



Prevalence and Characteristics of Adverse Drug Reaction among Patients in Jubail, Saudi Arabia

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Authors' contributions

This work was carried out in collaboration among all authors. All authors were involved in designing the study, statistical analysis, protocol design, and writing of the manuscript. All authors read and approved the final manuscript

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ABSTRACT

Introduction: Adverse Drug Reactions (ADRs) often causes prolonged hospitalization and have an increased risk of mortality. Adverse drug reaction can greatly affect the quality of life. It may lead to various undesired outcomes such as use of suboptimal alternative drugs, unnecessary investigations and delayed treatment. This study aims to evaluate the prevalence and characteristics of adverse drug reaction as well as, risk factors of allergic drug reactions among hospitalized patients at the secondary care center Royal Commission Hospital (RCH) in Jubail, Saudi Arabia.

Methods: A cross-sectional study conducted at the RCH in Jubail, Saudi Arabia. The study included all patients admitted to RCH during the period from 2017 to 2019. All patients admitted to RCH during the study period were reviewed to identify those with at least one documented drug allergy incident. The data was collected by the study authors from the hospital medical electronic data system by using a structured questionnaire that consists of two sections. The main section is the one adapted from the Adverse Drug Reaction Probability Scale (Naranjo).

Results: A total of 93 patients with reported ADR were recruited in the current study, more than half (55.91%) of them were females, with a mean age of 35.79 ± 21.18 . There was a statistically significant (P-value 0.042) difference in the prevalence of ADR by gender, and the "definitely"

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identified ADR cases were all males. Besides, the correlation was also significant ($P < 0.05$) between the prevalence of ADR and the use of specific antagonists as well as the committee action. The suspected medications for ADR were mainly antibiotics by 54%, particularly the third generation cephalosporins at 13%, followed by the penicillin subtype at 11%. Ceftriaxone was the highest at 13.54%, followed by vancomycin at 9.38%, and cefazolin at 8.33%. This was followed by analgesic class at 14%.

Conclusion: ADRs reported in the current study were mainly probable, and the definite ones were within the reported prevalence globally. The maximum number of ADRs reported was with antibiotics. The majority of patients had recovered from the ADRs.

Keywords: Adverse drug reaction probability scale (Naranjo); adverse drug reaction; prevalence; Saudi Arabia; Jubail; Royal Commission Hospital.

ABBREVIATIONS

ADRs : Adverse Drug Reactions

ADEs : Adverse Drug Events

WAO : World Allergy Organization

1. INTRODUCTION

Adverse drug reactions (ADRs) account for 3-6% of all hospital admissions and occur in 10-15% of hospitalized patients. These drug reactions result in morbidity, prolonged hospitalization, and risk of death. The World Health Organization (WHO) defined ADR as a response to a medicine which is harmful, unintentional, and occurs at doses normally used in human [1]. There are two types of ADRs, Type A which is predictable, dose-dependent comprising of up to 80% of all ADRs. Meanwhile, Type-B ADRs are unpredictable, dose-independent comprising from 15–20% of all ADRs. Immunologically induced drug hypersensitivity (drug allergy) or non-immune mediated/idiosyncratic responses are examples of ADRs [2]. ADRs should be differentiated from adverse drug events (ADEs), as ADEs extend beyond ADRs to include harm related to medication errors and drug/food interactions [3].

Drug allergy is characterized by the World Allergy Organization (WAO) as an immunologically induced drug hypersensitivity reaction. The mechanism of drug allergy may be either IgE or non-IgE mediated, with T-cell mediated reactions largely represented in the latter [4]. Drug allergy is a form of unpredictable adverse drug reaction (ADR) that encompasses a wide range of immunologically mediated hypersensitivity reactions with various mechanisms and clinical manifestations [5]. It accounts for almost 5–10% of all ADRs [6].

