

ADVERSE DRUG REACTIONS MONITORING: A PHARMACOVIGILANCE STUDY AT ERBIL AND DUHOK MAIN HOSPITALS IN KURDISTAN REGION / IRAQ

MOHAMMED GHANIM SULAIMAN, BSc*
FOUAD KASIM MOHAMMAD BVMS, MS, PhD**
ANSAM NAJI ALHASSANI BSc, MSc, PhD***

Submitted 12/3/2017; accepted 25/5/2017

ABSTRACT

Background and objectives: Adverse drug reactions (ADRs) are recognized as a common cause of hospital admissions and they constitute a significant economic burden for the hospitals. Many disasters caused by drugs occurred in the past, after that regulation for drug approval has taken place. The aim of this study was to evaluate ADRs and assess their causality, severity and preventability in Erbil and Duhok main hospitals.

Methods: This is a retrospective cross-sectional, hospital-based study, conducted at Rizgary hospital in Erbil and Azadi hospital in Duhok from January to October 2016. Each Adverse reaction was assessed for its causality, severity and preventability using Naranjo, Hartwig and Siegel, and Schumock and Thornton assessment scales, respectively. Data were analyzed using descriptive analysis.

Results: A total of 378 patients with ADRs were reported, 57.7% females and 42.3% males. The maximum percentage of ADRs was noted in patient's age 21-40 years, 66.4% occurred in patients taking two or more medications. Common ADRs were allergic reactions (30.2%) and these involved with the gastrointestinal tract (20.6%). Antimicrobials (30.7%) and analgesics (9.0%) were the common causes of ADRs. Oral (49.47%) and intravenous (37.30%) routes of drug administration were responsible for most of ADRs. Of these cases, 47.9% were preventable, of moderate severity (52.9%), while 7.7% hospitalized, 1.1% needed surgical intervention and 2.4% died from ADRs.

Conclusions: ADRs can be frequently detected; they increase cost of treatment although about half can be prevented. These problems are essential to be reported, analyzed and interpreted, then effectively communicated with health authorities.

Duhok Med J 2017; 11 (1): 19-32.

Keywords: Adverse Drug Reaction, Hospital Based Monitoring, Pharmacovigilance.

The word pharmacovigilance (PV) has been derived from the Greek word *pharmakon* which means "drug" and the Latin word *vigilare* means "to keep awake or alert, to keep watch".¹ World Health Organization (WHO) defines PV as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other

drug-related problem".² A simpler definition describes PV as the processes and science of monitoring drugs safety and taking action to reduce risk and increase benefit.^{3,4}

Historically, there are multitudes of examples of patients harmed by the use of prescribed medications. The thalidomide tragedy is one of the worst examples,

* Pharmacist, Mosul University - College of Pharmacy, University of Mosul

**Professor, Pharmacology & Toxicology, Ministry of Higher Education & Scientific Research, Baghdad, Iraq

***Assistant Professor, Toxicology, College of Pharmacy, Hawler Medical University, Erbil, Kurdistan Region, Iraq

nearly 10000 children were born with phocomelia, leading to the prohibition of thalidomide use in the most of countries in 1961.^{5,6} After this tragedy, rigid drug approval and monitoring systems begin to take place at the United States Food and Drug Administration (FDA).⁷

Prior to product registration and marketing, drugs safety and efficacy information are restricted to observations from pre-clinical animal studies and initial clinical trials (Phase I-III) and these data comprise the basis for the summary of product characteristics or the product label.⁸ Although such trials are appropriate for product registration, they usually evaluate only a small number of selected participants under ideal conditions and have limited statistical power to detect the uncommon side effects. As a result, clinical trials and the data that is derived from them are insufficient for the full evaluation of product safety and risks.⁹ Additionally, such trials better test the efficacy rather than the safety under the practical conditions of every day clinical utilization.¹⁰

Adverse drug reactions are common, often preventable cause of illness, disability and even death. They cause from 3% to 6% of hospital admissions at any age, and up to 24% in the elderly population; they rank fifth among all causes of death, representing from 5 to 10% of hospital costs.¹¹

In order to prevent or reduce harm to the patients and improve health, mechanisms for evaluating and monitoring the drug safety in clinical use are crucial. The aim of this study was to evaluate ADRs and assessing their causality, severity and preventability in Erbil and Duhok main

hospitals and to facilitate the development of a pharmacovigilance service in Kurdistan Region-Iraq.

