

SPECTRUM OF CUTANEOUS ADVERSE DRUG REACTIONS IN A TERTIARY HEALTH CARE CENTRE IN AJMAN, UAE

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ABSTRACT

OBJECTIVE: To study the clinical patterns of cutaneous adverse drug reactions (ADRs) and to identify the causative drugs.

MATERIALS & METHODS: A cross-sectional hospital based study was carried out in patients with cutaneous ADRs reporting to the Department of Dermatology at a tertiary care hospital in Ajman, U. A. E., between 2010 & 2012. Medical records of the patients were used to obtain demographic, diagnoses and ADR related information. The data were subjected to a detailed statistical analysis using SPSS.19 software.

RESULTS: A total of 43 patients were included (46.5% males and 53.5% female) in the study. Mean age of patients was 30.07 ± 13.63 years. Majority of the patients were from the Middle East followed by other Asian countries. The commonest cutaneous ADRs seen were a maculo - papular rash (48.8%), Erythroderma (18.6%), urticaria (11.7%) and Fixed drug eruption (11.7%). The most causative for the various cutaneous ADR were antimicrobials in 11(48.8%) and NSAIDs in 14 (32.5%) cases. Carbamazepine and Ciprofloxacin were attributed in two cases (6%) of Stevens Johnson syndrome. The mean reaction duration was 5.63 ± 0.5 days. Reactions were mild (46.7%), moderate (40%) and severe (13.3%). Based on the WHO-Causality assessment of ADRs, 34(80%) cases were probable; 8(27%) possible and 1 (3%) case uncertain in nature. A total of 5 (11.6%) cases had past history of ADRs. Three patients (9%) had secondary, bacterial infection of skin over the ADR lesions and required antimicrobial treatment.

CONCLUSION: The clinical pattern of ADRs and the drugs causing cutaneous ADRs was largely similar to that observed in other countries, except for minor variations in incidence.

Keywords: cutaneous adverse drug reactions, maculo - papular rash, antimicrobials, NSAIDs

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INTRODUCTION

Adverse drug reaction (ADR) as defined by The World Health Organization (WHO) is 'a reaction which is noxious and unintended and which occurs at doses normally used in humans for prevention, diagnosis or therapy of disease, or for the modification of physiological functions'¹. Adverse drug reactions (ADRs) are an important public health problem and one of the leading causes of morbidity². It has been shown that approximately 5.3% of hospital admissions are associated with ADRs³. ADRs have a considerable impact on public health by imposing a heavy economic burden on the

society and health-care systems⁴.

A wide variety of commonly prescribed drugs have been implicated in cutaneous adverse drug reactions. Cutaneous ADRs have resulted in disabling infirmities during hospitalisation and complications following outdoor drug therapy. Cutaneous ADRs can present across a wide spectrum, varying from a mild maculo-papular rash to toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS)⁵. Even though majority of the cutaneous reactions are of benign nature, reports have documented that serious cutaneous ADRs, such as SJS/TEN could be associated with significant morbidity⁶. The pattern of cutaneous ADRs and the drugs responsible for them change every year with the introduction of newer drugs and evolving prescription practices.

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Skin Adverse drug reactions can vary in pattern in different regions. In a study by Al-Raai F et al from Oman, 8.5% of the hospitalized patients experienced cutaneous ADRs⁷. The clinical profile observed in their study included Urticaria, Fixed Drug Eruptions (FDE) and Maculo Papular Eruptions (MPE). Al-Ghanem F et al from Kuwait and Rahmati - Roodsari M et al from Iran reported exanthematous skin eruptions, urticarial reactions and FDE as the most common cutaneous ADRs^{8,9}. Rahmati - Roodsari M et al from Iran reported a lower prevalence of cutaneous ADRs in comparison to the reported figures in literature⁹. Studies on cutaneous reaction could provide valuable information for health care providers and their beneficiaries.

This study describes the clinical profile of all cutaneous ADRs and the suspected drugs using the WHO causality definitions in patients reporting to the Department of Dermatology of a tertiary care Hospital, Ajman over a two years period.

OPERATIONAL DEFINITIONS

Adverse Drug Reactions: Any unintended effect of a drug occurring at normal doses used in humans for prophylactic management, diagnosis or treatment¹

'Certain' ADR: An undesirable clinical event with a plausible time relationship to drug administration which cannot be explained by concurrent disease or other medications and responds to dechallenge¹⁰. The event must be definitive of the drug using a rechallenge procedure if necessary.

