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ORIGINAL RESEARCH ARTICLE

Dermatological Adverse Drug Reactions in a Tertiary Care Teaching Hospital of Punjab, India—A Pharmacovigilance Study

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ABSTRACT

Introduction: Adverse drug reactions (ADRs) constitute a significant economic burden on society. ADRs to skin are common; however, information about their incidence, severity, and ultimate health effects is scanty. The aim of the present study was to detect, document, assess, and report the suspected ADRs in the Department of Dermatology at a tertiary care teaching hospital, Amritsar, so as to treat ADRs and also stop the indiscriminate use of drugs in clinical practice.

Materials and methods: A prospective study was undertaken in patients presenting with ADRs in the outpatient Department of Dermatology in the tertiary care teaching hospital, Amritsar, Punjab, from June 2015 to May 2018. The data obtained were collected, compared, and reviewed, calculating the percentage to assess their significance and evaluation. A total of 152 ADRs were detected during the study period.

Results: The most common age group presenting with adverse cutaneous drug reactions (ACDRs) was 18–35 years (54%) and the most common ADR was urticaria (30.2%) followed by fixed drug eruptions (16.4%). The most common drugs responsible for ACDRs were non-steroidal anti-inflammatory drugs (NSAIDs) and fluoroquinolones followed by systemic steroids, oral contraceptive pills, ampicillin, angiotensin converting enzyme (ACE) inhibitors, antimalarial, clofazimine, and so on. According to the WHO causality assessment, 13.0% cases were certain, 56.1% were probable, and 30.7% were possible in nature. On severity assessment by the modified Hartwig and Siegel scale, 72.3% ACDRs were mild, 25% were moderate, and 2.05% cases were of severe category. Preventability assessment by the modified Schumock and Thornton scale revealed that 69.1% ACDRs were definitely probable, 20.51% were probably preventable, and 13.8% were not preventable.

Conclusion: The study findings indicate that ADR reporting helps in identifying the most common drugs associated with dermatological reactions. Thus it helps us to provide better patient treatment by the early identification and management of dermatological reactions.

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INTRODUCTION

As per WHO, the definition of pharmacovigilance is "The Pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines".[1] The meaning of pharmacovigilance differs from the meaning of "side effect," as associated effects can be beneficial to some patients, where these effects can be used as therapeutic agents.[2] Pharmacovigilance or ADR monitoring, launched by WHO in the 1960s in the wake of "thalidomide" disaster, is currently an integrated global effort of more than 70 countries worldwide. After the "thalidomide tragedy", many countries have established drug-monitoring systems for early detection and prevention of possible drug-related morbidity and mortality. The use of traditional and complementary drugs (e.g., herbal remedies) may also pose specific toxicological problems, when used alone or in combination with other drugs.[3] An ACDR due to a drug is any undesirable change in the skin, its appendages, or mucous membranes. Drug eruptions are among the most common cutaneous disorders encountered by dermatologists.[4,5] In fact, monitoring of ADRs is now mandated by regulatory agencies in India. central drugs standard control organization (CDSCO) has mandated all medical institutions to report ADRs originating from their hospitals. The CDSCO is under the Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India. It is the National Regulatory Authority (NRA) of India, and its headquarter is located at FDA Bhawan, Kotla Road, New Delhi. It has 6 zonal offices, 4 sub-zonal offices, 13 port offices, and 7 laboratories spread across the country. There is a wide spectrum

