



The role of Clinical Pharmacists in the improvement of a pharmacovigilance system: A review of the reported adverse drug reactions during 2004-2010 in Mazandaran Province of Iran.

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ABSTRACT

Background: Following establishment of Iranian Adverse Drug Reaction (ADR) Monitoring Center in 1997, ADR committees were established in all hospitals of Mazandaran Province of Iran. Clinical pharmacists from Mazandaran University of Medical Sciences have been involved with these committees since 2007. The aim of this study was to compare the results of the pharmacovigilance system before and after active involvement of clinical pharmacists.

Methods: This study included Yellow Cards filled out by healthcare providers in Mazandaran Province during 2004-2010. Frequency of Adverse Drug Reactions (ADRs), route of administration, reporters, number of reports in each years and damaged organs were focuses. Statistical analysis was performed by SPSS 16 software. $P < 0.05$ was considered as significant difference.

Results: A total of 793 yellow cards were completed during 2004 – 2010. Only 38 ADRs (4.8%) were related to 2004-2007. Most of the reports generated by Nurses (49.3%) followed by Pharmacists and Physicians ($P < 0.001$). Forty-one reactions (5.2%) were serious, most related to Ceftriaxone, Desfonac and Vancomycin.

Conclusion: Clinical pharmacists' intervention regarding establishing ADR committees in the hospitals improved the output of the pharmacovigilance system, although under-reporting is still a major drawback of spontaneous reporting.

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Introduction

Adverse drug reactions (ADRs) are among the main factors contributing to life-threatening events which negatively impact the quality of life and impose large costs on the healthcare systems (1). ADRs with medication errors are the fourth cause of mortality in the United States (1). It is interesting that the number of deaths caused by medication errors and ADRs are more than the deaths caused by highway accidents, breast cancer and Acquired Immune Deficiency Syndrome (AIDS) (2) and seven

percent of hospital admissions are due to ADRs (1, 3).

Economic consequences resulting from ADRs are also significant. In Germany, it has been estimated that the direct cost of medical complications during 13 years (1980-1995) was 588 million dollars each year, of which 30.7% were preventable (4).

Due to the limitations of clinical trials, it is not possible to have a complete knowledge regarding all ADRs at the time of drug approval; necessitating drug safety follow-ups after releasing to the market. The World Health Organization (WHO) established the pharmacovigilance system in 1968 after the thalidomide tragedy (Phocomelia in babies of mothers used thalidomide during pregnancy) in 1961. Pharmacovigilance has been defined as a science regarding the detection, assessment, understanding

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Table 1. Frequency of Adverse Drug Reactions reported during 2004-2010.

Number	Year	Frequency	Percentage	P-value
1	2004	16	2	
2	2005	10	1.3	
3	2006	12	1.5	
4	2007	162	20.4	
5	2008	82	10.3	
6	2009	229	28.9	<0.001
7	2010	237	29.9	
8	Year Unknown	45	5.7	
Total		793	100	

and prevention of ADRs, with its ultimate goal being improving pharmacotherapy (5).

Although the Iranian ADR Monitoring Center (IADRC) was established in 1997, only since 2007, the ADR committees that were designed and conducted by the clinical pharmacists of Mazandaran University of Medical Sciences established in all hospitals of Mazandaran Province. The aim of this study was to compare the effects of this clinical pharmacy intervention on the number of ADRs reported to IADRC. Also, the data were further analyzed in terms of affected systems/organs, implemented drugs and the level of participation of different healthcare provider in the pharmacovigilance system.