'Probable' ADR: An undesirable clinical event with a reasonable time relationship to administration of the drug, not explained by concurrent disease or other medications and responds to dechallenge¹⁰.

'Possible' ADR: An undesirable clinical event with a reasonable time relationship to administration of the drug, but which can be explained by concurrent disease or other medications. Information on the dechallenge may be lacking¹⁰.

Serious adverse event: The American [Food and Drug Administration](#) defines a serious adverse event as one of the following patient outcome¹¹:

- Death
- Life-threatening incident
- Hospitalization (initial or prolonged)

- Disability - significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.
- Congenital anomaly
- Requires intervention to prevent permanent impairment or damage

MATERIALS & METHODS

A cross sectional, hospital-based, prospective study design has been adopted in this research. The study was carried out among all patients irrespective of gender and age attending the Outpatient Department of Dermatology and also in hospitalized patients from January 2010 to December 2011. A questionnaire was used to record the relevant data of patients with cutaneous ADRs. The questionnaire included demographic characteristics, clinical diagnosis, associated comorbid conditions and details of ADR such as type of ADR, drug history, the suspected drug, reaction time, dechallenge history, past history of similar condition, severity, history of drug allergy or atopy, management and outcome of the ADR. The ethics committee approved this study. Permission was also obtained from the Medical Records Department to access case records of both the OPD patients of Dermatology department and inpatients of all the wards with cutaneous ADRs in GMCHRC, Ajman. Anonymity was maintained by not entering any data revealing the identity of the patients.

RESULTS

A total of 43 patients reported to the Department of Dermatology (including OPD and inpatients) during the study period with cutaneous ADRs. Male patients constituted 46.5% and female 53.5% of the total. The maximum number of reactions was seen in patients in the age group between 20-39 years. Mean age of the patients was 30.07 ± 13.63 years. Majority of the patients were from the Middle East [19(44%)] followed by those from Asian countries [16(37.2%)]. The details of the age and gender-wise distribution of the patients with cutaneous ADR are shown in table.1

Table 1: Age and gender wise distribution of the patients with cutaneous ADRs

Age group	No. Of Patients-				Total	%
	Male	%	Female	%		
0-19	7	35	6	26	13	30.2
20-39	9	45	13	56.5	22	51.1
>/=40	4	20	4	17.5	8	18.6
Total	20	100	23	100	43	100

The commonest cutaneous ADRs seen in descending order were maculo - papular rash [21(48.8%)], Erythroderma [8(18.6%)], urticaria [5(11.7%)] and

Fixed drug eruption (FDE)[5(11.7%)]. Details of the clinical spectrum of cutaneous ADRs with the implicated drugs are presented in Table 2 & 3 below.

Table 2: Description of the cutaneous ADRs reported

Cutaneous ADR	No. (n=43)	%
Maculo - papular rash	21	48.8
Erythroderma	8	18.6
Urticaria	5	11.7
Fixed drug eruption	5	11.7
Steven Johnson Syndrome	2	4.6
Exfoliative dermatitis	1	2.3
Toxic Epidermonecrosis	1	2.3

The drugs responsible for most of the cutaneous ADR were antimicrobials [21(48.8%) cases] and non-steroidal anti-inflammatory drugs (NSAIDs)[14 (32.5%) cases]. Alternative medicine (Ivy leaves) was implicated in two cases of Maculo - papular rash.

Carbamazepine and Ciprofloxacin were attributed to two cases of Stevens Johnson syndrome. The detailed list of the cutaneous ADR and the causative drugs are depicted in Table 3 below.

Table 3: Cutaneous ADRs and the implicated drugs

Cutaneous ADR	Drug class(No)	Implicated drugs (No)	
Maculo - papular rash	Antimicrobials (10)	Amoxicillin (4)	
		Ciprofloxacin (2)	
		Cefotaxime (1)	
		Cefuroxime(1)	
		Cotrimoxazole(1)	
		Clarithromycin(1)	
		Analgesics (7)	Ibuprofen (2)
			Piroxicam(2)
			Celecoxib (2)
			Diclofenac (1)
Alternative medicine(2)	Ivy (CAM)(2)		
	Urinary spasmolytic (1)	Falvoxate(1)	
		Laxative(1)	Lactulose(1)

