996), and 5.5 for Italy (2004) hospitals [23–26].

The DDDs/100 BDs ratio of this study for ceftazidime was 5.96, which in comparison with those of other studies is also roughly at an average level, with reported ratios of other studies as 4.4 for southwest (1999) and 1.12 for east France, 2.1 for educational and 3.3 for noneducational hospitals of Switzerland (2008), 4.1 for Indonesia (2003), 4.1 for India (2008), 1.75 for the occupied Palestine (1991–1996), 5.2 for Turkey (2001–2006), 3.3 for the Netherland (2005), 0.14 for Germany (1991–1996), and 6.4 for Italy (2004) hospitals [23,25,26].The DDDs/100 BDs ratio of this study for metronidazole was 9.65, which in comparison with those of other studies is also roughly at an average level, with reported ratios of other studies as 10.1 for Germany (1998–2000), 12.2 for southwest France (1999), 3.32 for Indonesia (2003), 3.18 for Estonia (1995), 1.9 for Switzerland (1992), 6.12 for India (2008), 0.38 for Germany (1991–1996), and 9.87 for Sari Imam Khomeini Hospital of Iran (2000) [20,21].

According to the results of this study, 17.4% of the administrations of these antibiotics were irrational, with a total cost of 14 357 492 rials associated with it had been unnecessary. While including other associated costs, this could be stated that a much higher cost had been unnecessarily imposed on the health system for the 78 patients studied during current study. The most important limitations of the present study were as follows: one, it was a descriptive study, where the specific limitations of such studies should be considered when analyzing the results, and two, the study sample sizes were small, which may affect study power.

Conclusion

The present study showed that the utilization patterns of ceftazidime, ceftriaxone, and metronidazole in selected hospital were found to be virtually similar to global values.

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Availability of data and materials: The data set used in this study is available with the authors and can be made available upon request.

Authors' contributions: All the authors participated in the study design. Fatemeh Izadpanah and Mansoor Rastegarpanah collected and documented the data and assisted in preliminary data analysis. Sara S. Rad and Mansoor Rastegarpanah wrote the initial draft. Fatemeh Izadpanah participated in draft revision, data analysis, and editing of the final draft.

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Conflicts of interest

There are no conflicts of interest.

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