Another form of unpredictable ADR is pseudo allergic reactions (also known as non-allergic or non-immune-mediated reactions). These reactions are frequently clinically indistinguishable from

true immunologically mediated allergic reactions, however they lack immunological specificity. The Gell and Coombs classification system is used to classify immune-mediated allergic reactions to medications. It identifies the main immune mechanisms involved in these reactions. This classification system includes: immediate-type reactions mediated by immunoglobulin E (IgE) antibodies (type I), cytotoxic reactions mediated by immunoglobulin G (IgG) or immunoglobulin M (IgM) antibodies (type II), immune-complex reactions (type III), in addition to delayed-type hypersensitivity reactions mediated by cellular immune mechanisms, like the recruitment and activation of T cells (type IV) [7-9].

Patient-related factors (e.g., age, gender, genetic polymorphisms, or infections with some viruses) and medication-related factors (e.g., frequency of use) are also linked to an increased risk of having a drug allergy. Drug allergy is more common in women and classically occurs in young and middle-aged adults. Virus infections like the human immunodeficiency virus and the Epstein-Barr virus, as well as genetic polymorphisms in the human leukocyte antigen, have been related to an increased risk of experiencing immunologic reactions to drugs. Drug allergy susceptibility is affected by drug metabolism genetic polymorphisms. Besides, topical, intramuscular, and intravenous (IV) routes of administration are more likely to cause allergic drug reactions than oral administration. IV administration is associated with more severe reactions. Prolonged high doses or frequent doses of medication are more likely to cause hypersensitivity reactions than a large single dose. Besides, large macromolecular drugs (such as insulin or horse antiserum) and drugs that haptenate (bind tissue or blood proteins and induce immune response), such as penicillin, are often associated with a higher risk of hypersensitivity reactions. Although atopic patients do not have an increased risk for drug

allergy, they are at increased risk for serious allergic reactions [10-12].

Drug allergies may have a negative impact on patients' quality of life (QoL), as well as cause delays in care, the use of ineffective substitute drugs, needless investigations, increased morbidity, and even death. Furthermore, identification of drug allergy is challenging, given the myriad of symptoms and clinical presentations associated with the condition [13].

This study explored the prevalence of ADRs according to the ADR questionnaire, as well as risk factors of allergic drug reactions among hospitalized patients at secondary care center (RCH) in Jubail, Saudi Arabia. Since there is a scarcity of data in this regard in Saudi Arabia, the present study is considered a novel local study exploring the burden of drug allergies among inpatients.

2. METHODS

This was a cross-sectional study that was conducted at the Royal Commission Hospital (RCH), Jubail, Saudi Arabia. The study included all patients admitted to RCH during the period from 2017 through 2019. All patients admitted to RCH during the study period were reviewed to identify those with at least one documented drug allergy incident. The electronic medical record, the incident reports, and data of identified patients were reviewed for the history of adverse reactions, including the drug, administration route, nature of the reaction, treatment of the reaction, and time since the reaction. The inclusion criteria were all patients admitted by any specialty to RCH during 2017 through 2019, both genders, and all ages. The exclusion criteria were all other outpatients even if they are following for adverse drug reactions in outpatient clinics.

Data was collected using a structured questionnaire that consists of two sections. The main section is the one adapted from the "Adverse Drug Reaction Questionnaire" [14]. This is a 10 questions validated scale developed to help to standardize the assessment of causality for all adverse drug reactions. The questions are answered as either Yes, No, or "Do not know", and different point values (-1, 0, +1, or +2) are assigned to each answer. The total score concluded the outcome of ADR as definite, probable, possible, or doubtful accordingly. The questionnaire also included the socio-

demographic data section that includes: age, gender, nationality, weight, height, marital status.

The data was collected by the study authors from the hospital medical electronic data system.

2.1 Statistical Analysis

Data were analyzed by using Statistical Package for Social Studies (SPSS 22; IBM Corp., New York, NY, USA). Continuous variables were expressed as mean \pm standard deviation and categorical variables were expressed as percentages. Chi square test was used for categorical variables. A p-value <0.05 was considered statistically significant.

