Eur J Clin Pharmacol (2001) 57: 547–551
DOI 10.1007/s002280100351

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

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Use of systemic anti-infective agents in Iran during 1997–1998

Received: 5 January 2001 / Accepted in revised form: 2 July 2001 / Published online: 25 August 2001

Abstract *Objective*: Conduction of standardized national drug utilization review to investigate the pattern of systemic anti-infective agent use in Iran.
Methods: The wholesale data were used. The Anatomical Therapeutic Chemical (ATC) classification and the defined daily dose (DDD) methodology was employed. Data were presented as DDD/1000 inhabitants/day. Results were compared using national drug statistics of Norway, Sweden, and Denmark.
Results: The overall sales of systemic anti-infective agents was 43.5 DDD/1000 inhabitants/day. The parenteral form of drug accounted for 4.20% and broad-spectrum systemic antibacterial agents accounted for 86.2%. The three most commonly used agents, accounting for 74.1% of total sales, were amoxicillin, co-trimoxazole, and ampicillin. Seven kinds of anti-infective agents (17% of total available agents) accounted for 90% of antibacterial use, with dominance of broad-spectrum agents. Comparison showed differences in pattern and intensity of use. The sales of systemic anti-infective agents in general, particularly antibacterials and anti-tuberclotics, were greater in Iran than in three European countries. Broad-spectrum antibacterial agents accounted for a larger proportion of total sales in Iran.
Conclusion: The high use of systemic antibacterial agents in general, particularly broad-spectrum agents, suggest the possibility of irrational prescribing, higher prescribed daily doses than DDDs, and a drug wastage. This survey, as a first attempt, provided an overview of anti-infective use in Iran. Thus, it may serve as a basis for further investigative studies and advanced drug policies.

Keywords Anti-infective utilization · Antibacterial utilization · DUR · Iran

Introduction

The important therapeutic rule played by antibiotics coupled with the ongoing threat of bacterial resistance are compelling reasons for concern about adequate and appropriate use of these agents. The World Health Organization (WHO) estimates that up to 40% of health care costs may be for drugs. Furthermore, antibiotics account for 15–30% of drug expenditures, the largest share of any other therapeutic drug group. Antimicrobial agents make up a large proportion of the costs of the health care system in developing countries. These nations have severe problems in providing their vast populations with these essential drugs. They must spend a disproportionately larger amount of their resources on these agents than on other medical services, a situation that is critical with antimicrobial agents because of the proportionately greater frequency of infectious diseases, particularly among children, in these countries [1, 2].

In an era when cost-containment strategies are being developed, detailed information relating to antibiotic use has become critical. There are only limited data concerning the patterns of use of antimicrobial agents in the developing countries. Much of the current information is anecdotal [1]. Information on antibiotic use on a national level is scanty, and hospital use is a minority element in total drug use in much of the developing world. The types of data needed for an assessment of whether antibiotics are adequately and appropriately used are not widely available. Although many countries currently collect national data on antibiotic use, lack of standardized data collection system makes comparisons

A part of this study was accepted for poster presentation at the 16th International Conference on Pharmacoepidemiology – August 2000, Barcelona, Spain.

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difficult. Given the potential applications of such data, it would be invaluable to have uniform data-collection systems at a national level around the world [3].

In Iran, according to data published by the Food and Drug Affaires of the Ministry of Health, anti-infective agents accounted for 24% of total drug sales during 1995 and 1996, the largest share relative to any other drug group. Antibacterial agents accounted for three of the top five drugs by volume.

Limited unpublished surveys indicate that antibacterial agents are the most prescribed class of drugs. Nevertheless, drug utilization research (DUR) studies are generally scarce in Iran. This study was carried out to evaluate the incidence and type of antibiotic use in Iran using a standardized and internationally accepted methodology.

Methods

This study was carried out over a period of one Iranian calendar year from 21 March 1997 to 20 March 1998. During this year, the ordering and distribution of drugs was highly centralized in Iran. Nearly all drugs, either manufactured in Iran or imported, were distributed under the control and supervision of the Ministry of Health. A minority of drugs were imported and provided directly by the Red Crescent Organization of Iran. Drug advertisement was not permitted through media.

