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Original Research Article

Prospective monitoring of cutaneous adverse drug reactions in a secondary care hospital, UAE

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ABSTRACT

Background: Adverse drug reactions (ADRs) are one of the most important causes of morbidity, hospitalization, increased healthcare cost and even mortality. Cutaneous adverse reactions are most commonly documented for drugs. The aim of the study was to monitor the incidence and nature of cutaneous adverse drug reactions (CADRs) in the dermatology outpatients and identify the causative drugs.
Methods: A prospective observational study was conducted at the dermatology outpatient department of a secondary care hospital, UAE. All the patients attending dermatology outpatient and satisfying the inclusion criteria were monitored for ADRs. The required data were collected from the patients, their case files, and caretakers and entered in a suitably designed ADR reporting and documentation form. The causality, severity, and preventability of cutaneous ADRs were assessed using Naranjo, WHO, Hartwig and modified Schumock and Thornton scale.
Results: The prevalence of cutaneous ADRs was found to be 2.6%. Majority (43.4%) of the cutaneous ADRs were caused by nonsteroidal anti-inflammatory drugs. Majority (56.5%) of the study population reported itching as the most common cutaneous ADR. Also, 60.8% of the reported ADRs were "probable" in nature according to World Health Organization scale, whereas 56.5% reports were "probable" according to Naranjo's algorithm. Majority (97%) of the ADRs were not preventable.
Conclusions: Nonsteroidal anti-inflammatory drugs were the common causes of cutaneous ADRs in the study. Majority of the adverse reactions were mild in nature. The type and nature of cutaneous adverse drug reaction profile documented in this study is almost similar in many ways to other ADRs monitoring studies conducted in dermatology outpatient clinics.

Keywords: Cutaneous adverse drug reactions, Dermatology, Nonsteroidal anti-inflammatory drugs, Outpatients, Adverse drug reactions monitoring

INTRODUCTION

Adverse drug reactions (ADRs) are one of the most important causes of morbidity, hospitalization, increased healthcare cost, and even mortality.[1] Many studies have reported adverse reactions to different classes of drugs affecting various body/organ systems.[2-5] Dermatological system or skin is one of the most commonly affected organ systems.[6]

Cutaneous adverse drug reactions (CADRs) are the most commonly documented ADRs.[6] In many studies, the incidence of CADRs among hospitalized and outpatients was found to be 2%–3% and 2%–5%, respectively.[7,8]

Whereas the incidence rate of cosmetics-related ADRs ranges from 8%–26%.[9,10]

There is a dearth of data regarding the nature and type of CADRs from the Middle East region. A study conducted at a hospital at Sultanate of Oman revealed that 8.5% of total admission in the skin ward was due to CADRs (25/295) and incidence rate was 0.3% in outpatient departments.[11] Another retrospective study conducted at a hospital of Tabriz, Iran reported 300 patients (148 men and 152 women) with CADRs.[12]

The severity of the CADRs may vary from mild itching or urticaria to life-threatening ADRs such as toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS). Approximately, 2% of ADRs are considered severe or fatal.[13] The most commonly reported CADRs includes itching, urticaria, pruritus, maculopapular eruptions, angioedema, erythema multiforme, fixed drug reactions/eruptions, phototoxic and photo allergic reactions, vesiculobullous reactions (TEN and SJS), and exfoliative dermatitis.[14-17]

CADRs can be due to immunologic or nonimmunologic mechanisms.[18] The major risk factors for cutaneous skin reactions include age, female gender, previous history of ADRs, and environmental factors.[19,20]

Pharmacovigilance activity in UAE is in its developing stages. Hence monitoring and reporting of ADRs in health care settings play a significant role in creating awareness among healthcare professionals and thus preventing any potential harm to patients.[21] The data collected in this study will be an additional contribution to the local pharmacovigilance activities in the region.

