

Analysis of the National Pharmacovigilance Database in Jordan (2010-2014)

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ABSTRACT

The aims of this study were to analyze the adverse drug reactions reports (ADRs) submitted to the Jordan Pharmacovigilance (PV) department at Jordan Food and Drug Administration (JFDA) in the period from 2010 to 2014, determine the rate of reporting of ADRs per year, identify the most common drugs involved in ADRs, and finally the most commonly body systems implicated in ADRs. The total number of ADRs reports was 428. There was a 5-fold increase in the rate of reporting over the study period. The most commonly classes of drugs implicated in ADRs were antineoplastics (37.6%), followed by immunomodulators (14.1%), antibiotics (10.3%) and analgesics (6.6%). The most commonly reported system organ classes involved in these ADRs were skin and subcutaneous (19.2%), followed by gastrointestinal (16.5%) and nervous system (11.5%). This is the first study to analyze the Jordan national pharmacovigilance database and the results of this study are considered the cornerstone of post-marketing surveillance and it could be used an essential tool for signal generation in Jordan. More educational programs and awareness campaigns are needed to promote the concept of PV and to increase the role of healthcare professionals in the reporting of ADRs in Jordan.

Keywords: Pharmacovigilance; adverse drug reactions; Jordan.

INTRODUCTION

Pharmacovigilance (PV) also known as drug safety surveillance is the science of enhancing patient safety through collecting, monitoring, assessing and preventing of adverse drug reactions (ADRs)¹. The objectives of PV are to improve public health and safety in relation to the use of medicines, to contribute to the assessment of benefit, harm, and risks associated with the use of medicines and to encourage the safe, rational and more effective

use of drugs². PV is an important and integral part of clinical research. Both clinical trials safety and post-marketing PV are critical throughout the product lifecycle. Once released into the market, a medicine leaves the secure and protected scientific environment of clinical trials and is legally set free for consumption by the general population. At this point, most medicines will only have been tested for short-term safety and efficacy on a limited number of carefully selected individuals³. Therefore, it is essential that new and medically

still evolving treatments are monitored for their effectiveness and safety under real-life conditions post release ⁴.

Good pharmacovigilance practice will identify the risks in the shortest possible time after the medicine has been marketed and will help to establish and/or identify risk factors. When communicated effectively, this information allows for intelligent, evidence-based prescribing with potential for preventing many adverse reactions and will ultimately help each patient to receive optimum therapy at a lower cost ⁵. The post-marketing assessment of the benefits and risks of medical products can be achieved through collaborative efforts from regulatory bodies, healthcare providers, industry and the patients. Therefore, effective pharmacovigilance systems should communicate with the patients and healthcare professionals to ensure sharing of information related to drug safety ⁶. In order to prevent unnecessary suffering by patients and to decrease the financial loss sustained by the patient due to the inappropriate or unsafe use of medicines, it is essential that a monitoring system for the safety of medicines is supported by doctors, pharmacists, nurses and other healthcare professionals in the country ⁷.

In Jordan, the PV system was established in 2001 and Jordan joined the WHO programme for international drug monitoring in 2002. In 2006, the first PV guidelines were approved based on the International Council for Harmonization (ICH)-Guidelines, which clarify the relation among stakeholders (Health authorities, healthcare providers, industry and patients) ⁸. In order to increase the awareness about PV and promote reporting of ADRs, five PV regional centers have

been established recently in the north, middle and south part of Jordan ⁹. In this study, we aimed to analyze the national ADRs reports submitted to the PV department at Jordan Food and Drug Administration (JFDA).

METHODS

ADRs reports submitted to the rational drug use and pharmacovigilance department at JFDA from 2010 to 2014 were analyzed. The aims of analysis of ADRs reports were to create national PV database for the JFDA, to determine the rate of reporting per year, classes of drugs involved in causing ADRs, the most common reported drugs, the most frequently ADRs and system organ classes involved in these ADRs. System organ classes and body systems involved in ADRs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology ¹⁰.

