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Analysis of Antineoplastics, Immunomodulators, Antibiotics and Analgesics Adverse Drug Reactions Reports Submitted to the Pharmacovigilance Database in Jordan

Mohammed Alsbou[1], Adel Batarseh[2], Nidda Bawaresh[3], Jaber Jaber[3], Gadeer Qawasmi[3] and Hayat Banat[3]

[1]Department of Pharmacology, Faculty of Medicine, Mutah University, Jordan.
[2]Royal Medical Services, Jordan.
[3]Rational Drug Use & Pharmacovigilance Department, Jordan Food & Drug Administration, Jordan.

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A national pharmacovigilance database was created recently at the Rational Drug Use and Pharmacovigilance Department at Jordan Food and Drug Administration (JFDA). This study was based on the analysis of the adverse drug reactions (ADRs) reports submitted to the national pharmacovigilance (PV) database in Jordan from 2010 to 2014.The aims of this study were to identify the most frequently body system classes and the most common ADRs for the four major classes of dugs implicated in the PV database and include: antineoplastics, immunomodulators, antibiotics and analgesics. The most affected systems by ADRs in our study were the skin and the gastrointestinal (GI) systems. The skin ADRs associated with the use of antineoplastics were skin rash, hand and foot syndrome and acral erythema, and the most frequent GI ADRs were vomiting and diarrhea. The most affected system by the use of the immunomodulators was the blood system and the most common ADRs were anemia, thrombocytopenia and neutropenia. The most commonly ADRs following analgesics use were GI bleeding and duodenal ulcer and the skin reactions were rash, itching and flushing. Analysis of the national PV database provides close monitoring and more information about the safety of medicine in Jordan. All Health care provider should be aware of the importance of reporting of adverse reactions and should be encouraged to report suspected ADRs and be trained in detecting, diagnosing and treating patients with adverse effects of drugs.

Keywords: Pharmacovigilance database, adverse drug reactions, Jordan.

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem[1]. The objectives of PV are to prevent harm from adverse reactions and to promote the safe and effective use of medicines, in particular through providing timely information about the safety of medicines to patients, healthcare professionals and the public [2].

* To whom all correspondence should be addressed.
Tel.: +962 795754724; Fax: +962 3 2397180;
E-mail: mohsb74@yahoo.com

Jordan was one of the leader countries in drug industry in the region, therefore, regulators at the Jordan Food and Drug Administration (JFDA) had the vision to comply with the worldwide regulations toward industry and committed to patient protection through the conduction of clinical studies law and pharmacovigilance regulations. Pharmacovigilance system was established in 2001 in Jordan, and had WHO membership in 2002. Therefore, promotional campaigns started among healthcare providers based on the needs mentioned above specially improving patient care and industry prospective

to facilitate drug export worldwide [3]. In 2006 was the first approval of adverse drug reactions guidelines based on the International Council for Harmonization (ICH)- Guidelines, which clarify the relation among stakeholders (Health authorities, healthcare providers , industry and patient), and in 2010 there was another updating for different articles in the guidelines according to JFDA/PV post marketing practical experience in Jordan [4]. In 2014, a new era for pharmacovigilance has been arising specially with the final approval of the arab guidelines for Good Pharmacovigilance Practices (GVP). The new guidelines are largely adapted from the European Good Pharmacovigilance Practices. The final draft of the common guidelines was approved by arab ministers of health in Amman-Jordan under the umbrella of Arab League. These guidelines are beneficial for regulators at the regional level because all arab countries will have a unified system for pharmacovigilance with some changes at the national level, and in countries with no pharmacovigilance system, the arab guidelines will enable them to set up their own system [5].

Pharmacovigilance efforts were integrated with the tasks of Health Hazard Evaluation Committee (HHEC), the responsibilities of this committee were to discuss issues related to quality or safety of the registered medicines in Jordan, analyse the available local PV database and provide recommendations to the decision makers to take the right action toward drugs [4]. On the basis of World Health Organization (WHO) art work for reporting system, in Jordan the system for data collecting, collating and assessment is similar to WHO- recommendation and worldwide regulations. Moreover, recently five PV peripherals centers (one in the south, two in the middle, one in the north, and one office at Jordan University) have been established to motivate reporting of ADRs (from patients, healthcare providers) and increase the number and quality of received reports by further training, interaction and communication [6].

Aims

To analyse the ADR reports submitted to the national PV database in Jordan with the aim to identify the most common system organ classes and the most frequent ADRs for the most common classes of drugs implicated in the national PV database: antineoplastics, immunomodulators, antibiotics and analgesics.

METHODS

ADRs reports submitted from 2010 to 2014 to the national PV database at JFDA and involved the following classes of drugs were analysed: antineoplastics, immunomodulators, antibiotic and analgesics. System organ classes involved in ADRs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology [7].