The main objective of this research was to enrich the pharmacovigilance activity and promote the role of pharmacist in pharmacovigilance. The aims of the study were to (1) determine the prevalence of CADRs (2) assess the causality, preventability, predictability, and severity of CADRs; and (4) analyze the ADRs according to demographic, illness characteristics, and predisposing factors.

METHODS

This prospective observational study was conducted at the Dermatology Outpatient Department of a secondary care hospital of UAE for eight months (November -2015 to June -2016) after obtaining both Institutional and MOH Research, and Ethics Committee approval.

Patients of all age-groups and genders presenting to the dermatology outpatient department with cutaneous manifestations after taking any class of drugs were included. Patients who were referred to dermatologic outpatient department from other departments and admitted in the hospital for further management were also included. However, patients who presented to the dermatology clinic with a repeated ADR to the same drug, were unable to give complete medication history (drug abusers and terminally ill patients), and had cutaneous manifestations that were not well-matched with drug were excluded.

For all the patients with suspected ADRs, the required data were collected from the patient case notes, concerned dermatologists, and patient caretakers and documented in an ADR-reporting and documentation form. Demographics, disease characteristics, medication history, type of reaction, history of ADR, date of onset, history of drug therapy or cosmetic usage before the development of reaction, treatment given to the patients to manage ADR, and other relevant information were recorded in the documentation form. The causality assessment of documented ADRs was done using Naranjo and WHO probability scale.[22,23] Severity of ADRs was assessed using Hartwig et al scale and preventability was assessed using modified Schumock and Thornton scale.[24,25]

Data analysis

The collected data was entered in the Microsoft excel sheet and Statistical Package for the Social Sciences [Version 24.0, IBM, Armonk, New York, USA] was used to analyze the data. The categorical data were represented in the form of frequency, percentage, and chi-square test was used to assess the association between the categorical variables and occurrence of ADRs. Pearson correlation test was performed to find out relationship between ADRs and continuous socio-demographic, disease, and treatment-related variables. The predictors of ADRs were determined using multivariate linear regression analysis. $p<0.05$ was considered statistically significant.

RESULTS

Demographic characteristics

Out of 2652 patients who visited the hospital in eight months, only 69 CADRs were reported with a prevalence rate of 2.60%. Majority (97.1%) of the patients were adults. The number of women (79.7%) was more than men. This study was carried out in a multiethnic community involving participants from different nationalities, where there was not much published data regarding CADRs. However, majority (88.4%) of the study patients were Emirati nationals. Demographic variables such as gender (p=0.186), nationality (p=0.079), history of drug allergy (p=0.515), and number of drugs were not significantly associated with number of ADRs (Table 1).

Out of 69 patients with CADRs, only 21 (30.4%) had a previous history of allergy to medications and a total of 224 drugs were used prior to development of ADRs. Majority of the patients (26%) used one drug, followed by 24.6% patients who used four drugs and only one (1.4%) patient used seven drugs.

Table 1: Association between demographic variables and number of adverse drug reactions.

Variables	Number of ADRs (%)				
	One	Two	Three	X^2	P value
Gender					
Male	5 (13.9)	7 (24.1)	2 (50)	3.36	0.186
Female	31 (86.1)	22 (75.1)	2 (50)		
Nationality					
Emirati	32 (88.9)	26 (89.7)	3 (75)	21.99	0.079
Camoran	0 (0.0)	1 (3.4)	0 (0.0)		
Indian	1 (2.8)	0 (0.0)	0 (0.0)		
Yemeni	1 (2.8)	0 (0.0)	0 (0.0)		
Nepalese	1 (2.8)	0 (0.0)	0 (0.0)		
Egyptian	1 (2.8)	1 (3.4)	0 (0.0)		
Palestinian	0 (0.0)	0 (0.0)	1 (25)		
Egyptian	0 (0.0)	1 (3.4)	0 (0.0)		
History of drug allergy					
Yes	9 (25)	11 (37.9)	1 (25)	1.32	0.515
No	27 (75)	18 (62.1)	3 (75)		
Number of drugs					
One	12 (33.3)	5 (17.2)	1 (25)	12.75	0.387
Two	3 (8.3)	2 (6.9)	0 (0.0)		
Three	7 (19.4)	6 (20.7)	0 (0.0)		
Four	9 (25)	7 (24.1)	1 (25)		
Five	3 (8.3)	5 (17.2)	0 (0.0)		
Six	2 (5.6)	3 (10.3)	2 (50)		
Seven	0 (0.0)	1 (3.4)	0 (0.0)		