RESULTS

The total number of ADRs reports received was 428 over the 5-year period. Eighty

Table 1: Classes of drugs implicated in causing ADRs

Classes of Drugs	Total No. of reports (348)	Percentage (%)
Antineoplastics	131	37.6%
Immunomodulators	49	14.1%
Antibiotics	36	10.3%
Analgesics	23	6.6%
Antihypertensives	19	5.5%
Antivirals	15	4.3%
Antiepileptics	13	3.7%
Anticoagulants	9	2.6%
Antidiabetics	9	2.6%
Corticosteroids	7	2%
Antihyperlipidemics	4	1.2%
Hormones	4	1.2%
Antipsychotics	2	0.6%
Vitamins & iron	2	0.6%
Anti-acne	2	0.6%
Peptic ulcer-healing	2	0.6%
Antidepressants	1	0.3%
Others	20	5.7%

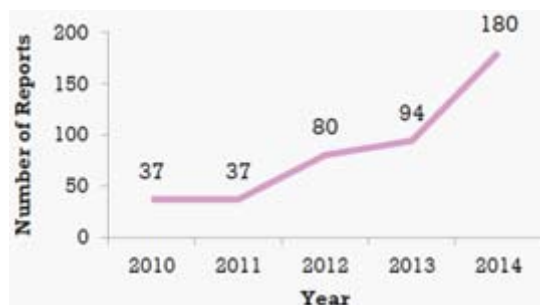


Fig. 1: Number of ADR Reports/Year

Table 2: Drugs involved in causing ADRs

No of reports	Drugs	Total no of reports N= 348	No of drugs	Classes of drugs
28	Docetaxel	131	25	Antineoplastics
15	Oxaliplatin			
11	Nilotinib			
11	Capcitabine			
10	Rituximab			
10	Filgrastim G-CSF			
8	Bevacizumab			
5	Erlotinib			
5	Cabazitaxel			
4	Imatinib			
3	Everolimus			
3	Paclitaxel			
2	Carboplatin			
2	Fluorouracil			
2	Trastuzumab			
2	Pegfilgrastim			
2	Hydroxyurea			
1	Cisplatin			
1	Cyclophosphamide			
1	Cytarabine			
1	Dacarbazine			
1	Ruxolitinib			
1	Vincristin			
1	Bortezomib			
1	Vemurafenib			
12	Lenalidomide	49	10	Immunomodulators
10	Thalidomide			
6	Adalimumab			
4	Cyclosporine			
4	Infliximab			
4	fingolimod			
4	Tacrolimus			
3	Tocilizumab			
1	Mycophenolate			
1	Basiliximab			
8	Ceftriaxone	36	15	Antibiotics
6	Vancomycin			
4	Doxycycline			
3	Teicoplanin			
2	Ciprofloxacin			
2	Gemifloxacin			
2	Imipenem + cilastatin			
2	Amoxicillin			

1	Azithromycin			
1	Amikacin			
1	Cefdinir			
1	Cefuroxime			
1	Erythromycin			
1	Metronidazole			
1	Tigecycline			
8	Diclofenac	23	10	Analgesics
4	Aspirin			
3	Paracetamol			
2	Pethidine			
1	Codeine			
1	morphine			
1	Piroxicam			
1	Lornoxicam			
1	Etoricoxib			
1	Ibuprofen			
4	Amlodipine	19	10	Antihypertensives
4	Furosemide			
3	Irbesartan			
2	Candesartan			
1	Enalapril			
1	Valsartan			
1	Hydrochlorothiazide			
1	Atenolol			
1	Metoprolol			
1	Amiloride			
8	Peg interferon alfa 2a	15	7	Antivirals
2	Valganciclovir			
1	Ganciclovir			
1	Micafungin			
1	Interferon alpha			
1	Acyclovir			
1	Ribavirin			
5	Lamotrigine	13	6	Antiepileptics
3	Carbamazepine			
2	Topiramate			
1	Phenobarbital			
1	Oxcarbazepine			
1	levetiracetam			
3	Enoxaparin	9	4	Anticoagulants &Fibrinolytics
2	Heparin			
2	Bemiparin Sodium			
2	Streptokinase			
4	Metformin	9	4	Antidiabetics
3	Insulin			
1	Vildagliptin			
1	Glibenclamide			
3	Prednisolone	7	5	Corticosteroids
1	Dexamethasone			