3. RESULTS

As shown in Table 1 a total of 93 patients with reported ADR were recruited in the current study, more than half (55.91%) of them were females, with a mean age of 35.79 ± 21.18 , and 60.26% were married. The highest percentage of the participants was in the severity category E at 31.33%, followed by severity category C, and D at 28.92% for each. The action taken for the vast majority (90.70%) of the patients was drug discontinuation, and the outcome was recovery in the majority also at 95.40%. the event subsided after stopping among 89.41% of the patients, and a specific antagonist was used for most (73.26%) of the patients. The subcutaneous route of administration was the one with the minimum reported ADR frequency at 2.12%.

The prevalence of the outcomes of the ADR questionnaire among the studied patients is shown in Table 2 and Fig. 1. The highest prevalence was for the "probable" ADR at 44.9%, followed by "possible" at 38.8%, but, "definitely" ADR was the lowest at 5.1%.

There was a statistically significant (P-value 0.042) difference in the prevalence of ADR by gender, and the "definitely" identified ADR cases were all males. Similarly, there was a significant correlation between the ADR prevalence and event reappear after re-introduction, where the majority (4 out of 5) of the "definitely" ADR cases showed reappearance after reintroduction. Besides, the correlation was also significant (P<0.05) between the prevalence of ADR and the use of specific antagonists as well as the committee action. On the other hand, the prevalence of ADR did not differ significantly by age and marital status, as shown in Table 3.

The suspected medications for ADR were mainly antibiotics by 54%, particularly the third generation cephalosporins at 13%, followed by the penicillin subtype at 11%. Ceftriaxone was the highest at 13.54%, followed by vancomycin at 9.38%, and cefazolin at 8.33%. this was followed by analgesic class at 14%. Data is shown in Table (4a, b, c), Fig. 3.

Table 1. Characteristics of the Patients (N=98)

Variable	Category	Number	%
Age(Mean± SD)		35.79	21.18
Age	<14	14.0	15.2
	14-20	9.0	9.8
	20-35	26.0	28.3
	35-55	24.0	26.1
	>=55	19.0	20.7
Gender	Male	41	44.09
	Female	52	55.91
Weight(Mean± SD)	63.4 ± 39.4	68.52	24.36
Height(Mean± SD)	143.7 ± 38.4	157.30	17.41
Are you married	Yes	47	60.26
	No	31	39.74
Severity Category	A	4	4.82
	B	2	2.41
	C	24	28.92
	D	24	28.92
	E	26	31.33
	F	3	3.61
Action Taken	Drug Discontinued	78	90.70
	Dose Not Changed	5	5.81
	Not Applicable	3	3.49
Outcome of ADR	Recovered	83	95.40
	Recovering	4	4.60
Event subsided after stopping(dechallenge)	No	6	7.06
	Yes	76	89.41
	Unknown	3	3.53
Event reappear after reintroducing	No	7	8.14
	Yes	8	9.30
	Unknown	71	82.56
Specific antagonist used	No	23	26.74
	Yes	63	73.26
P&T Committee Action	Flagging Patient	62	72.94
	Add To Database R	23	27.06
Route	IV	67	71.28
	Oral	19	20.21
	IM	6	6.38
	SC	2	2.12

Table 2. Prevalence of adverse drug reactions among patients

	Number	Prevalence (%)
Definitely an ADR	5	5.1
Probable	44	44.9
Possible	38	38.8
Doubtful	11	11.2