Drugs implicated and type of CADRs

Non-steroidal anti-inflammatory drugs (NSAIDs) were the most (43.4%) common class of drugs suspected to have caused CADRs, followed by penicillin (20.2%). Benzene diols, benzodiazepines, cineole derivatives, dopamine D_2 receptor antagonists, female hormones, macrolides, sulfa drugs, sulfonated shale oil, and tumor necrosis factor (TNF) blockers were the suspected classes that contributed for one ADR from each class (Table 2). The number of days of onset of CADR was 6.3±5.4 days.

The most common CADRs were itching (56.5%), followed by rash (47.8%), and redness (21.7%) (Table 3). Majority (40.5%) of the CADRs occurred all over the body, followed by hands (17.3%), and lower extremities (17.3%). According to WHO probability scale, majority (60.8%) of the CADRs were probable in nature and remaining (39.1%) were of possible type. According to Naranjo's algorithm, the causal relationship between the suspected drug and the ADR was found to be probable and possible in nature in 56.5% and 43.5% of CADRS, respectively (Table 4).

Among 69 CADRs, 37 were mild [level 1 (n=5); level 2 (n=32)] and 32 CADRs were moderate (level 3) in nature. Among 69 reported CADRs, 79.5% were predictable and 20.3% were not-predictable type. Majority (97%) of the CADRs were judged not preventable type and only two (3%) CADRs were judged preventable (Table 4). In 72.4% of the cases, the suspected drug was withdrawn, followed by in 23.1% of cases in which no change was observed with respect to use of suspected drug. In three cases, the dose of suspected drug was altered. In majority (68.1%) of the cases, the CADRs was treated symptomatically and in two cases specific treatment was given.

Among 49 patients who received treatment for suspected CADR [2 (specific) and 47 (symptomatic)], cetirizine was the most commonly (13, 26.5%) prescribed drug among the drugs given for the treatment of suspected CADRs, followed by loratadine [6 (12.24%)]. Among 69 CADRs, 51% were recovered, 17% were continuing, and in 22 cases the outcome was unknown. Out of 69 patients with CADRs, 66 had at least one predisposing factor identified for development of CADR. Majority (42%) of them had one predisposing factor for the development of CADRs, followed by 36.2% with two, and only 2.8% of patients with four predisposing factors. No single demographic variables were the significant predictors of number of CADRs, as confirmed by linear regression analysis (Table 5).

A statistically significant positive correlation (r=0.288, p=0.017) was observed between age and number of CADRs. In addition, a statistically significant positive correlation (r=0.266, I=0.027) was also documented for number of drugs and number of ADRs.

Table 2: Drug classes and drug types implicated in cutaneous adverse drug reactions.