1	Fluticasone			
1	Hydrocortisone			
1	Betamethasone			
2	Atorvastatin	4	3	Antihyperlipidemics
1	Gemfibrozil			
1	Simvastatin			
2	Oxytocin	4	3	Hormones
1	levothyroxin			
1	Progesterone			
2	Paliperidone	2	1	Antipsychotics
1	Alfacalcidol	2	2	Vitamins & iron
1	Iron			
2	Isotretinoin	2	1	Anti-acne
1	Famotidine	2	2	Peptic ulcer-healing
1	Omeprazole			
1	Venlafaxine	1	1	Antidepressants
2	Immunoglobulin	20	17	Others
2	Atracurium			
2	Zoledronic acid			
1	Cyclopentolate			
1	Omalizumab			
1	Brimonidine			
1	Misicrom			
1	Sulbutamol			
1	Hydroxychloroquine			
1	Deferasirox			
1	Rifampicin			
1	Epoetin beta			
1	Ibandronic acid			
1	Salbutamol			
1	Midazolam			
1	Hydroxychloroquine			
1	Pseudoephedrine			

reports were excluded from the analysis as they were related to quality issue; therefore 348 reports were included in the study. The annual rate of reporting increased gradually over the study period. There was about a 5-fold increase in the number of received ADR reports (Figure 1).

Classes of drugs involved in ADRs

Seventeen classes of drugs were involved in causing ADRs. The most common classes were antineoplastics (37.6%), immunomodulators (14.1%), antibiotics (10.3%) and analgesics (6.6%) (Table 1).

A total of 125 drugs were involved in causing ADRs. Antineoplastics were the first most common class of drugs, 131 reports. The most frequent antineoplastic drugs were docetaxel (28) reports, followed by oxaliplatin (15) reports. Immunomodulators were the second most common class of drugs involved in ADRs, 49 reports. The most commonly drugs were lenalidomide (12), and thalidomide (10) reports. Antibiotics were the third most commonly class of drugs involved in ADRs, 36 reports. The most common drugs were ceftriaxone (8) reports, and vancomycin (6) reports (Table 2).

System Organ Classes involved in ADRs

The total number of ADRs was (417). The most frequently reported systems were skin and subcutaneous 80 ADRs (19.2%), gastrointestinal (GI) 69 ADRs (16.5%) and nervous system 48 ADRs (11.5%) (Tables 3 & 4).

DISCUSSION

The rationale drug use and pharmacovigilance department at JFDA with the cooperation of Health Hazard Evaluation Committee (HHEC) has analyzed the domestic adverse drug reactions (ADRs) reports submitted to JFDA. The results of this study summarized the last 5 years experience of PV in Jordan. This study shows that there was a 5-fold increase in the number of received ADRs reports. Although these results indicated that reporting rate increased over the study period, however, the rate of reporting is still low in Jordan. Under-reporting of ADRs is a challenge for PV system worldwide, this is because most countries including Jordan follow the spontaneous or voluntary reporting system of ADRs¹¹⁻¹⁴. A study was conducted in the UK by Venulet *et*

