



Cephalosporins Usage in Hospitals Before and After Iran's Health Reform Plan



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ABSTRACT

Background: This study aimed to investigate the usage patterns of some parenteral cephalosporins in hospitals affiliated to Shahid Beheshti University of Medical Sciences. The study design consisted of one year before and one year after the implementation of Health Reform Plan (HRP) in Iran.

Methods: The data were collected from 6 university hospitals, including Taleghani, Mofid, Akhtar, Loghman Hakim, Shohadaye Tajrish, and Mahdieh hospitals from 2014 to 2015. The obtained data were analyzed using the GraphPad Prism software. The total consumption of parenteral cephalosporins in the 6 hospitals was expressed in Defined Daily Dose (DDD) per 100 Bed Days (BD).

Results: DDD/100 BD increased from 149.132 to 149.454 DDD/100 one year following the implementation of HRP. This data indicates that the consumption of cefazolin, cefotaxime, ceftizoxime, ceftriaxone, ceftazidime, and cefepime were not significantly changed. Although lower doses (g/d) of ceftizoxime and cefotaxime were used, compared to the standard doses in hospitals, the consumed dose of ceftriaxone (g/d) was significantly higher than the standard DDD.

Conclusion: The obtained results suggest that the HRP was probably not effective in improving irrational antibiotic consumption in Iran. Thus, it is necessary to employ stewardship programs to control such irrational usage. This program should be conducted under the supervision of clinical pharmacists and infectious disease specialists.

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1. Introduction

Medications are one of the most important ways of treating a disease; however, an irrational use of drugs, along with a non-effective treatment, can cause adverse effects. Bacterial resistance to antibiotics, the lack of optimal treatment, adverse effects, and undesired complications are some of the probable consequences of an irrational use (based on irrational prescription) of antibiotics [1].

Antibiotic resistance is the most prevalent complication in the treatment of microbial infections. The alarming rise of antibiotic resistance and the emergence of resistant strains highlight the need for developing therapeutic guidelines for managing infectious diseases. This can be achieved by summarizing and analyzing worldwide studies. Antibiotic overuse may extinct pathogenic agents; however, this might also have numerous complications. The most important of which is the selection of resistant strains and the acquisition of resistance [2].

The rational prescription of antibiotics requires a rather thorough knowledge of pharmacological and microbiological principles and informed clinical judgment. Furthermore, patients' conditions and the nature of disease should also be taken into account. However, such matters are often ignored when deciding to prescribe antibiotics [2]. The study of antibiotic usage in hospital settings is important. This is because of their high cost, adverse effects, the odds of mortality and disability, high rates of hospital infections, and the chance of bacterial resistance [3].

To address this issue, a technical unit of measurement, called the Defined Daily Dose (DDD) was developed. The DDD enables us to observe changes in drug consumption over time, make international comparisons, evaluate the outcome of a medication use intervention, document the relative therapy intensity with the various groups of medications, follow the changes in the use of a class of medications, and evaluate regulatory effects and the interventions impact on prescribing patterns [4]. The current study aimed to investigate the usage of some parenteral cephalosporins in hospitals affiliated to Shahid Beheshti University of Medical Sciences one year before and one year after the implementation of Iran's Health Reform Plan (HRP).

2. Methods

In this retrospective, descriptive, and analytical study, data on the consumption of certain parenteral cephalosporins expressed in DDD per 100 Bed Days (BD) were

collected from 6 hospitals affiliated to Shahid Beheshti University of Medical Sciences, as follows: Taleghani Hospital, Mofid Hospital, Akhtar Hospital, Loghman Hakim Hospital, Shohadaye Tajrish Hospital, and Mahdih Hospital. The consumption (mg) of cephalosporins, including cefazolin 250, cefazolin 500, cefazolin 1000, cefuroxime 750, cefuroxime 1500, ceftizoxime 500, ceftizoxime 1000, ceftriaxone 250, ceftriaxone 500, ceftriaxone 1000, cefotaxime 500, cefotaxime 1000, ceftazidime 500, ceftazidime 1000, ceftazidime 2000, cefepime 500, cefepime 1000, and cefepime 2000 mg were assessed.