Drug class	N (%)	Drug name and type	N (%)	ATC code
Benzene diol	2 (2.8)	Hydroquinone cream	2 (2.8)	D11AX11
Benzodiazepines	1 (1.4)	Chlordiazepoxide	1 (1.4)	N05BA02
Cineole derivative	1 (1.4)	Eucalyptus oil	1 (1.4)	R05CA13
Disease-modifying antirheumatic drugs (DMARDs)	2 (2.8)	Methotrexate	2 (2.8)	L04AX03
Dopamine D_2 antagonist	1 (1.4)	Metoclopramide	1 (1.4)	A03FA01
H_2 receptor antagonist	3 (4.3)	Ranitidine	3 (4.3)	A02BA02
Female hormone	1 (1.4)	Desogestrel	1 (1.4)	G03AC09
Cephalosporin	2 (2.8)	Ceftriaxone	1 (1.4)	J01DD04
		Cefixime	1 (1.4)	J01DD08
Fluoroquinolone	6 (8.6)	Ciprofloxacin	3 (4.2)	J01MA02
		Ofloxacin	2 (2.8)	J01MA01
		Moxifloxacin	1 (1.4)	J01MA14
Macrolide antibiotics	1 (1.4)	Clarithromycin	1 (1.4)	J01FA09
Nitroimidazoles	2 (2.8)	Metronidazole	1 (1.4)	A01AB17
		Metronidazole	1 (1.4)	G01AF01
Penicillins	14 (20.2)	Amoxicillin/clavulanic acid	9 (13)	J01CR02
		Amoxicillin	4 (5.7)	J01CA04
		Ampicillin	1 (1.4)	J01CA01
Sulfa drug	1 (1.4)	Sulfasalazine	1 (1.4)	A07EC01
NSAIDs	30 (43.4)	Celecoxib	1 (1.4)	M01AH01
		Diclofenac sodium	3 (4.2)	M01AB05
		Diclofenac gel	5 (7.2)	M02AA15
		Diclofenac eye drops	1 (1.4)	S01BC03
		Ibuprofen	17 (24.6)	M01AE01
		Indomethacin	2 (2.8)	M01AB01
		Piroxicam	1 (1.4)	M01AC01
Sulphonated shale oil	1 (1.4)	Ichthyol ointment	1 (1.4)	D10AX12
TNF blocker	1 (1.4)	Adalimumab	1 (1.4)	L04AB04

Table 3: Different types of CADRs implicated.

Type of reaction	N (%)	Drugs implicated
Itching/pruritus	39 (56.5)	Ibuprofen (n=10); Diclofenac gel (n=5); Amoxicillin (n=4); Amoxicillin/Clavulanic acid (n=4); Diclofenac sodium (n=3); Ranitidine (n=3); Indomethacin (n=2); Metronidazole (n=1); Chlordiazepoxide (n=1); Adalimumab (n=1); Moxifloxacin (n=1); Celecoxib (n=1); Desogestrel (n=1); Hydroquinone cream (n=1); Methotrexate (n=1)
Rash	33 (47.8)	Ibuprofen (n=9); Amoxicillin/clavulanic acid (n=6); Metronidazole (n=2); Ranitidine (n=2); Ciprofloxacin (n=2); Diclofenac gel (n=1); Piroxicam (n=1); Ampicillin (n=1); Chlordiazepoxide (n=1); Amoxicillin (n=1); Ofloxacin (n=1); Adalimumab (n=1); Celecoxib (n=1); Diclofenac sodium (n=1); Indomethacin (n=1); Ceftriaxone (n=1); Cefexime (n=1)
Redness	15 (21.7)	Ibuprofen (n=6); Metoclopramide (n=1); Piroxicam (n=1); Hydroquinone cream (n=1); Moxifloxacin (n=1); Ranitidine(n=1); Clarithromycin (n=1); Eucalyptus oil (n=1); Sulfasalazine (n=1); Indomethacin (n=1)
Urticaria	5 (7.2)	Metoclopramide (n=1); Ciprofloxacin (n=1); Ibuprofen (n=1); Chlordiazepoxide (n=1); Ofloxacin (n=1)
Lesions	4 (5.7)	Ibuprofen (n=3); Amoxicillin/clavulanic acid (n=1)
Hyperpigmentation	2 (2.8)	Amoxicillin/clavulanic acid (n=1); Hydroquinone cream (n=1)
Burning sensation	1 (1.4)	Ichthyol ointment (n=1)
Angioedema	1 (1.4)	Diclofenac eye drops (n=1)
Red patches	1 (1.4)	Methotrexate (n=1)
Skin ulcer	1 (1.4)	Amoxicillin/clavulanic acid (n=1)
Allergic dermatitis	1 (1.4)	Ibuprofen (n=1)
Dermatophytosis	1 (1.4)	Ibuprofen (n=1)

Table 4: Causality assessment of suspected CADRs.

