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RESEARCH ARTICLE

Adverse Drug Reaction (ADR) as a Cause of Hospitalization at a Government Hospital in Saudi Arabia: A Prospective Observational Study

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Abstract: ***Background*:** ADRs represent a substantial burden on health care resources worldwide and are considered as one of the leading causes of morbidity and mortality which significantly affects hospitalization rates. However, ADR related hospital admissions are not well explored in Saudi Arabia.

***Objective*:** The current study aims to evaluate ADR-related admissions at King Saud Hospital, Unaizah, Qassim, Saudi Arabia.

***Methods*:** A prospective, observational study was conducted at King Saud Hospital Unaizah. Over a period of 6 months, patients above 12 years of age who visited the Emergency Department (ED) with an ADR were included in this study. The investigators collected patient data by reviewing the patient's medical records and the ED records for admission. The Naranjo algorithm was used to assess the causality of the suspected ADR, and Hartwig's Severity Assessment Scale was used to assess the severity of the ADR.

***Results*:** Out of 4739 admissions to the wards, 38 (0.801%) were related to an ADR. The majority of patients were male (52.6%), with a mean age of ± 49.08 years. The total length of hospital stay was 565 days with a mean of ± 14.87 days. The causality assessment shows that 35 (92.1%) cases were probable ADRs, whereas 3 (7.9%) cases were possible ADRs. Moreover, the severity assessment showed that 6 (15.1%) cases were mild, and 27 (71.1%) and 5 (13.2%) cases were moderate and severe, respectively. In regard to the outcome of patients, most patients recovered after the ADR, and 2 ADRs resulted in the death of the patient.

***Conclusion*:** Our study shows that ADRs as a cause of hospitalization in Qassim population is considerably low. However, ADRs may contribute to morbidity and mortality and result in a considerable financial burden.

Keywords: Adverse drug reactions, ADR monitoring, prevalence, naranjo algorithm, DRPs, Hartwig's severity assessment scale.

1. INTRODUCTION

Medications are the most common treatment prescribed in clinical practice. Hundreds of drugs are currently available in the local market. Being chemicals, all drugs have associated risks of adverse reactions. The World Health Organization (WHO) defines an ADR as "A response to a drug which is noxious and unintended, and which occurs in doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function." [1]. ADRs can be classified into six categories (A, B, C, D, E and F) according to their relation to time and dose taken and are as follows: type A dose-related reactions, type B non-dose-related reactions, type C dose-related and time-related reactions, type D time-related reactions, type E withdrawal and type F unexpected failure of therapy. Type A is related to the pharmacological action of the drug and is the most common type of ADR [2].

ADRs represent a substantial burden on health care resources worldwide and are considered as one of the leading causes of morbidity and mortality. In the United States, epidemiological research shows that ADR significantly affects the hospitalization rates [3]. Moreover, it is estimated that ADRs are responsible for hospital admission in a number of patients in the United States [4-7]. In Brazil, although data are limited, a study conducted by researchers from the State University of Campinas reported that ADRs were responsible for patients' admissions to a tertiary care school hospital [8]. On the other hand, within the Arab region, there is a substantial increase in ADR-related admissions among patients with chronic illnesses. In Egypt, among children aged one month until teenager who were hospitalized in the medical ward and Intensive Care Unit (ICU), as a result of Drug Related Problems (DRPs), were at higher risk and experienced at least one drug-related problem [9].

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Local records and studies evaluating ADRs in Saudi Arabia are limited to the main regions such as Riyadh, Abha, Jeddah and Almadinah. In Riyadh, researchers estimated that ADRs resulted in patient hospitalization, and fewer patients were hospitalized due to DRPs [10]. Additionally, in Jeddah, retrospective and prospective studies performed in hospitalized pediatric patients at Saudi Arabian University Hospital indicated that the incidence rate of ADRs was higher in the prospective study than in the retrospective study [11]. Qassim is among the most populated regions of the country and is located in the central part of Saudi Arabia. This region has well-established government and private hospitals to cater to the health care demands of its people [12]. Although certain hospitals have ADR reporting systems to meet the local requirements of the hospital [13], insufficient data are available to examine the ADR-related hospital admission in this region. The current study aims to evaluate ADR-related admissions at King Saud Hospital, Unaizah. The specific objectives of this study are to determine the most common causative drugs involved in ADRs, to assess the causality and severity of ADR incidences and to determine the association between ADR-related admission and age, sex and number of medications on admission.