RESULTS

The most common antineoplastic drugs involved in ADRs were docetaxel, oxaliplatin, rituximab, and capacitabine. They were involved in causing 37, 27, 14, and 13 ADRs, respectively. The most frequently system organ classes involved in these ADRs were the skin and subcutaneous, GI, and blood systems. The skin manifestations were skin rash, hand and foot syndrome and acral erythema. Vomiting and diarrhea were the most frequent GI related ADRs. The ADRs related to blood system were febrile neutropenia and thrombocytopenia (Table 1).

The most commonly immunomodulatory drugs involved in causing ADRs were lenalidomide (12 ADRs) and thalidomide (12 ADRs). The most frequently systems involved in these ADRs were blood, followed by skin and subcutaneous, nervous and GI systems. The most common ADRs of the blood system were anemia, thrombocytopenia and neutropenia. The most common skin reactions were skin rash, itching and angioedema. The most frequently ADRs of the nervous system were numbness, weakness, peripheral neuropathy and headache. The most common GI ADRs were nausea, vomiting, diarrhea and abdominal pain (Table 2).

The most common antibiotics involved in ADRs were ceftriaxone, vancomycin, teicoplanin, ciprofloxacin and doxycycline. They were involved in causing 11, 9, 9, 7 and 5 ADRs, respectively. The skin and GI were the most frequent systems involved in ADRs. Skin rash was the commonest reactions. The most common ADRs of the GI system was vomiting (Table 3).

The most common analgesic drugs implicted in ADRs were diclofenac and aspirin. The most frequent systems were the GI and skin. The most common ADRs of the GI system were GI bleeding and duodenal ulcer. The skin reactions were rash, itching and flushing (Table 4).

DISCUSSION

Previous analysis of the national PV database in Jordan in the period from 2010-2014 has shown that antineoplastics, immunomodulators, antibiotic and analgesics were the most frequently

Table 1. Antineoplastic drugs involved in causing ADRs

Drug	ADRs
Docetaxel	Skin rash (5), diarrhea (4), acral erythema (4), back pain (4), hand & foot syndrome (3), mucositis (3),anaphylaxis (3), vomiting (3), febrile neutropenia (2), flushing (2), neuralgia, difficulty in breathing, joint & muscle pain, cough
Oxaliplatin	Hypotension (5), difficulty in breathing (3), palpitation (3), dizziness (3), nausea, vomiting (3), diarrhea (2), abdominal pain, constipation, febrile neutropenia, abdominal distension, itching and rash, headache, vertigo
Rituximab	Vomiting (2), nausea (2), Herpes Zoster (2), headache (2), fever (2), difficulty in breathing (2), anaphylactic shock (1), abdominal pain (1)
Capacitabine	Neutropenia (2), hyperparathyroidism (2), hypercalcemia (2), hand and foot syndrome (2), mucositis, hypotension, nausea, vomiting, neuropathy
Nilotinib	Thrombocytopenia (3), cough (3)
Filgrastim	Back pain(5), sweating (2)
Bevacizumab	Thrombocytopenia (2), hallucination (2), thromboembolism (1)
Erlotinib	Skin rash
Cabazitaxel	Hypotension
Everolimus	Mucositis, acute renal failure
Paclitaxel	Neuropathy, skin rash, itching
Carboplatin	Neuropathy, skin rash, itching
Fluorouracil	Ischemia, skin rash, hyperthermia, hypertension
Pegfilgrastim	Respiratory depression, bone pain
Hydroxyurea	Leukocytosis, neuropathy
Cisplatin	Febrile neutropenia
Cyclophosphamide	Febrile neutropenia
Cytarabine	Febrile neutropenia
Dacarbazine	Fever, chills, sweating
Vincristin	febrile neutropenia
Bortezomib	Vocal cord paralysis
Vemurafenib	Fever, vomiting

Table 2. Immunomodulator drugs involved in ADRs

Drugs	ADRs
Lenalidomide	Anemia (3), neutropenia (2), hallucination, diarrhea, nausea, peripheral neuropathy, chest infection ,thrombocytopenia
Thalidomide	Itching (3), skin rash (3),numbness (2),weakness (2),tinnitus, renal impairment , anemia
Adalimumab	Abdominal pain, candida infection in lungs, fever, headache
Cyclosporine	Hallucination, gingival hyperplasia
Infliximab	Crigler -najjar syndrome (3)
Fingolimod	Elevation of liver enzymes (3)
Tacrolimus	Vomiting
Tocilizumab	Anaphylaxis, angioedema, skin rash, tachycardia, anemia, thrombocytopenia
Mycophenolate	Diarrhea
Basiliximab	Thrombocytopenia