Data were retrieved from both wholesale data published by the Food and Drug Affaires of the Ministry of Health and the report of the Red Crescent Organization of Iran on drug sale. The anti-infective agents were classified according to the Anatomical Therapeutic Chemical (ATC) classification [4]. The sales of systemic anti-infective agents (J class) were converted to DDDs valid in 1998 [5]. Excluded were the immune sera, immunoglobulins, and vaccines – J06 and J07 sub-classes – for which no DDDs had been assigned; hence, their use was not dealt with in this study. The national DDDs of 4 U cotrimoxazole and 14 g nafcillin were established according to WHO recommendations [4]. According to data obtained from the Statistics Institute of Iran, at the end of the study year, Iran had a population of 60.9 million, 39.5% of which was composed of people aged 0–14 years. The sale of drugs was presented as DDD/1000 inhabitants/day.

For comparison of data, the choice of countries was limited to Norway, Sweden, and Denmark for the similarity in data source, date of study, and the implemented version of ATC/DDD. The comparative data was obtained from the respective national statistics. At the end of 1997, the population of Norway was 4.4 million, and those of Sweden and Denmark were 8.8 million and 5.2 million, respectively. The proportion of people in the 0- to 15-year age class was 20.9% in Norway. In Sweden, 18.7% of the population was aged 0–14 years [6, 7, 8].

Results

During the period of the study, 55 kinds of systemic anti-infective agents in 120 dosage forms, with assigned DDDs, were available in Iran. The total sale of systemic anti-infective agents (J01–J05) was 43.50 DDD/1000 inhabitants/day. The sale of 23 dosage forms, supplied and dispensed by the Red Crescent Organization, was 0.094 DDD/1000 inhabitants/day. Parenteral forms of the drug accounted for 4.2% (1.81 DDD/1000 inhabitants/day). The three most commonly used agents, accounting for 74.1% (32.23 DDD/1000 inhabitants/day) of the total, were amoxicillin, co-trimoxazole, and ampicillin.

Table 1 shows the sales of systemic anti-infective agents in Iran relative to three European countries. Within J sub-classes, antibacterial agents for systemic use (J01), with 97.6% (42.45 DDD/1000 inhabitants/day) of total, were used the most, followed by antimy-

Table 1 Sales on systemic anti-infective agents in Iran over a period of 1 year, starting from 21 March 1997, in comparison with such data from three European countries in 1997. Data are given as defined daily dose (DDD) per 1000 inhabitants per day, where values in parentheses show the number of available drugs according to generic

Class	Iran	Norway	Sweden	Denmark
Antibacterials for systemic use (J01)	42.45	14.8	15.10	11.3
Tetracyclines (J01A)	2.43 (3)	3.55 (4)	3.20	5.2
Amphenicols (J01B)	0.08 (1)	0.005 (1)	0.00	< 0.05
Beta-lactam antibacterials, penicillins (J01C)	25.76	7.5	8.00	7.3
Penicillins with extended spectrum (J01CA)	23.3 (5)	1.863 (6)		
Beta-lactam-sensitive penicillins (J01CE)	1.41 (5)	5.32(2)		
Beta-lactam-resistant penicillins (J01CF)	0.814 (1)	0.32 (2)		
Combinations of penicillins, including beta-lactamase inhibitors (J01CR)	0.239 (1)	0.02 (1)		
Other beta-lactam antibacterials (J01D)	2.711	0.38	0.80	< 0.05
Cephalosporins (J01DA)	2.71	0.366		< 0.05
Cephalosporins, first generation	2.654 (4)	0.26 (2)		
Cephalosporins, second generation	NA*	0.0804 (2)		
Cephalosporins, third generation	0.057 (5)	0.025 (4)		
Monobactams (J01DF)	NA	0.001 (1)		
Carbapenems (J01DH)	NA	0.009 (2)		
Sulfonamides and trimethoprim (J01E)	8.95 (2)	1.45 (4)	0.90	0.8
Macrolides and lincosamides (J01F)	1.79 (3)	1.58 (6)	1.00	2
Aminoglycosides (J01G)	0.6 (5)	0.05 (3)	< 0.1	< 0.05
Quinolones (J01M)	0.1 (2)	0.27 (2)	1.20	0.2
Other antibacterials (J01X)	0.02 (4)	0.07 (6)	0.10	< 0.05
Antimycotics for systemic use (J02)	0.22 (5)	0.082 (4)		0.3
Antimycobacterials for treatment of tuberculosis (J04A)	0.77 (5)	0.13 (7)		0.1
Drugs for treatment of lepra (J04B)	0.001 (1)	0.14 (1)		0.1
Antivirals for systemic use (J05)	0.062 (3)	0.26 (12)		0.1

*Not available during the period of study

cobacterial (J04), antimycotic (J02), and antiviral (J05) sub-classes.