al. showed that about 85-98 % of doctors never submitted an ADR report to the national authority¹⁵. A recent study was conducted by Suyagh *et al.* to evaluate the pharmacist's knowledge, practice and attitude toward ADRs reporting in Jordan. This study suggested that the majority of pharmacists have insufficient knowledge about PV and ADRs reporting and the authors recommended that more educational programs are needed to increase the pharmacists role in the process of reporting¹⁶. A cross-sectional study by Abu Farah *et al.* was conducted to evaluate knowledge and perceptions of PV among pharmacy students in Jordan. This study found that the majority of students had lack of knowledge of PV and reporting, and PharmD students had better knowledge about PV and ADRs reporting system than Bachelor of pharmacy students. The authors suggested incorporation of PV into pharmacy curriculum in order to increase the awareness among pharmacy students¹⁷.

According to the results of this study, seventeen classes of drugs were involved in causing ADRs. The most common classes were antineoplastics (37.6%), immunomodulators (14.1%), antibiotics (10.3%) and analgesics (6.6%). These results are similar to previous studies. A study by Ozcan *et al.* demonstrated that antineoplastics, immunomodulators, and anti-infective agents were the most frequently reported drug groups involved in ADRs, they accounted for about 50% of all reported drugs¹⁸. A study by Khan *et al.* showed that antibiotics and anticancer drugs were the most frequent classes of drugs implicated in ADRs¹⁹. A study by Gharaibeh *et al.* was conducted to assess the prevalence rate of drug-induced admissions to the medical ward at Jordan University Hospital. They found that 3.6% of admissions were drug-induced, and chemotherapeutic drugs were the most common involved drugs, they were implicated in 36% of cases²⁰. A recent study by Alsbou *et al.* showed that the prevalence rate of ADRs was 3.2%, and antibiotics and analgesics were the most common classes of drugs involved in ADRs, they were involved in 33% and 25% of ADRs, respectively²¹. Another pilot study by Alsbou *et al.* showed that 8% of patients admitted to the internal medical department experienced an ADR, and antibiotics and analgesics were the most commonly drugs involved in causing ADRs²².

Table 3: System organ classes involved in ADRs

System Organ Class	Total No. of ADRs (417)	Percentage (%)
Skin & Subcutaneous	80	19.2%
Gastrointestinal	69	16.5%
Nervous	48	11.5%
Blood	39	9.4%
Respiratory	31	7.4%
General Disorder	31	7.4%
Musculoskeletal	30	7.2%
Vascular	21	5%
Endocrine	16	3.8%
Cardiac	15	3.6%
Renal & Urinary	10	2.4%
Hepatobiliary	9	2.2%
Immune	8	1.9%
Psychiatric	4	1%
Infections	3	0.7%
Eye	2	0.5%
Ear	1	0.2%

Table 4: Systems involved in ADRs according to MedDRA terminology

Systems	No of ADRs	ADRs	No of ADRs		
Skin & subcutaneous	80	skin rash	31		
		Redness	18		
		Itching	13		
		Acral erythema	4		
		Hand & foot syndrome GIII	4		
		Angioedema	4		
		Urticaria	3		
		Sweating	2		
		Photosensitivity	1		
		Gastrointestinal	69	Vomiting	22
Diarrhea	11				
GI bleeding	6				
Duodenal ulcer	6				
Abdominal pain	6				
Nausea	5				
Constipation	3				
Erosions antralgastropathy	3				
Heartburn	1				
Gingival hyperplasia	1				
Dysphagia	1				
Loss of taste	1				
Localized small bowel angioedema	1				
Poor appetite	1				
Abdominal Distension	1				
Nervous	48			Headache	7
				Convulsions	7
		Generalized weakness	6		
		Numbness	5		
		Drowsiness	4		
		Neuropathy	3		
		Extrapyramidal symptoms	2		
		Coma	2		
		Speaking disturbances	2		
		Hyperthermia	2		
		Tremor	2		
		Neuralgia	1		
		Increased intracranial pressure	1		
		Disorientation to time, place	1		
		Sleep disturbance	1		
		Vertigo	1		
		Blood	39	Vocal cord paralysis	1
Anemia	9				
Neutropenia	9				
Thrombocytopenia	7				
Pancytopenia	5				

