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Drug Safety Crises Management in Pharmacovigilance

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ABSTRACT

Background: Adverse drug events can cause serious consequences including death. A published report by Lazarou et al in 1998 showed that adverse drug events were the 4th to 6th leading cause of death in the United States. These events may lead to drug safety crises in some issues, which need to take crises management process for solving the problem and/or preventing similar events. To evaluate nature of drug safety crises based on adverse events reported to Iranian Pharmacovigilance Center from 1999 through 2012. To mention success and failure outcomes of crises management process taken against detected crises.
Methods: All adverse drug events received by Iranian Pharmacovigilance Center from 1999 through 2012 were evaluated for reports with fatal outcome. All alerting letters and manuscripts published by the Center during the same period were reviewed for detailed information on detected crises. World Health Organization definition was used for detecting drug safety crises.
Results: Among 42036 registered cases in our database, 463 deaths were recorded. The most frequent suspected drug for adverse events with fatal outcome was ceftriaxone (100 cases). Ten different drug safety crises issues were detected during the study period and their successful or failure outcomes were evaluated. There were 112 issued alerting letters and 17 published manuscript during the same period which was monitored for detailed information.
Conclusion: It is necessary for national pharmacovigilance centers to have prepared programs for crises management. This could be useful for reducing drug related mortality.

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Introduction

Adverse drug events (ADEs) can cause serious consequences including death. These negative outcomes have been as a matter of consideration for years; however they are going to be more and more included in published studies in the literature. A published report by Lazarou et al in 1998 showed that ADEs were the 4th to 6th leading cause of death in the United States (1). It was also estimated that annual death of drug related problems was more than annual death of breast cancer, Acquired Immunodeficiency Syndrome (AIDS) and highway accidents in that country.

Although some of these adverse events may be

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Table 1. Common features of a crisis.

The situation materialises unexpectedly
Decisions are required urgently
Time is short
Specific threats are identified
Urgent demands for information are received
There is sense of loss of control
Pressures build over time
Routine business become increasingly difficult
Demands are made to identify someone to blame
Outsiders take an unaccustomed interest
Reputation suffers
Communications are increasingly difficult to manage
There is an urge to defend and excuse

predictable based on the pharmacological effects of medicines, they might involve some serious consequences making the problem as a drug safety crisis. World Health Organization (WHO) defines a crisis as "any unplanned event or succession of events which lead to interruption or destabilization of the normal operations or activities of an organization" (2). It also defines crisis management as "a process through which organizations, in collaboration with external stakeholders, prevent crises, or effectively manage those which occur" (2). Table 1 shows common features of a crisis (2). In the field of drug safety, WHO International Drug Monitoring Program might be considered as one of the first global drug safety crises management programs which was started after thalidomide disaster. Iranian Pharmacovigilance Center (IPC) has started its activities as a full member of this program since 1998.

Several studies have been conducted to demonstrate the considerable proportion of drug related death (3-5), however reporting drug safety crises management has been less published. This study is performed to evaluate frequency and nature of drug safety crises with fatal or other serious outcomes reported to IPC from 1999 through 2012. We believe that evaluating pros and cons of drug safety crises management could be a useful tool for preventing drug related problems. Furthermore lessons learned by such reports may be used for correcting process involved in drug safety management.

Methods

The spontaneous reporting system for collecting suspected ADEs has been developed in Iran since 1998. The reports are submitted to IPC through designed yellow cards. These reports include both ADRs and medication errors. In order to achieve harmonization in registered data, the World Health Organization Adverse Drug Reaction Terminology (WHO-ART) was used for recording reported terms of ADEs. In this cross sectional study, all registered ADE case reports in the IPC database, from 1999 through 2012 were scanned for events with fatal outcome.

The trend of reporting over the study period was also investigated. Suspected medicines for inducing ADEs with fatal outcome were detected. All alerting letters issued by IPC during study period were reviewed. Also all published manuscripts in collaboration with IPC were scanned and reviewed (8-24). The WHO definition was used for detecting drug safety crises issues in evaluated reports, alerting letters and published manuscripts (2).

Results

Among 42036 registered cases in our database, 463 cases of deaths (1.1%) were recorded from 1998 through 2012. Although there had been an increase in the total ADE reports received by IPC over the study period, there was no significant increase in the proportion of reported fatal reactions (Table 2).

Ceftriaxone was the most common medicine responsible for fatal reactions with 100 cases. There were 112 alerting letters issued by IPC during study period. Also there were 17 published manuscripts in collaboration by IPC which were reviewed.

The most 10 important drug safety crises during the

Table 2. The trend of yearly received adverse drug events (ADEs) reports versus fatal ones.