Table 3. Prevalence of adverse drug reactions by characteristics of the patients

		ADR								P value
		Definitely an ADR		Probable		Possible		Doubtful		
		Number	%	Number	%	Number	%	Number	%	
Age	<14	0	0.00	5	35.71	6	42.86	3	21.43	0.710
	14-20	1	11.11	4	44.44	3	33.33	1	11.11	
	20-35	2	7.69	14	53.85	8	30.77	2	7.69	
	35-55	0	0.00	11	45.83	12	50.00	1	4.17	
	>=55	2	10.53	7	36.84	8	42.11	2	10.53	
Gender	Male	5	12.20	17	41.46	17	41.46	2	4.88	0.042*
	Female	0	0.00	24	46.15	21	40.38	7	13.46	
Are you married	Yes	2	4.26	21	44.68	20	42.55	4	8.51	0.772
	No	3	9.68	14	45.16	11	35.48	3	9.68	
Action Taken	Drug	5	6.41	40	51.28	31	39.74	2	2.56	0.181
	Discontinued									
	Dose Not Changed	0	0.00	2	40.00	2	40.00	1	20.00	
	Not Applicable	0	0.00	0	0.00	3	100.00	0	0.00	
Outcome of ADR	Recovered	4	4.82	42	50.60	34	40.96	3	3.61	0.33
	Recovering	1	25.00	1	25.00	2	50.00	0	0.00	
Event subsided after stopping(dechallenge)	No	0	0.00	1	16.67	4	66.67	1	16.67	0.32
	Yes	5	6.58	40	52.63	29	38.16	2	2.63	
	Unknown	0	0.00	1	33.33	2	66.67	0	0.00	
Event reappear after reintroducing	No	0	0.00	1	14.29	5	71.43	1	14.29	<0.001*
	Yes	4	50.00	2	25.00	2	25.00	0	0.00	
	Unknown	1	1.41	39	54.93	29	40.85	2	2.82	
Specific antagonist used	No	2	8.70	8	34.78	10	43.48	3	13.04	0.019*
	Yes	3	4.76	34	53.97	26	41.27	0	0.00	
P&T Committee Action	Flagging Patient	3	4.84	36	58.06	23	37.10	0	0.00	0.009*
	Add To Database R	2	8.70	7	30.43	11	47.83	3	13.04	

* Significant p value

Table 4a. Suspect medication: Name in generic

Name in Generic	Number	%
Ceftriaxone	13	13.54
Vancomycin	9	9.38
Cefazolin	8	8.33
Levofloxacin	6	6.25
Morphine	6	6.25
Augmentin	5	5.21
Aspirin	4	4.17
Azithromycin	4	4.17
Paracetamol	4	4.17
Tazocin	4	4.17
Visipaque	3	3.12
Ampicillin	2	2.08
Cefuroxime	2	2.08
Diclofenac	2	2.08
Immune Globulin	2	2.08
Ranitidine	2	2.08
Heparin	2	2.08
Rivaroxiban	2	2.08
Atorvastatin	1	1.04
Carbamazepine	1	1.04
Clindamycin	1	1.04
Clopidogril	1	1.04
DPT VACCINE	1	1.04
Ferrous sulphate	1	1.04
Gadoterate Meglumine	1	1.04
Ibuprofen	1	1.04
Omniscan	1	1.04
Perindopril	1	1.04
Pethidine	1	1.04
Propofol	1	1.04
Rituximab	1	1.04
Tenecteplase	1	1.04
Talproic acid	1	1.04
Warfain	1	1.04

Table 4b. Suspect medication: Drug class

Drug Class	Number	%
Antibiotics	54	54.0
Analgesics	14	14.0
Anticoagulant	5	5.0
Anticonvulsant	2	2.0
Antihypertensive	1	1.0
Antiplatelet	5	5.0
Contrast media	4	4.0
DMARDs	1	1.0
General anesthetics	1	1.0
H2 receptor antagonist	2	2.0
Immune Globulin (antibody)	2	2.0
lipid lowering agents	1	1.0
Supplement	1	1.0
Thrombolytic	1	1.0
Vaccines	2	2.0

Table 4c. Suspect medication: Drug sub-type

Drug sub-type	Number	%
First generation cephalosporin	8	8.0
Fluoroquinolone	6	6.0
Glycopeptide antibiotic	9	9.0
Lincosamide	1	1.0
Macrolide	4	4.0
NSAIDs	3	3.0
Opioid	7	7.0
others	4	4.0
penicillin	11	11.0
Second generation cephalosporin	2	2.0
Third generation cephalosporin	13	13.0