These medications were analyzed to investigate their usage based on Anatomical Therapeutic Chemical classification and the DDD (ATC/DDD) one year prior to and following the HRP implementation. We also explored the role of clinical pharmacists in drug consumption patterns in hospitals. Taleghani, Mofid, and Loghman Hakim Hospitals used clinical pharmacists' services; while the other three hospitals, including Shohadaye Tajrish, Akhtar, and Mahdih had no present clinical pharmacist.

Data analysis was performed based on the ATC/DDD method, which has been proposed by the World Health Organization for Drug Utilization Research (DUR). The achieved results were expressed in DDD/100 BD. Calculations were performed using the DDD/100 BD equation. DDD/100 BD is equal to (the number of vials of consumed drug × the dose of each vial × 100 beds divided by DDD [standard drug × the number of days × the number of beds × occupancy rate]). Data were analyzed using the PRISM software.

3. Results

In all hospitals, cefazolin consumption expressed in DDD and g/d before and after the implementation of the HRP did not significantly change during the HRP implementation ($P=0.9221$ and 0.7564 , respectively). In addition, the amount (g/d) of consumed cefazolin was consistent with the standard DDD ($P=0.7833$ and 0.8334 , respectively). Similarly, there was no significant difference in the amounts of consumed ceftizoxime expressed in DDD and g/d before and after the HRP implementation in all hospitals ($P=0.9999$ and 0.8340 , respectively). In addition, this study revealed that the amount of ceftizoxime (g/d) consumption before and after the HRP implementation was significantly lower than the standard DDD in all hospitals ($P=0.0016$ and 0.0015 , respectively).

Table 1. Parenteral cephalosporins consumption in the studied hospitals based on gram and DDD/100BD

Antibiotics	One Year Before HRP Implementation, gr	One Year Before HRP Implementation, DDD/100BD Mean±SD	One Year After HRP Implementation, gr	One Year After HRP Implementation, DDD/100BD Mean±SD
Cefazolin	193877.75	85.66±14.27	207894	81.79±13.63
Cefuroxime	0	0±0	0	0±0
Ceftizoxime	2450.5	0.70±0.11	1762.5	0.46±0.07
Ceftriaxone	106037.5	49.51±8.25	116020.5	51.82±8.63
Cefotaxime	2097	0.58±0.09	11250	2.78±0.460
Ceftazidime	41553	9.99±1.66	47046.5	10.49±1.74
Cefepime	5668.5	2.67±0.44	6802	2.08±0.34
Total	351684.25	149.13±24.85	390775.5	149.45±24.900



Likewise, the amount of consumed ceftriaxone expressed in DDD and g/d before and after the HRP implementation had no significant difference in any of the hospitals ($P=0.9050$ and 0.5714 , respectively). In all hospitals, the amount (g/d) of ceftriaxone consumption before the HRP implementation was not significantly different from the standard DDD ($P=0.0625$); however, this amount (g/d) increased following the HRP implementation and revealed a slight deviation from the standard DDD in all studied hospitals ($P=0.0405$). In all studied hospitals, the amount (DDD and g/d) of consumed cefotaxime before and after the HRP was not significantly different ($P=0.1688$ and 0.152 , respectively).

However, the amount (g/d) of cefotaxime consumption was significantly lower than the standard DDD before and after the HRP implementation in all studied hospitals ($P=0.0034$, and $P<0.0001$, respectively). The amount (DDD and g/day) of consumed ceftazidime before and after the HRP implementation was the same in all hospitals ($P=0.8983$ and 0.6445 , respectively). Accordingly, the amount (g/d) of ceftazidime consumption before and after the HRP implementation was not significantly different from the DDD ($P=0.3227$ and 0.1492 , respectively).