Methods

Following establishment of Iranian ADR Monitoring Center (IADRC) in 1997, we created pharmacovigilance committees in all hospitals of Mazandaran province in 2007. They consist of the pharmacist of the hospital (as the head of the committee), two interested specialist physicians, manager of the hospital, and the nursing supervisor. At the beginning, several pharmacovigilance workshops were held for hospital pharmacists, nursing supervisors and also for physicians as a part of the continuing medical education program by “clinical pharmacy department” and “Food and Drug Deputy of Mazandaran University of Medical Sciences”. The history of pharmacovigilance, morbidity and mortality of ADRs, limitations of clinical trials, the national and local structures of pharmacovigilance system, filling out the yellow cards, ADRs that must be reported, were among the most-focused entities in the workshops. After education on the policies/procedures and necessity of establishing the pharmacovigilance committees, an official announcement was made by the Food and Drug Deputy of Mazandaran University of Medical Sciences to the heads of all hospitals including governmental, social security organization-dependent and private hospitals.

Pharmacovigilance committees were required to have regular weekly meetings to follow all ADRs that occurred in the hospital and report them to the IADRC. The heads of the committees also participated in the regular meetings (generally once each 3 months) held at the Food and Drug Deputy of Mazandaran University of Medical Sciences to present and discuss the details of major reports.

The original yellow cards were sent to IADRC by mail and the copies of yellow cards were presented to the Pharmacovigilance office of the Food and Drug Deputy. In this report, all copies of the yellow cards were reviewed and analyzed with SPSS 16 software.

As noted, the primary goal was to assess the impact of above mentioned intervention on the rate of report of ADRs, specifically the number of reports before 2007 (2004 to 2006) and after 2007 (2007 to 2010). The data of yellow cards were further analyzed in terms of route of drug administration, reporters, and affected systems/organs.

Results

A total number of 793 yellow cards were completed by health care providers during 2004–2010 (Table 1). During 2004 to 2006, only 38 ADRs (4.8%) were reported. Most cases have been reported in 2010, had the most number of reports, followed by 2009 and 2007. Most of ADRs occurred with injectable drugs (73.9%), followed by oral routes (21.7%) ($P < 0.001$) (Table 2).

Table 3 shows the organ or system affected by ADR. Skin reactions were the most common (40.36%) and the statistical difference in terms of affected organ was significant (P -value < 0.001). It is noteworthy that, as there were more than one ADR in some cases, the total number of observed ADRs was more than 793. The most serious drug reactions were cardiopulmonary arrest, anaphylactic shock, severe necrosis, and seizure (Table 4).

The most common frequency of serious/life-threatening reactions were due to Ceftriaxone (14.15%), Desfonac (10.59%), Vancomycin (7.26%), Cefazolin (4.64%), Phenytoin (2.61%), Diclofenac, Metronidazole, Omnipaque, Imipenem and Hydrocortisone (2.02%) ($P < 0.001$).

Level of participation of different health-care providers is shown in Figure 1. Most of the reports were generated by nurses ($n = 391$, 49.3% of all reports), followed by Pharmacists ($n = 118$, 14.9% of all reports). The statistical difference was significant ($P < 0.001$). It is notable that 20.9% of reporters didn't mention their job in the yellow cards.

Discussion

The most important finding of this study is the significant improvement in ADR reporting after education and establishment of Pharmacovigilance Committees in

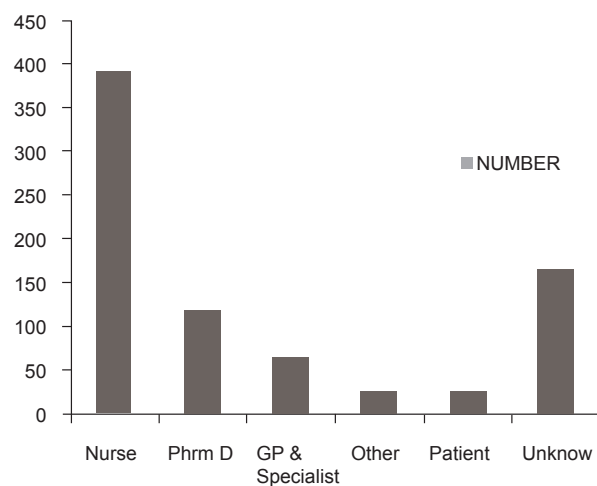


Figure 1. Frequency of reports sent to Food and Drug deputy of Mazandaran University of Medical Sciences, during 2004-2007.

our hospitals. It is interesting that despite sending the documents, posters and pamphlets of the IADRMC since 2004, the number of ADRs was very low during 2004 until 2007.