2. MATERIALS AND METHODS

2.1. Study Location

Data were collected over a period of 6 months from January-June 2018. During the data collection period, a total of 3314 patients visited the Emergency Department at KSHU, which is the only government hospital with a 352-bed capacity located in Unaizah, Qassim Region, Saudia Arabia.

2.2. Design and Study Population

This was a prospective, observational study to estimate the prevalence of admissions due to an ADR through the Emergency Department. The inclusion criteria included patients above 12 years of age who visited the emergency department with an adverse drug reaction, while those who were admitted for other reasons were excluded.

2.3. Data Collection and Variable Studied

Data were collected to evaluate the prevalence of admission through the ED due to an ADR, the types of ADR involved and the reasons for ADR. On a daily basis, the investigators collected patients' data on a data collection sheet by reviewing the patient's medical records (paper and electronic records) as well the ED records for admission during the study period to identify the suspected ADR cases.

For each patient, demographic data (age, sex, height, and weight), clinical information (admission diagnosis, department and length of hospital stay, and number of medications taken at the time of admission), and information about the suspected adverse drug reaction (suspected drug, reported symptoms, and type of ADR) were collected.

The Naranjo algorithm was used to assess the causality of the suspected adverse reaction, which was then classified as definite, probable, possible or doubtful [14]. We also assessed the severity of the ADR using Hartwig's severity assessment scale [15]. The confirmed ADR cases were classified into six categories as follows: type A (Augmented) dose-related reactions, type B (Bizarre) non-dose-related reactions, type C (Chronic) dose-related and time-related reactions, type D (Delayed) time-related reactions, type E (End of use) withdrawal reactions, and type F (Failure) unexpected failure of therapy. The data from the collection sheets were entered into a Microsoft Excel program, and reports were generated.

2.4. Statistical Analysis

The results are expressed as absolute numbers and percentages. Descriptive analysis was conducted for variables, such as age, sex, admission ward, number of drugs at admission and length of hospital stay. The chi-squared test was used to compare the distribution of categorical variables (incidence, causality, and severity of ADR). The association between hospital admission due to ADR and age, sex, or the number of medications at the time of admission was analyzed in a logistic regression model. A p value of <0.05 was considered significant for all the analyses. Statistical analysis was performed with SPSS version 21.

2.5. Ethical Approval

The study was approved by the Local Research Ethics Committee of Qassim Region (QREC), Ministry of Health, Saudi Arabia (number 20170901) for implantation and data collection, and (number 1440-1378-39) for publication. All patients' information was secured to maintain confidentiality throughout the study period.

3. RESULTS

Out of 4739 admissions to the wards, 38 (0.801%) were related to an ADR. Majority of the patients were from the age group 44-58 (31.6%) with a mean age of ± 49.08 years. The total length of hospital stay was 565 days for all patients with a mean of ± 14.87 days. Table **1** represents the patients' demographic characteristics and their admission wards. The logistic regression analysis showed that none of the demographic factors were significantly associated with the incidence of ADR-related admissions Table **2**.

Fig. (**1**) shows the distribution of patients over hospital wards. All patients were divided into five age groups, and the incidence of ADRs was higher in patients aged 14-28 and 44-58 years, which was found to be statistically significant (p= 0.008). Types of ADR were as follows: type A: 35(92.1%), type B 1(2.6%), type D 1(2.6%), type E 1(2.6%). Regarding drug classes causing adverse drug reactions, analgesics were found to be the highest with 12 cases (31.6%), followed by immunosuppressants 4 (10.5%), antiepileptics 3 (7.9%), anticoagulants 3 (7.9%) and antibiotics 2 (5.3%). The causality assessment shows that 35 (92.1%) cases were probable ADRs, whereas 3 (7.9%) cases were possible ADR. Moreover, the severity assessment showed that 6 (15.1%) were mild cases and 27 (71.1%), and 5 (13.2%) were moderate and severe cases, respectively. In regard to the outcomes of patients, most patients recovered after the ADR; however, 2 cases resulted in the death of the patient. The results are summarized in Table **3**.

Table 1. Demographic characteristics of patients.