		Septicemia, Septic cholangitis	3
		Bleeding	2
		Leukopenia	2
		Leukocytosis	1
		Febrile neutropenia	1
Respiratory	31	Difficulty in breathing	20
		Cough	5
		Respiratory depression	3
		Chest infection	2
		Candida infection in lungs	1
General disorders	31	Fever	27
		Chills	4
Musculoskeletal	30	Back pain	19
		Myalgia	3
		Muscle weakness	3
		Arthralgia	2
		Muscle cramps	2
		Sitting imbalance	1
Vascular	21	Hypotension	10
		Hypertension	5
		Septic shock	2
		Pulmonary embolism	2
		Leg edema	1
		Arterial thromboembolism	1
Endocrine	16	Hyperglycemia	4
		Hypoglycemia	3
		Hypocalcemia	2
		Hyponatremia	2
		Hypercalcemia	1
		Hypertrichosis	1
		Elevated TSH	1
		Thyroid disorders	1
		Hypokalemia	1
Cardiac	15	Palpitation	10
		Cardiac arrest	2
		Ischemia	1
		Myocardial infarction	1
		Bradycardia	1
Renal & urinary	10	Renal impairment	4
		Hematuria	2
		Renal colic	1
		Urinary tract infection	1
		Acute urinary retention	1
		Micro albuminuria	1
Hepatobiliary	9	Elevation of liver enzymes	3
		Biliary colic	2
		Crigler-najjar syndrome	2
		Jaundice	1
		Hyperbilirubinemia	1
Immune	8	Anaphylaxis	5

		Anaphylactic shock	1
		Reactivation of chicken box	1
		Arthritis	1
Psychiatric	4	Hallucination	4
		Herpes Zoster	2
Infections	3	Mucositis	1
		Retinopathy	1
Eye	2	Eyelid edema	1
		Tinnitus	1
Ear	1		

According to our results, the most common system organ classes involved in ADRs were skin and subcutaneous 80 ADRs (19.2%), gastrointestinal 69 ADRs (16.5%) and nervous system 48 ADRs (11.5%). These results are consistent with previous studies. Analysis of ADRs reports submitted to the WHO-ADR-VigiBase showed that skin and subcutaneous tissue disorders, nervous system and GI disorders were the most commonly reported ADRs²³. A recent study was conducted to analyze the ADR reports submitted to the Turkish PV center showed that skin and subcutaneous tissue, general disorders and administration site conditions, GI and nervous disorders were the most frequently reported ADRs, they were implicated in 15.3%, 13.5%, 10.7%, 9.6% of ADRs, respectively¹⁸. Another study by Khan *et al.* found that the most frequent body systems implicated in ADRs were GI, skin and nervous systems and the GI symptoms were vomiting, nausea and diarrhea, and the symptoms related to the skin were rash and urticaria¹⁹. A study by Alsbou *et al.* showed that GI symptoms (vomiting, diarrhea,

bleeding, peptic ulcer and nausea) and allergic reactions (skin rash) were the most commonly identified ADRs²¹. A pilot study showed that skin rash and GI bleeding were the most common reactions involved in ADRs²². Another study by Garaibeh *et al.* found that bone marrow was the most affected body organ implicated in drug-induced admissions (32%), followed by the nervous system (24%), and then the GI system (23%)²⁰.

CONCLUSION

In conclusion, this is the first detailed study to analyze the national PV database in Jordan. The results of this study is considered as a useful tool for JFDA to look for new safety concerns that might be related to the marketed drugs in Jordan and it will enable the health authority to take an appropriate action toward drugs at the proper time to ensure patient safety and improve public health. The success of PV system in Jordan depends upon government support and public awareness on need to report suspected ADRs.

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