Assessment	N (%) [n=69]
Naranjo causality assessment	
Probable	39 (56.5)
Possible	30 (43.5)
WHO probability assessment	
Probable	42 (60.8)
Possible	27 (39.1)
Hartwig's severity assessment	
Mild	37 (53.7)
Moderate	32 (46.3)
Predictability assessment	
Predictable	55 (80)
Not predictable	14 (20)
Preventability assessment	
Not preventable	67 (97)
Probably preventable	02 (03)

Table 5: Predictor of adverse drug reactions.

Variables	B	Beta	t	P value
Age	0.007	0.177	1.345	0.184
Sex	-0.333	-0.223	-1.854	0.068
Nationality	0.029	0.071	0.606	0.547
History of drug allergy	-0.174	-0.131	-1.07	0.289
No. of drugs	0.062	0.176	1.321	0.191

P<0.05 is considered as significant.

DISCUSSION

The incidence of CADRs observed in the present study was similar to the findings from other studies, which reported an incidence rate of 2–4%.[26–29] However, a few other studies have reported higher incidence of CADRs—approximately 10%.[30,31] This could be due to the differences in the study setting. A study conducted by Atzori et al reported an incidence of 8.4 cases per year. In this study, ADRs due to just one drug was studied.[31] These two factors might have played a role in better identification of the ADRs, resulting in higher incidence rate compared to our study.[30,31]

A study conducted by Acharya et al reported an incidence of 0.17%.[32] Another study conducted by Das et al. reported an incidence 0.21% over a period of one year involving 26000 outpatients.[33] In the present study, the mean number of days of onset of CDARs was 6.3±5.4 days. In a study conducted by Son et al, the time interval between the administration of drugs and appearance of symptoms was less than a week.[34] In another study, it was between 2 and 14 days.[35]

In our study, majority of the patients were women. Similar findings were documented in other studies.[28,35,36] This high incidence of CADRs in women may be due to their highly sensitive skin. The different stages in a woman's life (menarche, pregnancy, lactation, and menopause) can cause alterations in the pharmacokinetics of the drugs. Women have a raised level of concern about their skin and the medical attention-seeking habit when compared to men.[37] In the present study, 30% of patients reported history of previous drug allergy. Studies suggested that people with previous history of drug allergy were more likely of experiencing ADRs again.[37]

A study conducted in Oman, showed both NSAIDs and antimicrobials to be the most common drugs causing CADRs.[11] However, our study documented antimicrobial agents as the most common class of drugs implicated in CADRs.[27,28,35,36,38] Few studies have shown penicillin to be the most common antimicrobial agent causing CADRs.[11,29,34,39-41] Among penicillin, amoxicillin was implicated in few studies.[34] NSAIDS were the second most common class of drugs implicated in CADRs in few studies.[35,36]

In the present study, ibuprofen caused the highest number of CADRs, followed by diclofenac. Interestingly, a study conducted by Kasemsarn et al and Neupane et al revealed ibuprofen as the most common NSAID causing CADRs.[42,43] Whereas, Verma et al found diclofenac and aceclofenac as the most common NSAIDs causing CADRs.[36] Bharani et al. implicated paracetamol as the leading drug causing CADRs, followed by diclofenac and ibuprofen.[44] These differences can be attributed to the prescription patterns.