PATIENTS AND METHODS

A retrospective cross-sectional study was conducted during the period from January to October of 2016. The study was performed in two main tertiary care teaching hospitals located in Kurdistan Region of Iraq, Rizgary hospital in Erbil and Azadi hospital in Duhok.

The study involved all departments in the two hospitals and included inpatients who experienced any ADRs in the hospital or those who were admitted for treatment of ADRs. Patients admitted solely for investigations or with incomplete or unclear medical information were excluded from the study. During the study period, patients were reviewed for ADRs, especially for new drug and the unusual or unexpected reactions. Orientation about the study is being offered for healthcare practitioners (including physicians, pharmacists and nurses) and all of them were asked to report any observed ADRs.

Patients with the offending drugs were identified through routine ward rounds, prescription monitoring, and healthcare practitioners reports. The data were collected from patient case sheets and transferred to a separate data entry formats (Figure 1) specially designed for reporting ADRs. Data were then analyzed by using Naranjo's causality assessment scale, Hartwig and Siegel severity assessment scale, and Schumock and Thornton preventability assessment scale. All patients with suspected/detected ADRs were referred to respective physician to confirm the diagnosis.

Adverse Drug Reaction Template

A- Patient information:

- Age: _____
- Gender: Male Female
- Medication taken: Single Multiple Give number or names: _____

B- Suspected drug(s):

| No. | Drug name & manufacture | Dosage form | Dose | Route | Duration of treatment | Drug stopped (Yes / No) | Prescribed for |
|-----|-------------------------|-------------|------|-------|-----------------------|-------------------------|----------------|
| 1. | | | | | | | |
| 2. | | | | | | | |
| 3. | | | | | | | |

C- Suspected reaction:

- Description of reaction: _____
-
-
-
-
- Duration: _____
- Outcome: Recovered Continuing Other: _____
- Severity: Mild Moderate Severe

D- Reporter details:

Name and specialty: _____

Date: _____

Address: Hospital Private clinic

Additional information:
(ex test results)

Figure 1. Adverse drug reaction template

We designed a template (Figure 1) for reporting ADR containing the main information needed according to WHO and FDA criteria^{10,12} to identify the main medical problems related to the drug preparation in use including information about the patient, suspected drug(s), adverse reaction and the reporter.

The causality assessment scale examined the relation between the reaction and the suspected drug(s) taken by the patient by using the Naranjo Algorithm (Table 1).

Table 1: Naranjo Algorithm¹³

| QUESTION | Yes | No | Do not know |
|---|-----|----|-------------|
| Are there previous conclusion reports on this reaction? | +1 | 0 | 0 |
| Did the adverse event appear after the suspect drug was administered? | +2 | -1 | 0 |

Did the AR improve when the drug was discontinued or a specific antagonist was administered? +1 0 0

Did the AR reappear when drug was readministered? +2 -1 0

Are there alternate causes [other than the drug] that could solely have caused the reaction? -1 +2 0

Did the reaction reappear when a placebo was given? -1 +1 0

Was the drug detected in the blood [or other fluids] in a concentration known to be toxic? +1 0 0

Was the reaction more severe when the dose was increased or less severe when the dose was decreased? +1 0 0

Did the patient have a similar reaction to the same or similar drugs in any previous exposure? +1 0 0

Was the adverse event confirmed by objective evidence? +1 0 0

The severity assessment scale measured and scored the severity of each reaction according to the scale commonly used in the ADRs assessment which is Hartwig and Siegel severity scale (Table 2):

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Table 2. Hartwig and Siegel severity scale ¹⁴

| Level | DESCRIPTION |
|---------|---|
| Level 1 | An ADR occurred but required no change in treatment with the suspected drug. |
| Level 2 | The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay |
| Level 3 | The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed, and/or an antidote or other treatment was required. No increase in length of stay. |
| Level 4 | Any level 3 ADR which increases length of stay by at least 1 day. |
| Level 5 | Any level 4 ADR which requires intensive medical care. |
| Level 6 | The adverse reaction caused permanent harm to the patient. |
| Level 7 | The adverse reaction either directly or indirectly led to the death of the patient. |

The preventability assessment comes after the reaction causality and severity have been determined to examine if the ADR

could be prevented or not by using Schumock and Thornton preventability assessment scale ¹⁵ (Table 3).

