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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 Pharmacovigilace (PV) departmentat 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 studyareconsidered the cornerstone of post-marketing surveillance and itcould be used an essential tool for signal generationin 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.
KEWORDS: *Pharmacovigilance; adverse drug reactions; Jordan*

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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 drugs [2].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 individuals (3).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 PVguidelines 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). This is the first detailed study to analyze the national PV database in Jordan.

METHODS

ADRs reports submitted to the rational drug use and pharmacovigilance department at JFDA from 2010 to 2014 were analyzed.The aims ofanalysis of ADRs reportswere tocreate 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 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 graduallyover the study period. There was about a 5-fold increase in the number of received reports(Figure 1).

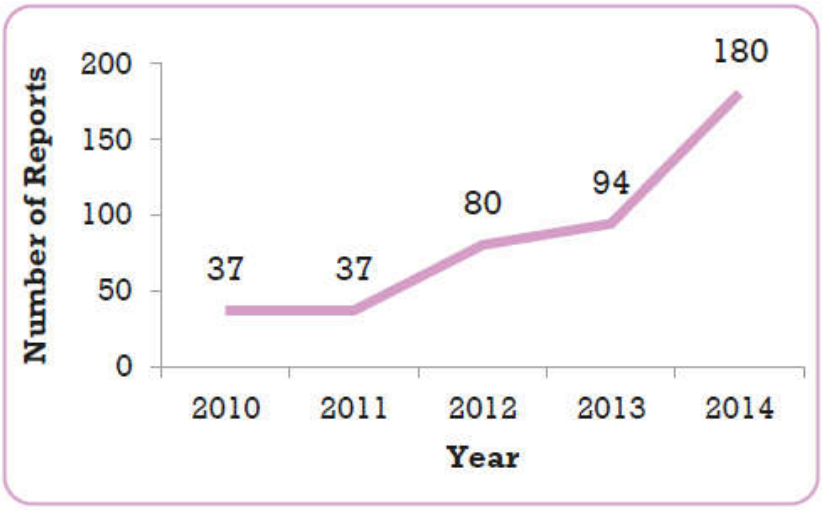

Figure 1.Number of ADR Reports/Year.

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%) (Table1).

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%**

A total of 125 drugs were involved in causing ADRs. Antineoplastics were the first most common class of drugs, 131 reports (37.6%). 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 (14.1%). 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 (10.3%). The most common drugs were ceftriaxone (8) reports, and vancomycin [6] reports (Table 2).

Table 2. Drugs involved in causing ADRs

Classes of drugs	No of drugs	Total no of reports N= 348	Drugs	No of reports
Antineoplastics	25	131	**Docetaxel**	**28**
			Oxaliplatin	15
			Nilotinib	11
			Capcitabine	11
			Rituximab	10
			Filgrastim G-CSF	10
			Bevacizumab	8
			Erlotinib	5
			Cabazitaxel	5
			Imatinib	4
			Everolimus	3
			Paclitaxel	3
			Carboplatin	2
			Fluorouracil	2
			Trastuzumab	2
			Pegfilgrastim	**2**
			Hydroxyurea	2
			Cisplatin	1
			Cyclophosphamide	1
			Cytarabine	1
			Dacarbazine	1
			Ruxolitinib	1
			Vincristin	1
			Bortezomib	1
			Vemurafenib	1
Immunomodulators	10	49	**Lenalidomide**	**12**
			Thalidomide	10
			Adalimumab	6