Although we observed an increase in the rate of ADRs after 2007, an important aspect of our experience is that the frequency of reports is not yet satisfactory (i.e., under-reporting). According to World Health Organization (WHO) definitions, countries with “Good reporting rate” report more than 200 reports of ADRs per one million people annually (6). Therefore, healthcare providers in Mazandaran province with 2,500,000 people should report at least 500 ADRs annually to be classified as “Good ADR reporters”. Although there was a significant increases in the number of reported ADRs in 2009 and 2010 (229 and 237, respectively), it has not yet reached 50% of the number needed to consider Mazandaran health

care providers as “Good reporters”.

On the national scale, we observed a similar problem. According to the reports of IADRMC (7), total ADRs received by national center were 4,511 in 2008 and 4,977 in 2009. This compares poorly with the expected 14,000 reports for a country with 70 million people.

Although under-reporting is considered as a general drawback of the spontaneous reporting system, there are countries with acceptable reporting of ADRs, such as Australia and France. About 12,000 ADRs are reported each year in Australia with a population of 20 million (8). In France, 210,000 serious ADR are sent by general physicians annually (8).

According to the previous studies, there are several causes for the under-reporting (9, 10). In the study of Ghasemian et al., which involved physicians, the national center not being aware, absence of serious drug reactions and doubt about the causality relationship between the reaction and suspected drug were mentioned as the most important reasons (9). Similar reasons were proposed by pharmacist and nurses (10).

Based on this study, Antibiotics were the top drugs that caused ADRs (45.4%) and the most common antibiotic associated with ADRs was Ceftriaxone with side effects including rash, hives and anaphylactic shock. This pattern is similar to data reported by IADRMC (11). Logically, high amounts of Antibiotic-associated ADRs could be related to the high usage of these drugs, both in the country and in the province. More than 50% of the patients receiving antibiotics encountered physicians; this rate increases to 59% for general physicians (12).

Nurses participated more in the reporting of ADRs compared to other healthcare providers, including physicians and pharmacists. It may be due to their role in drug administration and close contact with both the physicians and the patients.

It is notable that in some countries such as England, Nurses were not allowed to fill out yellow cards until

Table 2. Frequency of Adverse Drug Reactions with different rout of administration.

Number	Route of administration	Frequency	Percentage	P-value
1	Injection	586	73.9	
2	Oral	172	21.7	
3	Injection & Oral	12	1.5	
4	Topical	11	1.4	
5	Respiratory	4	0.5	
6	Intraspinal	3	0.4	<0.001
7	Rectal	3	0.4	
8	Ophthalmic	2	0.3	
Total		793	100	

Table 3. Systems or organs affected by Adverse Drug Reactions.