Year	Number of Deaths Reports	Number of Total Reports
1999	1	489
2000	3	1180
2001	8	238
2002	20	1542
2003	17	1441
2004	18	1368
2005	25	1292
2006	34	2427
2007	39	3015
2008	47	4389
2009	54	3745
2010	38	5262
2011	78	6246
2012	46	6405
Total	**463**	**42036**

study period are mentioned below:

1. Diclofenac sodium induced paralysis

IPC detected a new signal as sciatic nerve damage following intramuscular injection of diclofenac sodium in 1998. The reaction was recognized 3 years after marketing of the product in Iran. From June 1998 to June 2002, 249 reports of peripheral nervous system disorders including walking difficulties, foot drop and sciatic nerve palsy were received by IPC (chart 1). Evaluating hypothesis generated implied rare but serious reaction induced by intramuscular injection of diclofenac sodium as sciatic nerve palsy. To deal with the crisis, 9 different alerting letters were issued by IPC. Also the product was restricted to hospital use only. Chart 2 demonstrates the trend of reporting this event.

2. Bupivacaine induced death and paraplegia:

Bupivacaine, as an anesthetic medicine, was introduced to Iranian market from a new manufacturer. The vials were not specialized for intrathecal injection like as the previous ones. In 2001, two cases of deaths and 2 cases

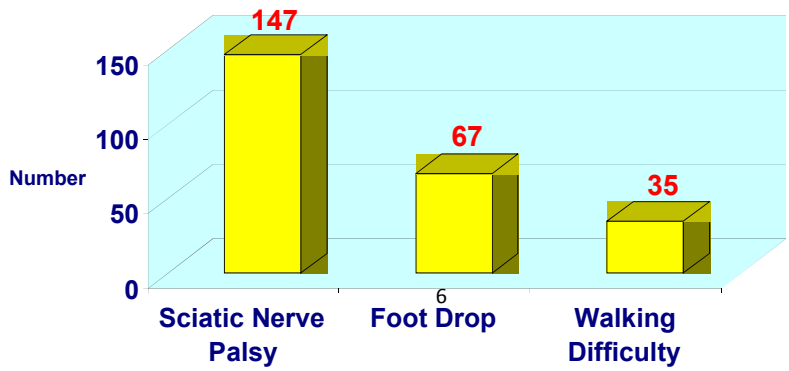

Chart 1. Reported diclofenac induced pripheral nervous system disorders based on WHO terminology.

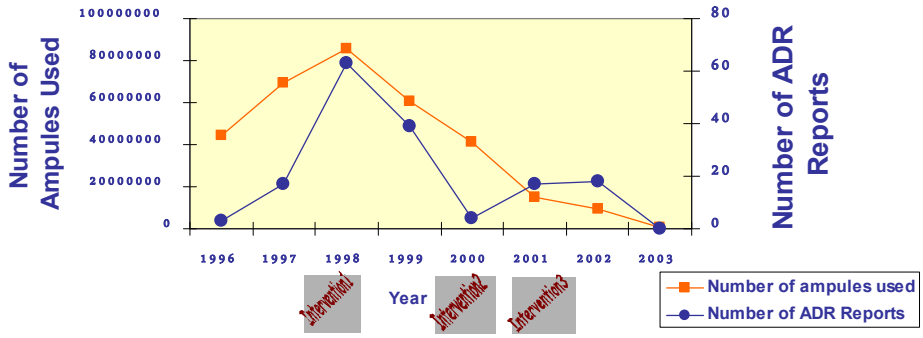

Chart 2. Diclofenac Sodium induced Nerve Damage and number of ampules used per year versus interventions.

of hemiplegia were reported as a result of mistakenly intrathecal injection of the product. The distribution of the product was immediately stopped till the reason of the reaction was recognized. An alerting letter was issued by IPC.

3. Death because of error in intravenous injection of animal solution:

In 2002, there was an error in the process of labeling, distribution, dispensing and administration of animal solution (CPM) leading to one report of death. The distribution was immediately stopped and an alerting letter was issued by IPC.

4. Mioflex induced death

Mioflex is trade name of succinylcholine, an anesthetic medicine. There is another product name as "Myoflex" which is an analgesic cream. Because of this name similarity, the product was mistakenly used as an analgesic injectable medicine, in 2006, leading to two cases of deaths. There was an error in nomenclature, distributing, dispensing, administration and use of the product. The distribution was immediately stopped in community pharmacies and an alerting letter was issued by IPC.

5. Death induced by intravenous immunoglobulin (IVIG)

In 2003, there were 3 cases of death due to change-colored IVIG. The product was immediately recalled and an alerting letter was issued by IPC.

6. Tramadol induced death

Following reports of suspected death and seizure induced by tramadol in 2003, the product was restricted for hospital use only. Also the power of the product changed from 100 mg to 50 mg in each vial. And an alerting letter was issued by IPC.