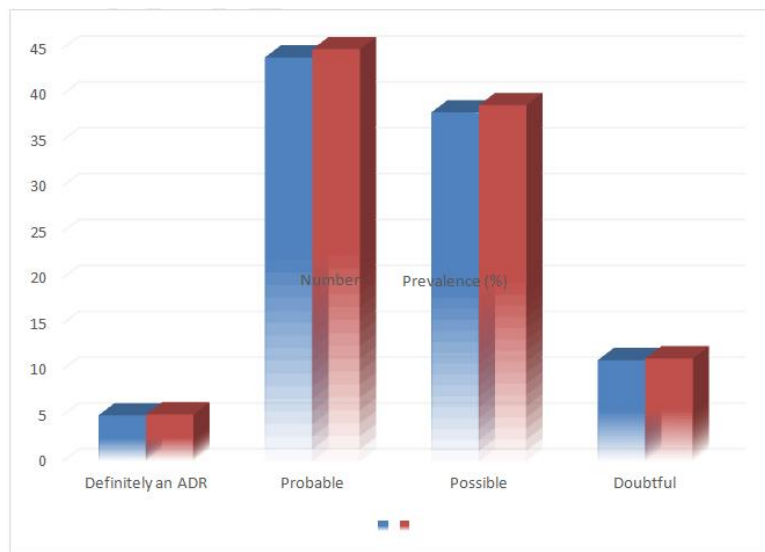


Fig. 1. Demonstrating Prevalence of Adverse Drug Reactions among Patients

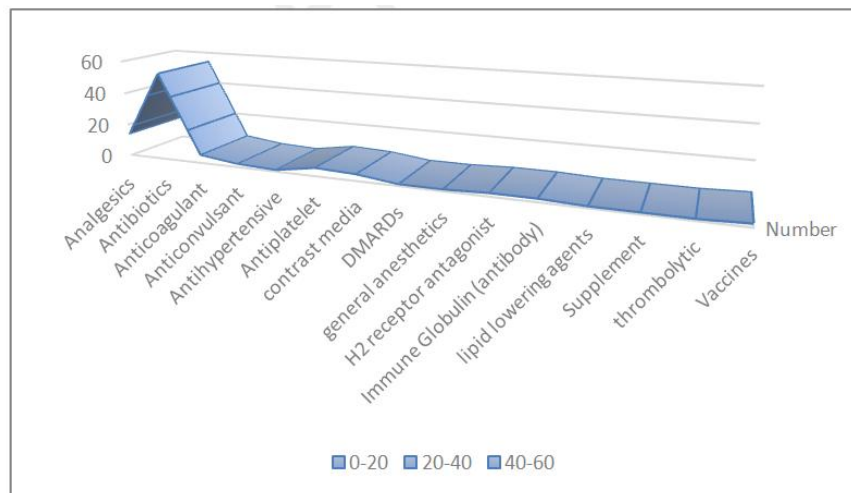


Fig. 2. Demonstrating suspect medication: Drug class

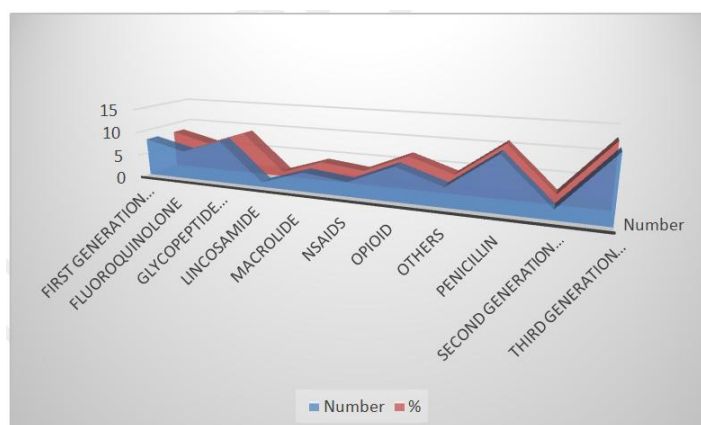


Fig. 3. Demonstrating suspected medication: Drug sub-type by numbers and percentages