			Cyclosporine	4
			Infliximab	4
			fingolimod	4
			Tacrolimus	4
			Tocilizumab	3
			Mycophenolate	1
			Basiliximab	1
Antibiotics	15	36	**Ceftriaxone**	**8**
			Vancomycin	6
			Doxycylcine	4
			Teicoplanin	3
			Ciprofloxacin	2
			Gemifloxacin	2
			Imipenem + cilastatin	2
			Amoxicillin	2
			Azithromycin	1
			Amikacin	1
			Cefdinir	1
			Cefuroxime	1
			Erythromycin	1
			Metronidazole	1
			Tigecycline	1
Analgescis	10	23	**Diclofenac**	**8**
			Aspirin	4
			Paracetamol	3
			Pethidine	2
			Codeine	1
			morphine	1
			Piroxicam	1
			Lornoxicam	1
			Etoricoxib	1
			Ibuprofen	1
Antihypertensives	10	19	**Amlodipine**	**4**
			Furosemide	**4**
			Irbesrtan	3
			Candesartan	2
			Enalapril	1
			Valsartan	1
			Hydrochlorothiazide	1
			Atenolol	1
			Metoprolol	1
			Amiloride	1
Antivirals	7	15	**Peg interferon alfa 2a**	**8**
			Valganciclovir	2

			Ganciclovir	1
			Micafungin	1
			Interferon alpha	1
			Acyclovir	1
			Ribavirin	1
Antiepileptics	6	13	**Lamotrigine**	**5**
			Carbamazepine	3
			Topiramate	2
			Phenobarbital	1
			Oxcarbazepine	1
			levetiracetam	1
Anticoagulants &Fibrinolytics	4	9	**Enoxaparin**	3
			Heparin	2
			Bemiparin Sodium	2
			Streptokinase	2
Antidiabetics	4	9	**Metformin**	**4**
			Insulin	3
			Vildagliptin	1
			Glibenclamide	1
Corticosteroids	5	7	**Prednisolone**	**3**
			Dexamethasone	1
			Fluticasone	1
			Hydrocortisone	1
			Betamethasone	1
Antihyperlipidemics	3	4	**Atorvastatin**	**2**
			Gemfibrozil	1
			Simvastatin	1
Hormones	3	4	**Oxytocin**	2
			levothyroxin	1
			Progesterone	1
Antipsychotics	1	1	**Palipeidone**	3
Vitamins & iron	2	2	Alfacalcidol	1
			Iron	1
Anti-acne	1	2	Isotretinoin	2
Peptic ulcer-healing	2	2	Famotidine	1
			Omeprazole	1
Antidepressants	1	1	Venlafaxine	1
Others	17	20	Immunoglobulin	2
			Atracurium	2
			Zoledronic acid	2
			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	1

System Organ Classes involved in ADRs:
The total number of ADRs is (**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).

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

Gastrointestinal	69	Photosensitivity	1
		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
		Vocal cord paralysis	1
Blood	39	**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, hepatitis		1
		Arthritis		1
Psychiatric	4	**Hallucination**		4
Infections	**3**	**Herpes Zoster**		2
		Mucositis		1
Eye	**2**	**Retinopathy**	1	
		Eyelid edema	1	
Ear	1	**Tinnitus**		1

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 indicatedthat reporting rate increased over the study period, however, the rate of reporting is still lowin 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 ADRs [11-14]. 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 authority [15]. 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 reporting [16]. 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 PhamD students had better knowledge about PV and ADRs reporting system than Bachelor of pharmacy (Bpharm) students. The authors suggested incorporation of PV into pharmacy curriculum in order to increase the awareness among pharmacy students [17].

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 drugs (18).A study by Khan et al. showed that antibiotics and anticancer drugs were the most frequent classes of drugs implicated in ADRs [19].A study by Gharaibeh et al. was conductedto 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 cases [20].A recent study by Alsbou et al. showed that the prevalence rate of ADRs was 3.2%, andantibiotics and analgesics were the most common classes of drugs involved in ADRs, they were involved in 33% and 25% of ADRs, respectively(21). 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 ADRs [22].

According to our results, the most common systemorgan 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 ADRs [23].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, respectively [18]. 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 urticaria [19].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 ADRs (21).A pilot study showed that skin rash and GI bleeding were the most common reactionsinvolved in ADRs (22). Another study by Garaibeh et al found that bone marrow was the most affected body organ implicatedin drug-induced admissions (32%), followed by the nervous system (24%), and then the GI system (23%) [20].

In conclusion, the results of this studyis 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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