Table 3. Schumock and Thornton preventability assessment scale ¹⁵

| No. | QUESTION |
|-----|--|
| 1. | Was the drug involved in the ADR not considered appropriate for the Patient's clinical condition? |
| 2. | Were the dose, route, and frequency of administration not appropriate for the patient's age, weight and disease state? |
| 3. | Was required therapeutic drug monitoring or other necessary laboratory test not performed? |
| 4. | Was there a history of allergy or previous reactions to the drug? |
| 5. | Was a drug interaction involved in the reaction? |
| 6. | Was a toxic serum drug level documented? |
| 7. | Was poor compliance involved in the reaction? |

Data collected were analyzed using software -Statistical Package for Social Sciences (SPSS) version 22. Results of the study were presented with standard

descriptive measures such as mean \pm standard deviation (for quantitative variables), median and numbers with percentages and/or graphical presentations.

RESULTS

During the study period (from January to October of 2016), a total of 378 patients with ADRs were reported. A higher number of ADRs was reported among females in comparison to males; 218 (57.7%) versus 160 (42.3%). The maximum percentage of ADRs (34.1%) was noted in the age group of 21-40 years, to be followed by the age group of 41-60 years (31.7%). The percentage of ADRs was 14.7% and 13.8% in the age group of less than 20 years and above 61 years, respectively (Table 4).

Table 4. Age and gender distribution of adverse drug reactions groups

| Age group (year) | Occurrence | Gender | | Total |
|------------------|--------------|--------|--------|---------|
| | | Male | Female | |
| 0-20 | Occurrence | 41 | 36 | 77 |
| | (%) of Total | (10.8) | (9.5) | (20.4) |
| 21-40 | Occurrence | 52 | 77 | 129 |
| | (%) of Total | (13.8) | (20.4) | (34.1) |
| 41-60 | Occurrence | 45 | 75 | 120 |
| | (%) of Total | (11.9) | (19.8) | (31.7) |
| ≥ 61 | Occurrence | 22 | 30 | 52 |
| | (%) of Total | (5.8) | (7.9) | (13.8) |
| Total | Occurrence | 160 | 218 | 378 |
| | (%) of Total | (42.3) | (57.7) | (100.0) |

The percentage of ADRs was 33.6% in patients taking single medication, whereas 66.4% of ADRs occurred in patients taking two or more medications concomitantly (Table 5).

Table 5. Adverse drug reactions associated with number of medications

| Number of Drugs | Occurrence (%) of ADRs* |
|-----------------|-------------------------|
| 1 | 127(33.6) |
| ≥ 2 | 251(66.4) |
| Total | 378(100.0) |

* Adverse drug reactions

Allergic reactions were reported in 114 cases (30.2%), followed by gastrointestinal tract adverse effects such as gastric perforation (22.2%). Others include cardiovascular (CV) and haematological ADRs (15.9%), and reactions on central nervous system (14.0%). Detailed description of organ systems affected by ADRs is shown in (Table 6).

Table 6. Adverse drug reactions on different organ systems

| No. | Systematic ADRs* | Occurrence (%) of ADRs* |
|-----|----------------------------|-------------------------|
| 1. | Allergic reactions | 114(30.20) |
| 2. | Digestive and Excretory | 78(20.60) |
| 3. | CV and Haematology | 60(15.90) |
| 4. | Nervous | 53(14.00) |
| 5. | Integumentary and Exocrine | 21(5.60) |
| 6. | Miscellaneous | 19(5.00) |
| 7. | Respiratory | 10(2.60) |
| 8. | Renal and Urinary | 7(1.90) |
| 9. | Endocrine | 6(1.60) |
| 10. | Muscular and Skeletal | 6(1.60) |
| 11. | Reproductive | 4(1.10) |
| | Total | 378(100.0) |

*Adverse drug reactions

Detailed description of different drug classes that caused ADRs is shown in (Table 7). Antimicrobials were associated with approximately one-third of all ADRs reported (30.7%) followed by analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) which were associated with 9.0% of ADRs.