7. Potassium chloride induced death

In 2005, three cases of death following error in administration of potassium chloride instead of metronidazole because of similarity in packaging were received by IPC. The manufacturer was urged to change the packaging of potassium chloride. An alerting letter was issued by IPC.

8. Counterfeit lidocaine induced death

In 2005, IPC received 11 reports of seizures, 2 cases of death and 2 cases of death in children following counterfeit lidocaine injection. An alerting letter was issued by IPC and the counterfeit product was removed from the market.

9. Chemical peritonitis induced fluids for peritoneal dialysis

In 2005, 224 cases of chemical peritonitis were reported to IPC. The reaction was due to glucose degradation in the product. The manufacturer was urged to remove the problem in the manufacturing process.

10. Ceftriaxone induced death

During 2004 to 2012, 100 cases of death induced by ceftriaxone were reported to IPC, making the product as the most frequent responsible medicine for registered adverse events with fatal outcome. Chart 3 shows the trend of ceftriaxone induced death versus year. The actions taken in response to this drug safety crisis include: 5 alerting letters issued by IPC, evaluating the quality of the product and changing the product information to include "IV infusion is necessary".

he success and failure outcomes of mentioned crises management issues are shown in Table 4.

Discussion

Medicines related fatalities may lead to silent epidemics of adverse events, if they have been ignored. Based on the results provided, it appears that although successful outcomes are gained in management of drug safety crises, there are still some gaps in complete success achievement. Failure outcomes mentioned in result section, e.g., delay

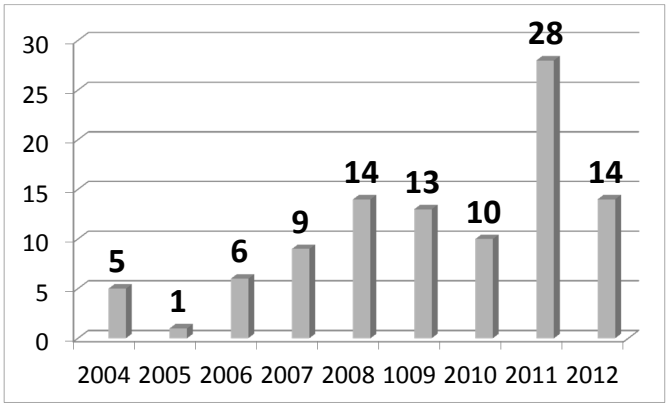

Chart 3. The trend of ceftriaxone induced death versus year.

in response to crisis, lack of necessary regulations and/ or inability to recognize the main reason of the reaction, reveals the need for more detailed programs on drug safety crises management. Logical framework approach (LFA) and PESTEL (25) are tools for designing managerial activities and project decision making methods development. LFA is also a powerful base for monitoring and evaluation of the project. We recommend 9 steps of LFA mentioned below in order to develop drug safety crises management:

1. Step one: Context analysis of the project of drug safety crisis management

This project is conducted in the context of drug safety. It is a subsystem of the international drug monitoring program. All processes influencing in the main process of drug safety should be reviewed. These processes include: manufacturing, prescribing, order communication, packaging, labeling, nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use. Sometimes it is necessary to make some changes in each of mentioned processes to conduct drug safety crisis management. All threats, weaknesses, strengths and opportunities should be monitored in this step. Table 5 shows a sample PESTEL approach for drug safety crises management.

2. Stakeholders analysis

Table 6 shows common stakeholders involved in drug safety crises.

3. Problem analysis

Root- cause analysis should be conducted in this section, e.g., in case of mioflex, there were errors in different levels of drug handling. Problem tree can be helpful in this section.

4. Objective analysis

Objectives should be discussed in different levels.

a. Overall objectives: e.g., Improving drug safety

b. Purpose: e.g., preventing adverse events induced by suspected medicine in drug safety crisis

c. Results: e.g., abrupt discontinuation of observed adverse event in drug safety crisis

5. Activities Scheduling

It is recommended to prepare a list of necessary activities to manage drug safety crises. These activities can be divided to two types. The first group includes activities required for controlling of the crisis. The second group includes required activities for preventing similar crises in the future.

6. Resource scheduling

It is recommended to preparing trained team for evaluating drug safety crises, predict budget recourses, issue necessary regulations and guidelines and prepare required equipment.

7. Indicators recognition

Success indicators should be determined and the tools for its assessment should be predicted, e.g., in Mioflex example, immediate recall of the product from community pharmacies and no other occurrence of the reaction can be considered as indicators which can be assessed by inspection and scanning IPC database.

8. Risk analysis:

Factors with possibility of negative impact on the project of drug safety crisis management should be recognized and alternative strategies should be taken, e.g., in case of counterfeit lidocaine, multiple resources for producing counterfeit product should be regarded.

Table 4. Success and failure outcomes of crises management.