4. DISCUSSION

In this study, we report the results of the first retrospective observational study of ADRs among the general hospitalized adult population in Jubail, Saudi Arabia. The key findings from this study are that 5.1% of the admitted patients had definite ADR, while 44.9%, 38.8%, had probable and possible ADR, respectively. ADR was significantly correlated with gender, and antibiotics were the main suspected medications for ADR.

Our finding that 5.1% of patients had an ADR during hospital admission is within what has been reported previously, namely 2.3–7.9% [15-18]. However, Chan SL et al. reported a higher prevalence at 12.4% [19]. Such difference in ADR prevalence among those studies might be explained basically by the type and number of medication received by each study population. Besides, a far higher prevalence was reported from an Italian study at 21.2%, however, the ADR diagnosis among 98% of those was deemed predictable and was not further analyzed, thus this prevalence could be overestimated, as the causality of those ADRs were unknown [19]. It is worthy to mention here that a higher prevalence of probable and possible ADR was reported in the current study compared to the Italian one at 44.9%, and 38.8%, vs. 21.2%, respectively [20].

Previous studies showed that patients with ADRs tended to be older, were more likely to be admitted to a medical ward, and received more drugs [21-28]. Such correlation with older age was explained by the increased chronic disease, polypharmacy (concomitant prescription of five or more drugs), and age-related physiological

changes affecting the pharmacokinetics and pharmacodynamics of drugs [29-31]. In the current study, we assessed ADR correlation with age was not statistically significant. The mean age of the current study participants was 35.79 (± 21.18), which was younger compared to that of other studies [32-34].

In this study, females comprised more than half (55.91%) of the study cohort who had experienced ADRs, and the correlation between ADRs and gender was statistically significant. Previous studies have suggested a preponderance of ADRs in female patients [35-37]. The higher adverse event rate in females has been found to result from differences in pharmacokinetic factors [35], hormonal factors [38], and drug prescription rate [37].

Antibiotics, the second most prescribed drug worldwide though deemed to be safe with rational use, is not without ADRs. Antibiotics have been reported to be a major cause of ADRs [39]. Prior reports have shown that quinolones, ciprofloxacin, in particular, are another common causative antibiotic [40]. Previous studies showed that penicillin and quinolones were responsible for the majority of ADRs [41,42]. Other studies showed beta-lactams [33]. In the current study, antibiotics accounted for 54% of the reactions, a percentage that is higher than the one reported in a study from Kerala at 33.1% [34].

As cited in some studies [34,43,44] causality by Naranjo's algorithm was mostly "probable" in this study while in others [33,45,46] majority of ADRs had a possible causality. Besides, in accordance with a previous study [34], the majority of the ADRs reported had recovered. Though, Remesh

et al. opined that the majority of the ADRs encountered in their study were not preventable [46].

5. STRENGTHS AND LIMITATIONS

The study attempts to bridge the gap in the literature on ADR data in Saudi Arabia. Though it has some limitations including the small sample size and that the sample was taken from one health care institution, therefore, the results cannot be generalized to the whole kingdom. Other aspects including polypharmacy, ADR site, duration of hospital stay of the study patients due to ADRs, and the related costs of ADRs were not calculated.

6. CONCLUSION

ADRs reported in the current study were mainly probable, and the definite ones were within the reported prevalence globally. The maximum number of ADRs reported was with antibiotics (54%) followed by analgesics (14%). Meanwhile, the most common ADRs antibiotics reported were third generation cephalosporins. The majority of patients had recovered from the ADRs.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The study was conducted after taking the ethical approval from the institutional review board committee at RCH.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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