The most frequent CADR observed in the present study was itching (pruritus). Approximately, 56.5% of the patients suffered from itching, followed by rash (dermatitis). Surprisingly, we could not find any other study reporting only itching as a manifestation of CADRs. A Korean study reported itching as the major presenting complaint; however, exanthematous eruption was the major manifestation of CADR.[34]

In a study published by Mbuagbaw et al, fixed drug eruptions were the most common CADRs.[26] However, Verma et al. and Nandha et al reports maculopapular rashes as the most frequent CADRs (29.4% and 42.85%, respectively).[36,35] In a study by Chatterjee et al, macular rashes were the third most common type (25.4%) of CADR.[28] Many studies have reported life-threatening CADRs including SJS and TEN.[35,36,38] However, in the present study, none of the patients developed severe CADRs.

It was the uniqueness of this study that the site of CADRs were categorized, as there are limited number of published studies that have done the same. Majority (60.8%) of the reported CADRs were probable according to WHO scale, whereas 56.5% reports were probable according to Naranjo's algorithm. These study findings are consistent with a study from India, which reported 76.9% of CADRs as probable.[35] Similar findings were

observed in majority of the studies, which reported CADRs as probable in nature.[30-33,45,46]

Among these studies, only one study used Naranjo's algorithm and all other studies used only WHO causality assessment scale.[45] None of the studies used both the scales and it is the uniqueness of the present study that both the scales were used for assessing the causality of reported CADRs, and it is important to note that the there was no significant difference between two scales with respect to causality of reported ADRs. Majority of the reported CADRs in our study were mild in severity belonging to either level 1 (5 patients) or level 2(32 patients). Another 32 CADRs were moderate in nature.

In a retrospective study by Mbuagbaw et al, 25% of the patients died due to severe CADRs.[26] A study conducted by Acharya et al showed that majority of the CADRs were moderate, seven were mild, and one was severe in nature.[32] Another study observed that most of the CADRs reported in their study were moderate and 13 were severe in nature.[45] A cross-sectional analytical study conducted by Jamunarani et al reported that 66.7% of CADRs were moderate, 27.3% were severe and life-threatening in nature.[46] Vijendra et al reported that majority of the CADRs in their study were mild to moderate.[41] Whereas, Sharma et al reported one case of TEN, which lead to mortality in their study.[42] Results pertaining to severity of reported CADRs from Vijendra et al are consistent with observations made in our study.[41]

Management and outcome of CADRs

Out of 69 CADRs, suspected drug was withdrawn from 50 patients and no change was observed with respect to use of suspected drug in 16 cases. Majority (68.1%) of the CADRs were treated symptomatically. No treatment was given in 20 cases, as the reaction was mild in nature and did not affect the health-related quality of life of patient. In a study by Acharya et al, most (81%) of the CADRs were managed by drug withdrawal, which is consistent with management of CADRs in the present study.[45]

A prospective observational study conducted in a teaching hospital of North India observed 71.4% of the patients recovered from CADR.[35] Another study by Atzori et al. also reported full recovery in 88% of patients; however, 10 patients died due to CADRs.[31] Acharya et al also reported that 58% of patients were recovered from CADRs.[45] A study by Faiza et al reported one death of patient due to intramuscular use of diclofenac.[11] Another study from North Tunisia also reported death of 12 patients related to acute CADRs.[47]

Predisposing factors for the development of CADRs

The present study also statistically assessed predictor of CADRs in the study population, which was not explored in many pharmacovigilance studies in the region. In the present study, female gender was the most common predisposing factor. These findings are consistent with the literature that the women are more prone for development of CADRs than men.[35,36]

Limitations of the study

This study was a single-center and of short duration, which limited the number of reported CADRs. Hence the findings of the study cannot be generalized to UAE population.

CONCLUSION

The most common class of drugs associated with CADRs was NSAIDs. Ibuprofen was the most commonly associated drug. Itching and rashes were the most commonly reported CADRs. Majority of the CADRs reported in the study was mild in nature. Majority of the ADRs was of predictable in nature and not-preventable type.

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