Characteristics	N (%)
Age (in years)	**Mean** ± 49.08, **SD** ± 22.37
14 - 28	11 (28.9)
29 - 43	5 (13.2)
44 -58	12 (31.6)
59 -72	2 (5.3)
73 -86	8 (21.1)
Gender	
Male	20 (52.6)
Female	18 (47.4)
Department	
Emergency department	6 (15.8)
Male medical ward	14 (36.8)
Female medical ward	12 (31.6)
Intensive care unit	4 (10.5)
Coronary care unit	2 (5.3)
Length of hospital stay (days)	
Median	5.00
Range	1-96
Cumulative stay	565

Table 2. The association between ADR related admission with age, gender and number of medications on admission.

Variable	B*	SE*	df*	*P* value
Gender	1.775	1.300	1	0.053**
Age	1.180	0.611	1	0.375**
Number of medications on admission	1.289	1.454	1	0.172**

* B, regression coefficient, SE, standard error.
** No statistically significant influence of gender, Age and number of medication on admission was observed on ADR.

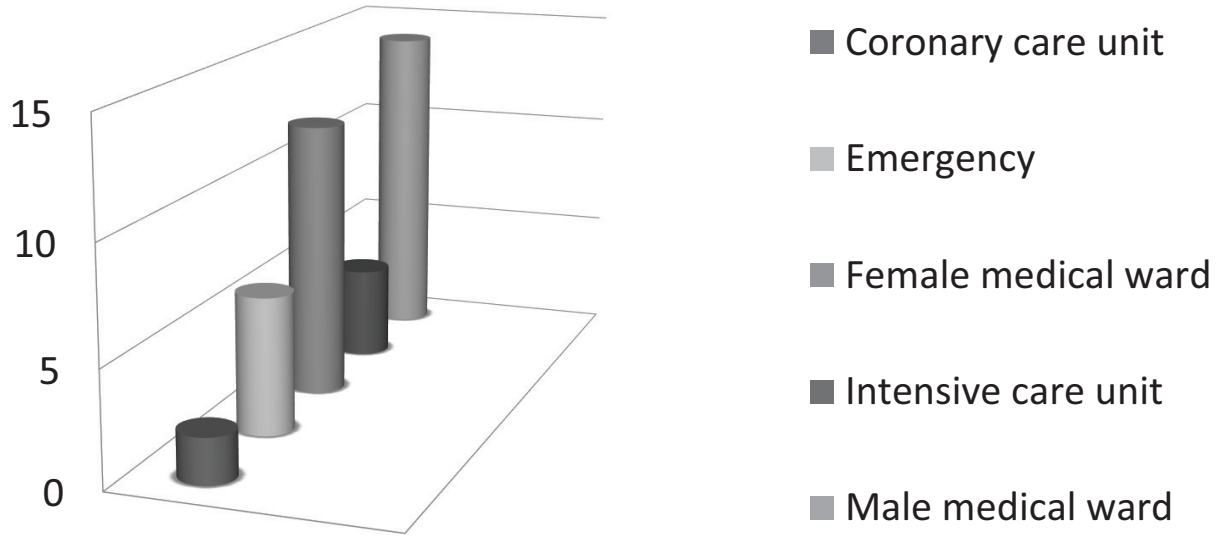

Fig. (1). Distribution of ADR cases.

Table 3. Incidence, causality and severity of adverse drug reactions in different age groups.

Character\ Age in Years	14 -28 Group 1 *n* (%)	29-43 Group 2 *n* (%)	44-58 Group 3 *n* (%)	59 -72 Group 4 *n* (%)	73 -86 Group 5 *n* (%)	Total *n* (%)	*P* Value
Drug Related Admission							
Yes	11 (28.9)	5(13.2)	10(26.3)	1(2.6)	3(7.9)	30(78.9)	0.008*
No	0 (0)	0 (0)	2 (5.3)	1(2.6)	5(13.2)	8(21.1)	-
Causality							
Probable	11 (28.9)	5(13.2)	10(26.3)	2(5.3)	7(18.4)	35(92.1)	0.550**
Possible	0 (0)	0(0)	2(5.3)	0 (0)	1(2.6)	3(7.9)	-
Severity							
Mild	0 (0)	1 (2.6)	1(2.6)	0 (0)	4(10.5)	6(15.8)	-
Moderate	10 (26.3)	4(10.5)	8(21.1)	2(5.3)	3(7.9)	27(71.1)	0.112**
Sever	1(2.6)	0 (0)	3(7.9)	0 (0)	1(2.6)	5(13.2)	-

*The difference between different age group was statically significant (Chi square 13.683).
** There was no statically significant difference observed.