In the case of cefepime, the consumption amount (DDD/100 BD and g/d) before and after the HRP implementation was not significantly different in any of the hospitals ($P=0.8312$ and 0.7165 , respectively), as well. Moreover, the amount (g/d) of consumed cefepime before and after the HRP implementation was not significantly different from the standard DDD in any of

the hospitals ($P=0.3269$ and 0.7971 , respectively). We investigated the two types of general and specialized hospitals. There was no significant difference between these two types of hospitals in terms of the studied parameters.

4. Discussion

There was no statistically significant difference in cephalosporin consumption in the studied hospitals; however, a slight increase in the consumption of most kinds of cephalosporins was evident after the HRP implementation (Table 1). This fact is directly correlated with the hospital occupancy rate, which was increased in all of the studied hospitals during the HRP courtesy of a dramatic decrease in out-of-pocket expenses for inpatients. In other words, the total consumption of parenteral cephalosporins in the hospitals rose from 149.132 to 149.454 DDD/100 BD over the one-year period after the implementation of plan.

We examined the use of some parenteral cephalosporins in 6 hospitals affiliated to Shahid Beheshti University of Medical Sciences. ATC/DDD is among the DUR methods, which can compare drug usage on national and international scales. This method is used to assess drug usage in the long term, determine the factors affecting drug usage, examine the safety of drugs, and avoid unnecessary prescriptions [5]. However, data obtained from the DUR expressed in DDD only represents a raw estimate of how the drug is consumed and fails to provide accurate details of drug usage. Therefore, we first used the DDD/100 BD equation for two one-year

periods, one year before the implementation of the HRP, and one year after that.

The daily consumed dose of cefazolin in the hospitals was reasonable; thus, the current microbial resistance to this drug can be attributed to its longer treatment duration in the past years. The lower consumption of ceftizoxime, compared to the standard DDD in the hospitals was probably due to its common indication in the hospitals as a prophylactic agent. In addition, the obtained results indicated that after the implementation of the HRP, the consumed dose (g/d) of ceftriaxone exceeded the standard DDD; this should be managed to avoid certain complications like microbial resistance to antibiotics. Moreover, irrational use consists of excessive consumption and low-dose consumption, which may lead to bacterial resistance. Similarly, ceftizoxime may have been more often used in these hospitals as a prophylactic agent, which could explain the difference between the consumed daily dose of drug and the standard value.

The amount of antibiotic consumption in the Intensive Care Unit (ICU) of Valiasr Hospital in Zanjan was reported to be 5.45 DDD/100 BD [6]. In the first 6 months of 2005, the use of antibiotics in the ICU of Imam Khomeini Hospital in Sari was reported to be 124 DDD/100 BD, which reflects the high rate of antibiotic consumption [7]. In two studies conducted in Iran, Imam Khomeini Hospital in Sari and Boali Hospital in Tehran, cefazolin, ampicillin, ceftizoxime, and gentamicin were the most frequently used antibiotics.

The increased prevalence of vancomycin-resistant Enterococci following the high consumption of vancomycin and the third generation of cephalosporins are concerning. Therefore, it seems more necessary than ever to consider the rational use of these drugs in the future. Reducing the use of these antimicrobial agents can prevent the spread of resistant microorganisms [8]. Additionally, there may be various reasons for the difference in the observed patterns of antibiotic usage in various studies. For example, the policy of imposing restrictions on the administration of the third generation of cephalosporins in European hospitals should be considered among such reasons [9, 10].

Other possible causes are the impact of racial differences and environmental conditions, different diseases, educational status, and inefficiency or the lack of active surveillance systems in hospitals. Limited available drugs in pharmacies, the problem of bioavailability, and the physicochemical properties of formulation of drugs

produced in Iran can also bear on this issue. Therefore, for a more in-depth exploration of the pattern of antibiotic usage and the reasons for consuming a certain type of antibiotics, qualitative studies on drug usage are required. To prevent the irrational consumption of antibiotics, measures should be taken at both micro and macro levels. These measures may include simple methods such as the provision and enforcement of standard therapeutic guidelines and leaflets providing information on antibiotic prescription order along with correct dosage, and academic detailing for physicians [11, 12].