The comparison of results with the same data from Norway, Sweden and Denmark [6, 7, 8] shows differences in both quantity and quality of systemic anti-infective use. The total sales in Iran were up to 2.8–3.7 times more than that in Norway (15.4 DDD/1000 inhabitants/day) and Denmark (11.9 DDD/1000 inhabitants/day).

The sales of systemic antibacterials(J01) in Iran (42.45 DDD/1000 inhabitants/day) were up to 2.8–3.8 times more than in Norway (14.8 DDD/1000 inhabitants/day), Sweden (15.1 DDD/1000 inhabitants/day), and Denmark (11.3 DDD/1000 inhabitants/day). Within this class, with the exception of tetracyclines and quinolones with less utilization and macrolides and lincosamides which were used at a similar rate, other agents were used more in Iran. Amphenicols and aminoglycosides were used in Iran 16 and 12 times more than in Norway. With the exception of beta-lactam-sensitive penicillins, all other antibacterial subclasses were used more in Iran than in Norway. Broad-spectrum antibacterial agents accounted for 76% of total antibacterial use in Iran and 52% in Norway. The use of third-generation cephalosporins in Iran was more than twice as high as in Norway.

Table 2 shows the drugs accounting for 90% (DU90%) of systemic antibacterial agent use (J01) in Iran compared with Norway. DU90% included seven drugs (17% of total available agents) in Iran with considerable dominance of broad-spectrum agents. However, in Norway, the number of drugs in DU90% was 12 (25% of total available agents); more of them were narrow-spectrum drugs.

Use of systemic antimycotic agents (J02) in Iran was 2.6 times more than Norway but less than Denmark. Anti-tuberclotic agents were used much more, and drugs for treatment of lepra seems to be used considerably less, in Iran than in these two European countries.

In Iran, systemic antiviral agents (J05), which included three drugs mainly supplied by the Red Crescent Organization of Iran, were used less than in Norway and Denmark.

Discussion and conclusion

The primary goal of this study was the estimation of the intensity and pattern of antibiotic use in Iran. The results were compared with available data from other countries to highlight those drugs that appear to be used too often or too infrequently. Certain sources of error should be taken into consideration when the data are interpreted.

Drug utilization was evaluated from the sales statistics which are an indicator of actual consumption. Yet, patient noncompliance, storage of drugs at home, spoilage, and no human use of antibiotics are examples of factors that contribute to disparity between sales and actual consumption, and are sources of overestimation in studies like this one.

Even though the DDD is a useful tool for evaluation of drug use and comparison, it should be interpreted with some caution. Some DDDs may be inappropriately high or low for certain countries, where dosages may vary, when one antibiotic may be used for more than one major indication or when drugs are used in combination [3].

Since the pediatric doses are substantially lower than established DDDs, this omission will lead to an underestimation. In Iran, where children account for a significant proportion of the population (39.5%), the error introduced can be significant.

From total systemic anti-infective sales, systemic antibacterial agents account for the greatest ratio. This quota mainly resulted from the large sales of the top three drugs – amoxicillin, cotrimoxazole, and ampicillin – all of them broad-spectrum oral antibacterial agents. A cross-sectional study showed that these three drugs accounted for a great proportion of unused drugs in a random selection of Tehran households [9]. Hence, it is possible that a considerable proportion of the most commonly prescribed drugs are unused or wasted.

The sale of drugs that have been imported and dispensed only by the Red Crescent Organization was a small proportion of total number (19% of dosage forms

Table 2 Drugs, according to generics, accounting for 90% of total utilization (DU90%) of systemic antibacterial agents (J01) in Iran over a period of 1 year, starting from 21 March 1997, and in Norway in 1997

Iran		Norway	
Drug	% of DU	Drug	% of DU
Amoxicillin	40.3	Phenoxymethylpenicillin	34.7
Co-trimoxazole	21	Doxycycline	16.7
Ampicillin	14.3	Erythromycin	7
Cephalexin	5.7	Trimethoprim	6.1
Erythromycin	4.2	Amoxicillin	5.7
Doxycycline	3.5	Pivampicillin	5.1
Phenoxymethylpenicillin	1.9	Tetracycline	4.6
		Co-trimoxazole	3.7
		Oxytetracycline	2
		Cephalexin	1.5
		Clarithromycin	1.5
		Ciprofloxacin	1.4

accounted for 0.2% of total sale). Therefore, availability affected the use. In addition, it can be assumed that sale of these less available drugs is closer to the actual consumption, although may be further from actual demand.