Table 7. Adverse drug reactions and therapeutic drug classes

| No | Therapeutic drug Classes | Occurrence (%) of ADRs* |
|----|--------------------------|-------------------------|
| 1. | Antimicrobial | 116(30.7) |
| 2. | Analgesic and NSAID** | 34(9.0) |

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| | | |
|--------------|-------------------------------|-------------------|
| 3. | Antineoplastic | 31(8.2) |
| 4. | Antihypertensive | 28(7.4) |
| 5. | Insulin and Antidiabetic | 26(6.9) |
| 6. | Drug in coagulation disorders | 23(6.1) |
| 8. | Corticosteroid | 15(4.0) |
| 9. | Anticonvulsant | 11(2.9) |
| 10. | Antiemetic | 9(2.4) |
| 11. | Lipid lowering | 8(2.1) |
| 12. | Inotropic | 8(2.1) |
| 13. | Nitrate | 8(2.1) |
| 14. | Anticholinergic | 6(1.6) |
| 15. | Antidepressant | 6(1.6) |
| 16. | Iron supplement | 5(1.3) |
| 17. | Others | 44(11.6) |
| Total | | 378(100.0) |

*Adverse drug reactions

** Non-Steroidal Anti-Inflammatory Drugs

The routes of drug administration in relation to ADRs are shown in Figure 2. Approximately half of ADRs were noted with the oral route. Drugs that were administered by intravenous (IV) route accounted for 37.30% of ADRs, whereas topically administered drugs caused only 1.56% of ADRs.

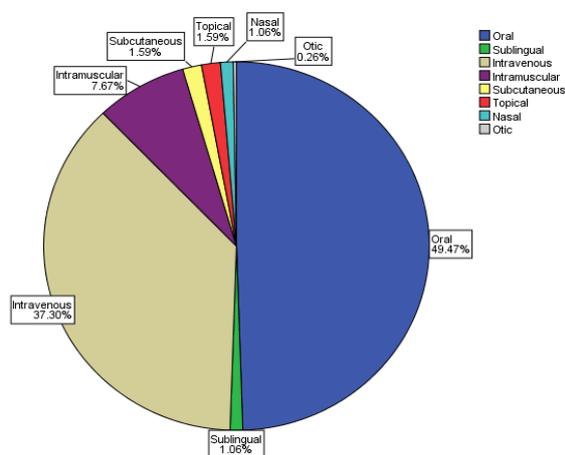


Figure 2. Distribution of adverse drug reactions according to the routes of drug administration

The dosage form which most commonly implicated in ADRs was the tablet form (39.7%); followed by injectable formulation in vials (29.4%). Only 4 cases

(1.1%) were caused by cream use. The distribution of different dosage forms among reported therapeutic drug classes and organ systems affected are shown in Figure 3.

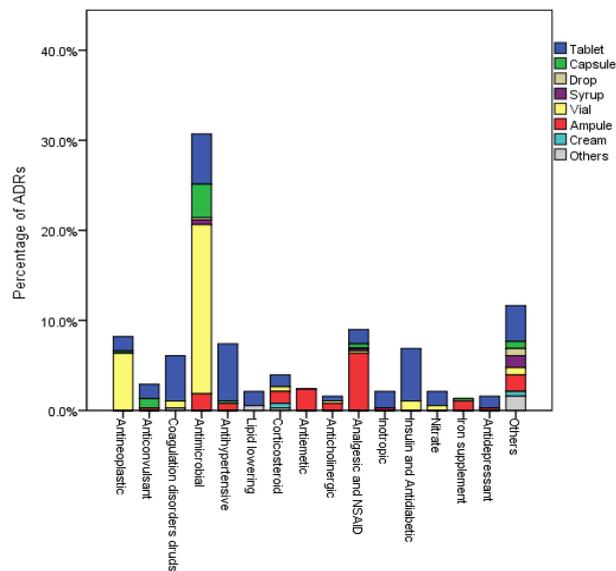


Figure 3. Drug classes of different dosage forms and the percentage of adverse drug reactions (ADRs)

Upon causality assessment using Naranjo's algorithm, majority of the ADRs were rated as probable (57.9%), only 0.5% were considered as doubtful, 14.6% possible, and 27.0% were classified as definite ADRs (Table 8).