Erythroderma	Antimicrobials(5)	Ciprofloxacin (2) Ceftriaxone (1) Cefuroxime(1)
		Amoxicillin (1)
	Analgesics(1)	Paracetamol(1)
	Antiemetic (1)	Metoclopramide (1)
Urticaria	Corticosteroid (1)	Betamethasone(1)
	Antimicrobials(1)	Cefdinir(1)
		Paracetamol(1)
	Analgesics(3)	Diclofenac (1) Piroxicam(1) Terbutaline (1)
Fixed drug eruption	Bronchodilator(1)	
	Antimicrobials (3)	Amoxicillin (1) Clarithromycin (1) Cefotaxime (1) Diclofenac (2)
	Analgesics(2)	
Steven Johnson Syndrome	Antimicrobials(1)	Ciprofloxacin (1)
	Antiepileptics (1)	Carbamazepine(1)
Exfoliative dermatitis	Analgesics(1)	Diclofenac (1)
Toxic Epidermonecrosis	Antimicrobials(1)	Cefixime (1)

Reaction time (RT), which is the time taken for the adverse drug reaction to appear since the last exposure to the suspected drug, varied from 1 day to 45 days. Mean reaction time was 5.63 ± 0.5 days. Based on the severity of the ADRs, 46.7% were mild, 40% moderate and 3.3% were severe cutaneous reactions.

Based on the WHO-Causality assessment of ADRs, 34(80%) cases were probable in nature; 8(27%) possible and 1 (3%) case was uncertain. Five (11.6%) patients had past history of ADRs. Two patients had history of atopy. Three patients had secondary bacterial infection over the lesions and required antimicrobial treatment. No mortality occurred due to the cutaneous reactions.

DISCUSSION

The results of the present study highlight the clinical pattern and the implicating agents of the cutaneous ADRs over a period of two years.

We found a slightly higher occurrence rate of ADRs among females, which is in concordance to earlier studies across the world including the Eastern Mediterranean region^{9,12-14}. In comparison

to the males, females have a 1.5 to 1.7 fold higher risk for adverse drug reactions including cutaneous reactions. The reasons for this increased risk are not entirely clear but gender-related differences in pharmacokinetic, immunological and hormonal profiles and differences in the medications used by both gender are likely to be responsible³. Majority of the patients with the cutaneous reactions were young, in the age group of 20-39 years, similar to reports of Jelvehgari et al and Solensky R et al^{15,17}. The probable reason for this observation could be an increased exposure to antimicrobials in this age group which increases the risk of drug eruptions¹⁶. In contradiction, elderly and adult aged patients were the most affected according to Al-Raaie F et al from Oman⁷.

There is no gold standard investigation for confirming a drug-induced reaction. The causality assessment takes into consideration the timing of drug exposure, reaction time, course of reaction with drug withdrawal, recurrence on rechallenge, history of similar reaction to the suspected drug¹⁷ etc. In this study, WHO causality definitions are simple and widely recognized method to assess causality¹². In the present study, 34(80%) cases were probable

in nature; 8(27%) possible and 1 (3%) uncertain. The reaction time observed for all the reactions in the present study was in accordance with earlier reports¹³.

A wide clinical spectrum of cutaneous ADRs was noticed in this study. The most common cutaneous ADRs observed in this study were maculo - papular rashes (48.8%), erythroderma (18.6%), and urticaria (11.7%). Our findings were similar to those reported in studies from Iran^{9,13}, but differed from reports from Oman and Kuwait, wherein, the most common morphologic patterns were Urticaria followed by FDE^{7,18}. This variation could be due to differences in patterns of drug usage and ethnic group characteristics. In agreement with other studies from the Middle East and across the world, cutaneous ADRs were most frequently caused by antimicrobial agents and NSAIDs^{7,9,14,19}.

Occurrence of ADRs is influenced by several host factors. Patients with previous history of a drug reaction are more likely to develop reactions from other drugs. In the present study, 11% of the patients gave history of previous drug reaction, while Al-Raaie F et al reported the percentage being 18%⁷. Atopy background was present in 40% of cases of urticarial rashes which could be considered as a predisposing factor for the reactions. Other studies also have emphasized the role of atopy in drug allergy^{7,20}.

Dechallenge of the offending drug was done in all the cases immediately after identification of the ADR and the patients were treated appropriately. Severe cases were effectively managed and closely monitored till discharge.

CONCLUSION

To conclude, the profile of cutaneous ADRs in the present study was similar to various other studies from the Middle East region. A wide clinical spectrum of cutaneous ADRs was observed. Antimicrobials were implicated in the majority of the cases. Future studies on cutaneous reaction could add to valuable data beneficial for health care deliverers and their beneficiaries.

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