Table 4. Characteristics of adverse drug reactions developed by individual drugs.

Medication Classes\ Number of Cases (%)*	Individual Drugs \ Number of Cases	Characteristics of ADR
NASID, Analgesic 12(31.6)	Ibuprofen (1) Paracetamol (5) Aspirin (3) Diclofenac sodium (3)	Exacerbation of bronchial asthma, cholistic hepatitis, acute kidney injury, GI bleeding, gastric ulcer, acute hepatitis, drug overdose
Immunosuppressant, Antibiotics, Chemotherapy, Antifungal 8(21.1)	Aminostril, Intralipid (1) Rituximab (1) Colistin (1) Infliximab (3) Linezolid (1) Azathioprine (1)	Exacerbation of crhon's disease, exacerbation of ulcerative colitis, thrombocytopenia, acute kidney injury, agranylocytosis, elevated liver enzyme
Antiepileptic, Antiparkinson\Anticholinergic 4(10.5)	Carbamazepine (2) Valopric acid (1) Benztropine (1)	Elevated liver enzyme, severe anemia, acute confessional state, drug overdose
Antiplatelate, Anticoagulants 4(10.5)	Aspirin (1) Warfarin (1) Heparin (1) Rivaroxaban (1)	Hemorrhage, heparin induced thrombocyto-penia, drug overdose, gastric ulcer
Antipsychotics, Antidepressants 4(10.5)	Amisulpride, Mirtazapine (1) Clomipramine (1) Olanzapine, Paroxetine (1) Quetiapine (1)	On- off cogwheel rigidity, drug overdose, arrhythmia, seizure,
*ARBs**, Beta blocker, ACE inhibitor**** 3(7.9)	Valsartan (1) Metoprolol (1) Enalapril (1)	Dry cough, hyperkalemia, bradycardia

(Table 4) Contd…

Medication Classes\ Number of Cases (%)*	Individual drugs \ Number of Cases	Characteristics of ADR
Antidiabetic 1(2.6)	Insulin (1)	Seizure
Diuretics 1(2.6)	Furosemide (1)	Dysuria, drippling and hyestinsy
Calcimimetics 1(2.6)	Cinacalcet (1)	Dizzniss, hypotenstion

*Total percentage may not be 100% as multiple drugs were involved.
** Angiotensin receptor blocker.
*** Angiotensin converting enzyme inhibitors.

Table **4** represents the drugs involved in ADRs. The majority of cases were due to the following: painkillers for 12 patients (31.6), medications acting on immune system for 8 (21.1%), nervous system for 4 patients (10.5%), hematology for 4 patients (10.5%), and psychiatry for 4 patients (10.5%), and medications involved with cardiac system for 3 patients (7.9%), metabolic system for 1 patient (2.6%) and nephrology system for 1 patient (2.6%). ADR-related admissions were divided into two groups according to the number of medications on admission; in total, 30 (78.9%) patients had 1 to 5 medications on admission, and 8 (21.1%) patients had 6 to 10 medications on admission. Most ADR cases (25 patients (65.8%)) were due to an orally administered drug while 11 patients (28.9%) were due to intravenous administration. On the other hand, subcutaneous (1 patient (2.6%)) and intramuscular route (1 patient (2.6%)) were the least common cases. Patients admitted due to an ADR were having the following: hypertension in 6 patients (15.8%), psychiatric illness in 5 patients (13.2%), epilepsy 3 (7.9%), Crohn's disease in 3 (7.9%), and drug overdose in 3 patients (7.9%). Very few patients were asthmatic (2 (5.3%)), had a fever (2 (5.3%)) or had thrombosis (2 (5.3%)).

4. DISCUSSION

A total of 38 (0.08%) admissions to the wards were due to an adverse drug reaction. Our findings are somewhat less than what has been reported in other hospitals in Saudi Arabia. Aljehadi *et al*., reported that the incidence of ADE-related admissions was 6.1 per 100 admissions [16], and other studies reported similar results [11]. Another German study conducted by Schurig *et al*., reported that the prevalence of ADR in four German hospitals was 6.5% [17]. These variations from our results could be due to the reason that the current study focused only on one hospital. Furthermore, we only included ADR-related cases of patients being admitted to wards through the Emergency Department. Other patients developing an adverse drug reaction during their admissions were excluded from this study.