Table 8. Causality assessment of adverse drug reactions

| Causality Assessment | Type | Occurrence (%) of ADRs* |
|----------------------|-------------------|-------------------------|
| | Doubtful | 2(0.5) |
| Possible | 55(14.6) | |
| Probable | 219(57.9) | |
| Definite | 102(27.0) | |
| Total | 378(100.0) | |

*Adverse Drug Reactions

Based on Hartwig and Siegel scale to evaluate the severity of ADRs, it was evident that most of ADRs reported in the study were of moderate severity (52.9%), 34.1% were of mild severity and 13.0% of ADRs were severe (Table 9).

Table 9. Severity assessment of adverse drug reactions

| Severity Assessment | Type | Occurrence (%) of ADRs* |
|---------------------|----------|-------------------------|
| | Mild | 129(34.1) |
| | Moderate | 200(52.9) |
| | Severe | 49(13.0) |
| | Total | 378(100.0) |

*Adverse Drug Reactions

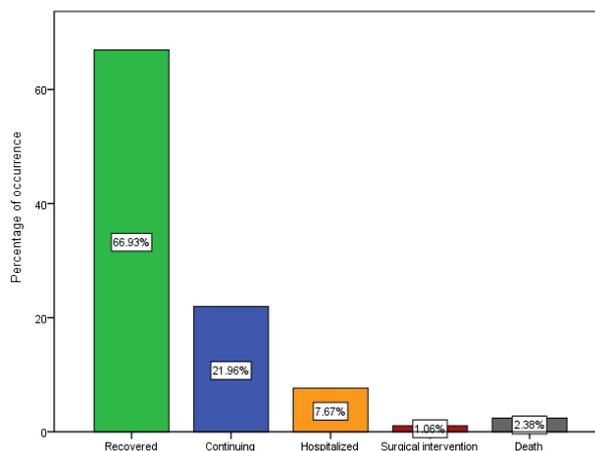
On evaluation of the chances of preventability of ADRs using Schumock and Thornton scale, it was evident that about half of ADRs were preventable (Table 10).

Table 10. Preventability assessment of adverse drug reactions

| Preventability Assessment | Type | Occurrence (%) of ADRs* |
|---------------------------|-------|-------------------------|
| | Yes | 181 (47.9) |
| | No | 197 (52.1) |
| | Total | 378 (100.0) |

* Adverse Drug Reactions

Drug-induced morbidity was an important cause of hospitalization and was significantly associated with mortality. Out of the 378 reported ADRs cases, recovery was noted in 253 cases (66.9%), whereas symptoms continued in 83 cases of ADRs (22.0%). Hospital admission was required in 29 cases (7.7%) (e.g. patient administered cefotaxime injection and suffered from pseudomembranous colitis), and in 4 of them (1.1%) surgical intervention was needed to correct the problem (e.g. naproxen tablet caused gastric perforation). ADRs related death occurred in 9 cases (2.4%) (e.g. alteplase caused haemorrhagic stroke which lead to death), (Figure 4).



affected patients

In 248 (65.6%) of cases, the suspected drug was withdrawn and one or more drugs were required for symptomatic or specific treatment, whereas no change was needed with the suspected drug in 61 (16.1%) of the cases. Also, in 143 (37.8%) of cases, ADRs increased patient's hospital stay by at least one day.

DISCUSSION

Events such as the thalidomide tragedy highlighted the extreme need for effective drug monitoring systems of all drugs. Safety monitoring of drugs in common use should be an integral part of clinical practice.