Crisis Event	Success outcomes	Failure Outcomes
Diclofenac sodium induced paralysis	• Successful management of the crisis by limitations to hospitals use only and increasing awareness of health care professionals • No need to drug withdrawal	• Delay in response to the crisis led to increased number of the reaction • Main reason of the reaction remained unknown, making the reaction repeatable in the future
Bupivacaine induced death and paraplegia	• Rapid response led to prevent more reactions • Increased trust reported by stakeholders	• No change in regulations for preparing required translation of the product information
Death because of error in intravenous injection of CMC solution	• Rapid response led to prevent more reactions • Increased awareness of health care professionals on possible medication errors during administration process	• No change in regulations for making necessary differences in packaging of medicinal products
Mioflex induced death	• Rapid response led to prevent more reactions • Issuing guideline for immediate reporting of serious reactions • Preparing guideline for evaluation of immediate reports of serious reactions	• No change in regulations for preparing required translation of the product information • Decreased trust reported by stakeholders
Death induced by intravenous immunoglobulin (IVIG)	• Rapid response led to prevent more reactions • Increased awareness of health care professionals on possible medication errors during administration process	• Main reason of product discoloration remained unknown
Tramadol induced death	• Rapid response led to prevent more reactions • Management of the crisis by limitations to hospital use only and decreased product power • Decreased level of irrational use of the product	• Nothing found
Potassium chloride induced death	• Management of the crisis by making difference in packaging of the product • Increased awareness of health care professionals on possible medication errors during administration process	• Delay in product re-packaging led to increased reports of the reaction • No change in regulations for making necessary differences in packaging of medicinal products • Decreased trust reported by stakeholders
Counterfeit lidocaine induced death	• Rapid recall of the counterfeit product led to prevent more reactions • Increased awareness of health care professionals on preparing medicinal products from valid resources	• Nothing found
Chemical peritonitis induced by solutions for peritoneal dialysis	• Detecting main reason of the reaction led to complete management of the crisis	• Delay in response to the reaction, led to more adverse events • Decreased trust reported by stakeholders
Ceftriaxone induced death	• Decreased level of irrational use of the product • Increased awareness of health care professionals on severe reactions of the product and preventive ways for decreasing drug related problems	• Delay in response to the reaction, led to more adverse events • Decreased trust reported by stakeholders • Irrational use of the product continued

Table 5. PESTEL approach for drug safety crises management.

SWOT / PESTEL	Strengths	Weaknesses	Opportunities	Threats
Political	Authority of Food and Drug Organization	Limitations in human resources and budget	Intersectional collaboration	Reduced collaboration of people due to fear of legal aspects
Economical	Resources of Food and Drug Organization	Special budget for drug safety crises is no available	Manufacturer responsibility for suspected medicine	Economical aspects of required changes for manufacturers
Social	Possibility of scientific consultation	Lack in quick communication with health care professionals	Public attitude for preventing ADEs/other countries experiences/media available	Counterfeit and tampering products
Technological	Intranet available for communication with medical universities in the country	Lack of new methods in information technology	43 different universities can share their equipments	Failure in perfect technological tools, e.g. interruption in internet
Legal	Possibility of issuing country wide guidelines and regulations	Lack in regulations for preventing drug safety crises	Membership of WHO international drug monitoring program/ similar regulations in health sector	Legal complaints of manufactures
Environmental	----------	----------	Possibility to have appropriate conditions for distribution and stock of medicines by using technology	Inappropriate conditions for distribution or conserving medicines

Table 6. Common stakeholders involved in drug safety crises.

Stakeholder	Group	Role, benefit or impact	Programming/execution
Food and drug organization	Decision makers/ Budget resource/ users	Conducting drug safety	Programming/execution
People	Users	Preventing from being affected by ADEs	execution
Pharmacies	Users	Prevention of ADEs	execution
Medical centers	users	Improving pharmacotherapy/ reducing cost	execution
Manufactures	Users	Improving quality of the product/ improving trust and reputation/ prevention of drug withdrawal	execution
Distributors	Users	Prevention of error in distribution	execution
WHO	Users	Improving international drug monitoring program	Programming
Health Sector	Users/ decision makers	Reducing cost/improving pharmacotherapy	Programming/ execution
Heath care professionals	Users	Improving pharmacotherapy/ prevention of legal issues	execution
Scientific medical NGOs	Users	Improving scientific programs for members	Programming/ execution
Media	Users	Improving information quality	execution

9. Assumptions analysis

In this step, social, legal, political and financial aspects of the project of drug safety management should be reviewed, e.g., it should be determined that what information can be exchanged with regard to confidentiality. How public information should be performed without making fear among people.

Conclusion

Drug safety crises management is an important part of pharmacovigilance. It is necessary for national pharmacovigilance centers to have prepared programs for drug safety crises management. Prevention of occurring drug safety problems is an essential section of drug safety crises management. This could be useful for reducing drug related morbidity and mortality.

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