The majority of our patients were men, which is consistent with other studies in Saudi Arabia [10, 16, 18]. However, in one of the European studies, the majority of ADR-related admissions were most commonly seen among female patients [19-21]. Patients aged 14-28 and 44-58 developed more ADRs than patients in other age groups, and we also found that patients in the latter group were more likely to suffer from severe ADRs.

In terms of ADR-related hospital stay, we estimated that the overall length of the hospital stay was 565 days during the six-month period, which is shorter than what has been reported in other studies. For example, Pedrós *et al*., reported that patients stayed for 1,785 days, and 150 patients required special units [22]. Similarly, Pirmohamed *et al*., estimated that the percentage of bed occupancy over a year in two hospitals was 7.9% [6]. Moreover, Gallelli *et al*., compared the length of hospital stay between men and women and found that the time of hospitalization was significantly higher in women [23]. Occupying a bed in a hospital for a long period of time as a result of an adverse drug reaction is a burden for the health care system; the cost per bed is approximately $847 million per year [6]. Early recognition of an ADR case at the emergency room where it can be treated would result in less expenses to health care resources.

Our data showed that 92.1% of the documented ADRs were probable. Khan *et al*., found that in a prospective and retrospective study in a pediatric unit that most of the ADRs were possible (46.9%, 48.2%, respectively) [11]. Aljehadi *et al*. reported that 35% of ADE cases admitted to public and private hospitals were preventable [16]. In 2018, Schurig *et al*. assessed the causality of adverse drug reactions in four emergency departments in Germany and found that 287 cases were possible ADRs [17]. Moreover, we identified 71% moderate adverse drug reactions and 13.2% severe ADR cases, of which two resulted in the death of the patient. Our findings are contrary to the findings of Khan *et al*., who stated that none of the cases were severe or resulted in mortality [11]. However, in 2004, Pirmohamed *et al*. reported 28 of 18820 patients who died as a result of an ADR [6]. The classification of an ADR is a measure of identification and reporting; in our study, we mostly found that adverse drug reactions were type A and related to the pharmacology of the drug (91.2%), which was similar to that reported by others [11, 24].

Pharmacological classes of drugs that caused an adverse drug reaction were mostly analgesics, immunosuppressants and antiepileptics. This is consistent with other studies that reported NSAIDs as a major cause of ADRs [6, 25, 26], whereas other studies reported that ADRs were caused by antibiotics [16, 24], anti-infective drugs [11] and diuretics [19, 22, 27, 28]. We found that most patients had hypertension at the time of admission, which was a similar medical diagnosis of cardiovascular origin to patients in other studies [18, 26]. Although the current study did not evaluate the in-

dications for prescribing the causative drug of an ADR, as what has been reported by Pratico *et al*., who found that 36.7% of ADR in pediatrics units occurred after an off label prescription, which might be a methodological flaw, indicating that other studies evaluating the indication behind prescribing are needed [29]. The majority of patients reported gastrointestinal symptoms associated with ADRs, resembling other studies in Italy [20], the Netherlands [21], the United Kingdom [6] and Germany [17]. Other studies reported skin disorders [11, 24] and renal and urinary disorders [19, 22].

There are some limitations to our study. First, although the system in our hospital uses medical records, some systems use files and/or papers, which may result in incomplete documentation of data. Second, there are no standardized protocols for immediately reporting ADRs, which may limit the estimation of real ADR cases and leads to misdiagnosis of actual ADR cases. Third, the small sample size and inclusion of only one hospital are also limitations of our study. This study is the first to explore the prevalence, type, severity and causality of adverse drug reactions in Qassim Region. Further investigations are needed to assess ADRs as a cause of hospital admissions retrospectively and prospectively in other government and private hospitals in the region and to explore reporting and understanding of adverse drug reactions from pharmacists and doctors.

CONCLUSION

In conclusion, our study shows that ADRs as a cause of hospitalization in Qassim population are considerably low. However, ADRs may contribute to morbidity and mortality and result in a considerable financial burden. For this reason, health care professionals should be aware of ADR reporting systems and must be trained to prevent ADRs among patients with chronic diseases receiving multiple medications at one time. Hospitals must be well-equipped, and staff must be well-trained in ADR reporting and monitoring programs.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Local Research Ethics Committee of Qassim Region (QREC), Ministry of Health, Saudi Arabia (number 20170901).

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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