There is no agreement among studies regarding the incidence of ADRs with respect to gender¹⁶. Rademaker (2001) reported that females were more susceptible to ADRs, the reasons for this increased risk are not completely clear but include gender-related differences in pharmacokinetic, immunological and hormonal factors.¹⁷ Others have found the incidence of ADRs to be unrelated to gender,^{16 18} which support our finding that ADRs did not differ significantly between males and females (Table 4).

In our study the majority of ADRs were in 21-40 years age group (Table 4). The reason might be attributed to modern sedentary lifestyle and increased stress in daily life make this age group more prone to diseases.¹⁹ So it is anticipated that this age group used drugs more frequently and repeatedly visited the hospital for their regular check-up and complaints for drug related adverse effects.

The incidence of ADRs was not directly proportional to the number of drugs being taken but increases remarkably as the number of drugs rises; it could be attributed to drug-drug and drug-disease interactions.²⁰ This was observed in our study in table 5.

Moreover, we found that allergic reactions were the most frequent ADRs detected (Table 6). This finding is in accordance with the results of a previous study done by Patidar et al. (2013)²¹ but it differs from those of others where gastrointestinal (GI) manifestations had the highest rate.¹⁹ In our study, the GI system was the second most frequent cause of ADRs. The reason for this could be that we had given a great attention to detect unusual or uncommon ADRs which were observed in our study. Drugs most frequently trigger allergic reactions were antimicrobial agents and NSAIDs.²² In this study, the drug class most commonly implicated with ADRs was antimicrobials with the highest percentage, followed by analgesic and NSAIDs (Table 7). A similar finding was reported by Malladi (2016).²³

Majority of the ADRs were associated with oral route of drug administration followed by parenteral then topical route (Figure 2) as reported by Shrivastava et al. (2011).²⁴ One of the possible explanations

is that the most frequent organ system affected by ADRs were GI tract and allergic reactions, ADRs on the GI tract were most commonly observed with oral medications,¹⁹ whereas most of the ADRs observed with injectable medication were hypersensitivity reaction, as the parenteral route is considered the most immunogenic one.²⁵

To strengthen and further emphasize the validity of the findings of our study, causality assessment was done by using the Naranjo's scale (Table 1). The majority (57.9%) of ADRs were classified as probable, 14.6% possible, 27% were rated as definite while only 0.5% were considered as doubtful ADRs as shown in table 8. These results were consistent with other studies which revealed comparable results.²⁶

On evaluation of the ADRs severity by the Hartwig and Siegel severity assessment scale (Table 2), it was clear that most of ADRs reported in this study were of moderate severity followed by mild then severe (Table 9). However another study found that the majority of the reactions were moderate in severity,²⁷ whereas others reported that most of the reactions were of mild severity.²⁸ This could be attributed to different ADRs of varying degrees of severity can be caused by various drug types and formulations used by the patients.

On evaluation of the chances of preventability of ADRs using Schumock and Thornton scale (Table 3), it was evident that about half (47.9%) of the reactions were preventable (Table 10). Some of those preventable cases have a previous history of similar reaction following same drug intake; which shows

the lack of awareness. Our result was consistent with another study that measured the preventability of ADRs at four hospitals in South Africa,²⁹ and with a meta-analysis study which also found that approximately half of adverse drug reactions are preventable, demonstrating that further evidence on prevention strategies is required.³⁰ Some researchers found that only little percentage of the ADRs can be prevented.^{31,32} Others reported that most of the ADRs were definitely preventable.³³ In the last study the occurrence of ADRs was higher when compared to that reported in other studies, so preventability of ADRs may differ from one study to another depending on different factors and most resulted from inadequate monitoring of therapy or inappropriate dosing.³⁴

Our results on the hospital admission caused by ADRs were comparable to results obtained by researchers who reviewed 45 studies for the prevalence rates of hospitalization resulting from ADRs.³⁵ In the present study, 2.4% of all ADRs had fatal effect on the patients and this finding is in accordance with the result of a review article that found that the rate of fatal ADRs among a 47 studies was quite consistent,³⁶ and 66.9% of the patient were recovered from the reaction (Figure 4), as shown in another study.³⁷