The international differences in antibiotic utilization are suggested to be related to the respective socioeconomic and demographic structures, health care systems, prescribing preferences and actual prescribed daily doses, availability and efficacy of drugs, drug tolerance and prevalence, and severity of various infections. These contributory factors should always be considered when making international comparisons.

Results show differences in both the amount and pattern of systemic anti-infective use in Iran, relative to three European countries. The use of anti-infective agents was nearly three times as high as in Norway and Denmark. Since in Iran the ratio of children to the total population was nearly twice that in Norway and Sweden, the difference in actual use may be even greater. Iran had 12.5 times more use of extended-spectrum penicillins (J01C) than did Norway. Cotrimoxazole use was 16 times as high as in Norway. Both the top three drugs and the kind of drugs in DU90% segment (Table 2) show the dominance of a limited number of drugs, mainly broad-spectrums in Iran compared with Norway. Prescribing a limited number of drugs was discussed to be more rational; from this point of view, number of drugs accounting for DU90% was more rational in Iran than in Norway. Nevertheless, the proportion of broad-spectrum antibacterial use (79%) does not seem logical when one considers the risk of increasing microbial resistance.

The sale of oral antibacterial agents can reflect the utilization pattern in the general community. Broad-spectrum oral antibacterial agents were sold more in Iran than in the three European countries, but with a different pattern of use. Use of quinolones and tetracyclines in Iran is near to the minimum use of these drugs in European countries. It is suggested that the lower availability of the newly introduced drug family quinolones, in addition to their high price, limited their use during the study. However, less use of inexpensive tetracyclines and more use of an expensive drug, such as co-amoxiclav, in Iran may indicate different drug preferences than in Norway.

The considerably higher sale of aminoglycosides and third-generation cephalosporins implies substantially more hospital use of broad-spectrum parenteral drugs in Iran. Considering the high cost of the third-generation cephalosporins, less economic prudence in hospital drug use may be concluded. Second-generation cephalosporins were not registered in the *Iran National Formulary*; therefore, it might have caused greater use of available drugs with a wider spectrum of activity.

The sale of drugs used for treatment of specific or a narrow spectrum of diseases, in case of availability and affordability of physician, laboratory support, and drugs, can reflect the prevalence of those diseases. Accordingly, higher prevalence of tuberculosis in Iran than in Norway and Denmark is possible. The same explanation cannot be used for antimycotic agents, drugs for treatment of lerpa, or antivirals, since during the study year they were relatively expensive and/or difficult to obtain; the same is true for laboratory support to diagnose the diseases. However, for the same reason, the sale of antimycotics, dapsone, and antivirals is a closer estimation of the actual consumption.

It is assumed that antibiotic consumption is generally greater in developed countries than in less developing countries [3]. The present study showed greater sale of antibiotics in Iran than in developed countries. The pattern of antibiotic use in Iran seems to be something between that of developing and developed countries, as reported in the study by Col and O'Connor [3]. However, the prevalence of infectious diseases and microbial resistance affects the intensity and pattern of antibiotic use, and there are a number of other complex factors that influence the pattern of antibiotic use in Iran, alike to what is suggested for developing countries [1]:

1. Difficulty in diagnosing infectious diseases
2. The tendency of medical practitioners to treat using a "shot-gun" approach
3. Prevalent cultural preferences and beliefs

It is assumed that antibiotics may be purchased without prescription in most developing nations [1]. This is a real problem in Iran. Several unpublished surveys have implied that amoxicillin accounted for most of the anti-infectives and a considerable proportion of all drugs purchased without prescription. Furthermore, it is argued that the great subsidy paid by the Iranian government for drugs without efficient policies, laws, and regulations to rationalize drug use results in irrational utilization. The influence of contributors to antibiotic use in Iran are prospected for further investigations.

In conclusion, it can be argued that there is a need for more appropriate use of those drugs we already use. Thus, we urgently need to assess the problem in more detail and develop strategies that will promote a more rational use of antibacterial agents in Iran, involving various disciplines.

The appropriate use of antibiotics in Iran seems to be too complex a subject to assess accurately with this retrospective study. Conducted using a standardized method, the present survey provided an overview of anti-infective use in Iran and highlighted inconsistencies, a fact not weakened by limitations of ATC/DDD methodology. Therefore, it can improve awareness of drug use if implemented by national health administrative authorities and provides data from Iran to fill the gap of information for the global estimation of anti-infective use.

Acknowledgements The authors wish to thank Morten Andersen, Ulf Bergman, Hege Salvesen Blix, Kerstin Burman and Marit Ronning for their assistance in the realization of ATC/DDD methodology and providing data from Norway, Sweden and Denmark.

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