The results of this study suggested that after the implementation of HRP, the occupancy rate increased in all of the 6 hospitals. This was because in this plan, the inpatients were required to only pay for 6% of their treatment cost in the hospital. In addition, following the increased occupancy rate in the hospitals since the implementation of HRP, the consumption of these antibiotics (g) was increased, as well. Furthermore, the total amount of consumed cephalosporins in the 6 hospitals rose from 149.132 DDD/100 BD over the one-year period before the implementation of HRP to 149.454 DDD/100 BD over the one-year period after its implementation.

A similar study was conducted in Israel in 6 general hospitals. The researchers investigated the consumed amount of antibiotics expressed in DDD/100 BD. The total amount of consumed penicillins, cephalosporins, fluoroquinolones, and macrolides as well as a number of other antibiotics was studied [13]. The average consumption of the first generation cephalosporins was found to be 1.5 DDD/100 BD, the second generation cephalosporins was 14.3 DDD/100 BD, the third generation cephalosporins was 5.3 DDD/100 BD, and the fourth generation cephalosporins was 1.3 DDD/100 BD.

Despite the limitations in the comparison of the obtained results, the average consumption of cefazolin was much higher in Israeli hospitals than that of the first generation cephalosporins. In addition, the average consumption of ceftriaxone, ceftizoxime, cefotaxime, and ceftazidime was higher than that of the third generation cephalosporins in Israeli hospitals. The consumed doses of cefazolin and ceftazidime per day both before and after the HRP implementation were not significantly different from the standard DDD (1); however, the consumed doses (g) of cefotaxime and ceftizoxime per day before and after the implementation of HRP were lower than the standard DDD (2). Moreover, in the case of ceftriaxone, only after the HRP implementation,

the consumed dose (g/d) was higher than the standard DDD (3).

Therefore, extensive studies are required to explore the reasons for the high consumption of antibiotics in terms of DDD. Additionally, using antibiotics as a prophylactic agent for surgeries (especially selective ones) is considered as an irrational use of those. In conclusion, the HRP had no effect on the amount of consumed doses of these drugs expressed in DDD and g/d.

5. Conclusion

Cefazolin was practically less frequently used in the 6 studied hospitals. In most cases, vancomycin was used as an alternative. The consumed dose per day in these hospitals was higher than the standard DDD after the HRP implementation. This fact is very important and requires careful planning and budget allocation to educate physicians and medical teams on the correct usage of antibiotics.

It is also recommended to consider the presence of clinical pharmacists in hospitals. As for the use of ceftazidime in Loghman Hakim Hospital, after the recruitment of a clinical pharmacist, the consumption of this drug per day approached the standard value. However, ceftazidime was reported to be used as a prophylactic agent before performing neurosurgery on some patients. In addition, after surgery courtesy of a lack of supervision over physicians' performance, patients received several medications for several days until the clinical pharmacist intervened to discontinue the medication.

In Mofid Children's Hospital, after the implementation of HRP, as well as the antibiotic stewardship program by clinical pharmacists and because of the lack of piperacillin/tazobactam to manage *Pseudomonas* and Extended Spectrum Beta-Lactamase (ESBL) producing bacteria, the amount of cefepime consumption per day was increased. Finally, for the rational usage of antibiotics, the supervision of an infectious disease specialist (rather than a general physician) on the administration of antibiotics, prescribing antibiotics based on an antibiogram, developing a guideline on antibiotics and distributing those in pharmacies are necessary. Moreover, conducting certain interventions to train physicians and review their feedbacks can be the issues of vital importance for the authorities.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences.

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Conflict of interest

The authors declared no conflict of interest.

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