Number	Organ/System affected	Frequency	Percentage	P-value
1	Dermatologic & Hair disorders (Hairloss, Rash, Urticaria, Acne, Erythema ,Itching, ...)	394	40.36	
2	General effects (Fever ,Chill ,Edema , Weakness, ...)	99	10.14	
3	Respiratory reactions (Cough, Bronchospasm,...)	94	9.63	
4	GI effects (Nausea, Vomiting, Stomatitis, GI bleeding,...)	83	8.5	
5	CNS effects (EPS, Seizures, Headache, Vertigo, ...)	80	8.19	
6	Injection site reactions (Pain, Absces, Necrosis,...)	38	3.89	
7	Cardiac effects (Hypotension, Chest pain, Palpitations, Arrhythmia, Tachycardia ,...)	50	5.11	
8	Loss of drug effect	20	2.04	
9	Vascular system disorders (Phlebitis ,Vasculitis,...)	12	1.22	
10	Effects on coagulation (Thrombocytopenia, Haemorrhage, Ecchymosis,...)	15	1.53	
11	Musculoskeletal effects (Arthralgia/Myalgia, Muscle Cramps, Back pain, ...)	12	1.22	
12	Anaphylaxis/Shock	25	2.56	
13	Psychiatry disorders (Anxiety, Hallucinations, Insomnia, Sleep disturbance, Withdrawal syndrome ,)	12	1.22	<0.001
14	Autonomic nervous system disorders (Dry mouth, Flushing, Sweating, Mydriasis, ...)	14	1.43	
15	Ocular effects (Visual disturbance ,Blurred vision, ...)	9	0.92	
16	Hematologic disorderst (Anemia, Leukopenia, Agranulocytosis,...)	4	0.4	
17	Hepatic effects (Increases in liver enzymes, Jaundice, ...)	3	0.3	
18	Sensory Systems Effects (Taste disturbance ,...)	3	0.3	
19	Urinary Tract/ Renal disorders (↑ Cr,Polyuria, Urinary frequency, Urinary retention, ...)	4	0.4	
20	Immunologic dysfunction (Thrush, Mouth Ulcers, ...)	1	0.1	
21	Smell disorders (Nasal Irritation,...)	2	0.2	
22	Female Genital Disorders (Dysmenorrhea, Vaginitis, Menstrual disturbances, Galactorrhoea, ...)	1	0.1	
23	(Impotency , ...) Sexual Dysfunction	1	0.1	
Total		976	100	

CNS: Central Nervous System; Cr: Creatinine; EPS: Extrapyramidal Symptom; GI: Gastro-Intestinal

2002. Correlating with previous studies (13, 14), our experience also emphasizes the pivotal role of nurses in the pharmacovigilance system.

In our study, 73.9% of ADRs were related to injectable drugs. The role of injectable drugs inducing ADRs was more than predicted based on the previous reports (53%) (7). According to the reports published by “National Rational Drug Usage Committee” in 2008, 45% of prescriptions consist of at least one injectable drug (15). Clearly, avoiding unnecessary injections could be an

important factor in reducing ADRs.

Considering that injectable drugs are not necessarily more effective than oral agents and their higher cost and difficulty of managing adverse reactions, it would be prudent to administer oral drugs or other dosage forms, when possible, to decrease the risk of ADRs associated with injectable drugs.

In Conclusion, in our experience, considering the significant improvement of pharmacovigilance activity after establishment of specified committees with clearly

Table 4. Frequency of the most serious drug reactions.

Number	Serious drug reactions	Drug(n)	Frequency	Percentage	P_Value
1	Anaphylactic Shock	Ceftriaxone (8), Cephalexin (1) Cephalexin with lidocain (1) Ciprofloxacin (1), Penicillin (2) Cephazolin (2), Intralipid (1) Amphotericin-B (1), Vancomycin (2) Hyoscine & Diclofenac (1), Ceftriaxon & Vancomycin (1) Ceftriaxon & lidocain (1)	22	53.65	
2	Cardiopulmonary Arrest	Adenosin (1), Penicillin (1) Ampicilin (1), Ceftriaxone (3)	6	14.63	
3	Severe Necrosis	Diclofenac (2), Nitrocantin & Captopril & Allopurinole (1) Sodium valproate & Lamotrigin (1)	4	9.75	
4	Seizure	Imipenem (1), Tramadol (1) Desfonac (1) Ciprofloxacin & Theophyllin (1) Ciprofloxacin & Ceftazidim (1)	5	12.19	<0.001
5	Anaphylactic Shock & Cardiopulmonary Arrest	Ceftriaxone (2)	2	4.87	
6	Seizure & Cardiopulmonary Arrest	Ceftriaxone (1) Imipenem (1)	2	4.87	
Total			41	100	

defined objectives and tasks, clinical pharmacy service has an excellent role in designing and conducting the pharmacovigilance system in the hospitals. Practical education via workshops and follow-up of the output of the committees' activity is crucial for maintaining and improving the implemented system.

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