The impact and the management of ADRs will increase the costs per patient due to increased hospitalization, prolongation of hospital stay, additional clinical investigations and prescription of new drug for the patient condition.³⁸ Most of ADRs cases in our study required withdrawal of the suspected drug and one drug or more was needed for symptomatic

or specific treatment, with low percentages that required no change in treatment. These results were comparable to the results of another study.²¹

In the present study the length of hospital stay was prolonged in 37.8% of ADRs affected patient by at least one day. This is confirmed by Davies et al. (2009) study who concluded that there is a direct relationship between ADRs and the length of patient hospital stay.³⁹ Moreover another study showed that the severity of adverse drug events was also associated with higher costs and a longer length of stay therefore adverse drug events could be economically costly.⁴⁰

Adverse drug reactions were frequently detected in the main teaching hospitals in Kurdistan Region of Iraq. Some cause hospital admissions, intensive medical care and even death; all increases cost of treatment although about half can be prevented. These problems are essential to be reported, analyzed and interpreted then effectively communicated.

ACKNOWLEDGEMENT

This report represents a portion of a thesis submitted by the first author to the University of Mosul, Iraq in partial fulfillment of the requirements of MSc degree in Pharmacology and Toxicology. The study was supported by the College of Pharmacy, University of Mosul, Mosul, Iraq. The authors thank the staff of Azadi and Rizgary teaching hospitals for their support and cooperation.

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الخلاصة

مراقبة التفاعلات الدوائية الضارة: دراسة رصد دوائي في مستشفيات أربيل ودهوك الرئيسية في إقليم كردستان/العراق

خلفية وأهداف البحث: تعد التفاعلات الدوائية الضارة سبباً شائعاً لدخول المرضى المستشفى وأنها تشكل عبئاً اقتصادياً كبيراً على المستشفيات. حصلت العديد من الكوارث في الماضي وكان سببها الأدوية، بعد ذلك سنت قوانين للموافقة على تسويق الأدوية. كان الهدف من هذه الدراسة هو الكشف عن التفاعلات الدوائية الضارة وتقييم مدى تسببها بالدواء وشدها وفرصة الوقاية منها في مستشفيات أربيل ودهوك الرئيسية.

طرائق البحث: هذه الدراسة مستعرضة بأثر رجعي، أجريت في مستشفى رزكري في أربيل ومستشفى آزادي في دهوك من كانون الثاني إلى تشرين الأول 2016. وجرى تقييم كل تفاعل دوائي ضار عن مدى تسببه بالدواء، وشده و فرص الوقاية منه باستخدام جداول تقييم نارنجو، هارتويك و سيكال، و سكوموك و ثورنتون على التوالي. وقد تم تحليل البيانات باستخدام التحليل الوصفي.

النتائج: تم رصد ما مجموعه 378 مريضاً تعرّضوا للتفاعلات الدوائية الضارة، 57.7% إناث و 42.3% ذكور. وقد لوحظ أن النسبة القصوى من التفاعلات في سن 21-40 عاماً، 66.4% من المرضى كانوا يتناولون دوائين أو أكثر. التفاعلات الدوائية الضارة الأكثر شيوعاً كانت الحساسية (30.2%) والتي أثرت على الجهاز الهضمي (20.6%). مضادات الميكروبات (30.7%)، والمسكنات (9.0%) أيضاً كانت أسباباً شائعة لهذه التفاعلات. الأدوية الفموية (49.47%) والوريديّة (37.30%) كانت مسؤولة عن معظم التفاعلات. من مجموع هذه الحالات، 47.9% يمكن الوقاية منها، و 52.9% ذات شدة متوسطة. أدت هذه التفاعلات للبعث (7.7%) الدخول إلى المستشفى، و 1.1% للتدخل الجراحي، و لوفاة 2.4% من الحالات.

الإستنتاجات: التفاعلات الضارة للأدوية من الممكن الكشف عنها بشكل متكرر وهي تزيد من كلفة العلاج على الرغم من أن حوالي النصف ممكن تجنبه. من الضروري الإبلاغ عن هذه المشاكل فضلاً عن تحليلها وتفسيرها ومشاركة المعلومات بشكل فاعل مع السلطات الصحية.