reported classes of drugs implicated in the ADRs reports submitted to the JFDA. They accounted for 37.6%, 14.1%, 10.3%, and 6.6% of all reported drugs [8]. In this study the aims were to analyse the most common body systems implicated in ADRs for each drug group and to identify the most common ADRs for each individual drug. According to the results of this study, the most frequently system organ classes involved in the antineoplastic associated ADRs were the skin and subcutaneous, GI, and blood systems. Antineoplastic agents have been used for the past six decades and their adverse reactions are well known [9,10]. Chemotherapeutic agents have numerous adverse effects that may affect the skin, hair, mucous membranes, or nails [11]. The skin and cutaneous adverse reactions of the chemotherapeutic agent vary from rash, hand-foot syndrome, acral erythema, and Steven Johnson syndrome and toxic epidermal necrolysis [12,13]. Physicians should be able to recognize the range of cutaneous adverse reaction of the newly chemotherapeutic agents and find the appropriate treatment for each case [14]. Garaibeh et al studied the drug-induced admissions to the medical wards at Jordan University Hospital and found that chemotherapeutic drugs were the most commonly drugs involved in ADRs and bone marrow was the most affected body organ implicated in drug-induced admissions (32%), the nervous system (24%), and followed by the GI system (23%) [15]. A study by Khan et al showed that anti-infective drugs, anticancer drugs, non-steroidal anti-inflammatory drugs (NSAIDs) and immunomodulators were the most commonly drugs implicated in ADRs, and skin, GI and nervous were the most frequently systems involved in ADRs [16].

According to our results the most frequently systems involved in the

Table 3. Antibiotics drugs involved in ADRs

Drug	ADRs
Ceftriaxone	Skin rash (4), vomiting (2), itching, acute urinary retention, swelling in all body, nausea, fever
Vancomycin	Skin rash (5), difficulty in breathing, respiratory depression, erythema, urticaria
Teicoplanin	Fever (3), difficulty in breathing (3),chills (3)
Ciprofloxacin	Skin rash (2), hypotension, back painabdominal pain, vomiting, itching
Doxycycline	Abdominal pain, dysphagia, heartburnphotosensitivity, pancytopenia
Imipenem + cilastatin	Convulsions, vomiting
Amoxicillin	Skin rash (2), diarrhea, hyperthermia, difficulty in breathing
Azithromycin	Diarrhea
Cefdinir	Jaundice, abdominal pain, elevated liver enzymes, vomiting
Cefuroxime	Diarrhea
Erythromycin	Diarrhea
Metronidazole	Nausea, vomiting
Tigecycline	Septic shock

Table 4. Analgesic drugs involved in ADRs

Drug	ADRs
Diclofenac	GI bleeding (2), duodenal ulcer (2), anaphylactic shock, erosions antral gastropathy, vomiting
Aspirin	GI bleeding (2), duodenal ulcer (2), erosions of antrum, abdominal pain
Paracetamol	Skin rash, itching
Pethidine	Hypotension, swelling around eyes, skin rash, flushing
Codeine	Constipation
Morphine	Constipation
Piroxicam	GI bleeding
Etoricoxib	Hypertension
Ibuprofen	Anaphylactic shock

immunomodulators associated ADRs were blood, skin and subcutaneous, nervous and GI systems. Immunomodulatory therapy has been developed over the past decades, and are used for prevention and treatment of a wide range of diseases such as autoimmune disorders, inflammatory disease, and cancer. Unfortunately, most of these agents have adverse reactions and sometimes can be serve and may require treatment interruption [14,17]. A recent study by Ozcan et al analysed the ADRs report submitted to the national PV center in Turkey from 2005 to 2014, and this study showed that antineoplastic and immunomodulators were the most commonly reported drugs and the most frequently reported ADRs were related to skin and subcutaneous system [18].

Our study showed that the most frequent systems involved in antibiotics-induced ADRs were the skin and GI systems. According to the results of our previous observational study, antibiotics and analgesics were the most common classes of drugs implicated in ADRs, they represented 33% and 25 of ADRs cases, and vancomycin, doxycycline, ceftriaxone and ciprofloxacin were the most reported drugs, skin rash, vomiting and abdominal pain were the most common identified ADRs [19]. Moreover, our previous pilot study has found that antibiotics and analgesics were the most frequently drugs involved in ADRs and skin rash due to the use of antibiotics was the most common reaction identified [20].

According to this study the GI and skin were the most frequent systems involved in the ADRs associated with the use of analgesics. These results are similar to previous studies [21.22]. NSAIDs are associated with a significant risk of GI side effects, bleeding and duodenal ulceration are the most widely injuries caused by NSAIDs [23]. Pirmohamed et al., found that 6.5% of all admissions to two large hospital in the UK are due to ADRs, the most common drugs implicated in ADRs were NSAIDs (aspirin, diclofenac) and GI bleeding and peptic ulcer are the most identified ADRs [24]. Another study by Lim and Heatley was conducted to assess the use of NSAIDs and their relation to upper GI bleeding, the results of this study have shown that NSAIDs are associated with a significant risk of GI bleeding, even if COX-2 selective drugs are being prescribed [25].

CONCLUSION

PV is an important system to monitor the safety and efficacy of medicines and can help to minimize the risk of harms by ensuring that medicines are prescribed appropriately. Establishment and analysis of the national PV database is crucial and improve drug safety through continuous monitoring of adverse drug reactions in Jordan. All health care providers should be engaged and encouraged to report suspected ADRs, with the ultimate goal to improve patients care and safety and to improve public health.

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