of ACDRs seen in the Department of Dermatology, varying from transient maculopapular rash to fatal toxic epidermal necrolysis. The wide and indiscriminate use of drugs has increased the incidence and the modes of presentation of cutaneous drug reactions.[6] It is the prime responsibility of health care professional (HCPs) to identify potential and actual treatment-related problems, resolve problems, and prevent the future onset of problems due to drug administration. HCPs are encouraged by various regulatory agencies to take responsibility in ADR monitoring and reporting programs. Due to this reason, regulatory agencies regularly disseminate the information regarding ADRs to the general public as well as to HCPs. This would increase awareness about ADRs, motivate the reporting people, benefit medical professionals in drug selection, and enhance better prescription for patients with better patient outcome.[7] However, underreporting of ADRs is observed among Indian clinicians due to inadequate training on the use of drugs and patient safety monitoring, resulting in humanistic and economic burden to the patients as well as to the society.[8] ADR reporting helps in drug monitoring and may even guide clinicians, pharmaceutical companies, and regulatory authorities in better drug usage. Thus, ADR monitoring and reporting are important, while prescribing drugs to the patients. Many a times, ADRs are relatively mild and disappear when the drug is stopped or there is reduction in dose, but some of the side effects are serious and last longer. So, it can be concluded that ADRs increase morbidity and mortality of the patients as well as add up to the financial cost to the patients. However, some ADRs are predictable in nature and, hence, with the knowledge of these ADRs, patients can be circumvented from such deleterious effects of the drug treatment, such as in patients with a known allergy or with comorbidities.

MATERIALS AND METHODS

This was a retrospective, observational, noninterventional, cross-sectional study carried out at the Department of Pharmacology and Department of Dermatology at the tertiary care teaching hospital in Amritsar, which is a 1,000 bedded multispecialty hospital. This study was conducted on patients presenting with dermatological reactions due to medications at the Department of Dermatology at SGRDIMSAR, Amritsar from the month of June 2015 to May 2018. The study was approved by the Institutional Ethics Committee. The inclusion criteria of the study were patients of all age groups, both genders, presenting in outpatient department (OPD)/indoor patient department (IPD) of dermatology, patients with any disease and comorbid condition, and patients hospitalized due to dermatological ADR or referred to the OPD of the dermatological department. However, pregnant women, nursing mothers, and patients having any of the chronic illness like chronic renal failure/liver disease were excluded. The demographic data of the patients like patient initial, hospital number, age, sex, marital status, medical history, medication history, past drug allergies, and herbal and cosmetic use were recorded on the case record form provided by CDSCO. In addition, the prescription given to the patient including the drugs prescribed with dose, frequency, and duration of the treatment was noted on this case record form. Diagnosis of ACDRs was done by dermatologists and the assessment of the probability of the reactions was done in the pharmacovigilance cell, Department of Pharmacology. All the doctors, residents, interns, and students were encouraged to notify any suspected ACDRs by either telephonic or direct reporting to the pharmacovigilance cell, Department of Pharmacology. Reporting was done according to "CDSCO ADR Reporting Form".[9] On the basis of collected data, the incidence rate was calculated and the ACDRs were classified on the basis of age, sex, and the most common drug causing them.

CAUSALITY ASSESSMENT

The ADR algorithm and the causality assessment scale were also included in the data entry format. The patients and offending drugs were identified through the history of medications taken, prescription monitoring, and reports obtained from the HCPs (nurses, doctors, etc.). Data were collected from patient's case sheet and transferred to data entry format for evaluation. The collected data were analyzed by using the Naranjo causality assessment scale (Table 1),[10] WHO probability assessment scales (Table 2),[11] and Hartwig and Siegel severity assessment scale (Table 3).[12] The collected data were further analyzed for their appropriateness and suitability, and the interpretation was made for the collected data. The suspected ADRs were reported to the regional pharmacovigilance center and the peripheral center. Causality assessment was done by the WHO causality assessment scale, classifying ADRs into certain, probable, possible, unlikely, unclassified, and inaccessible. ACDRs reported under certain, probable, and possible were included in the study. Severity assessment was done by the modified Hartwig and Siegel scale,[12] which classifies the severity of ADRs as mild, moderate, or severe based on factors like the necessity of change in treatment, increased duration of hospital stay, and disability produced by ADRs. Patients presenting difficulties in communication, mental illness, and accidental or intentional poisoning due to drugs were excluded from the study. Preventability of ADRs was evaluated by Schumock and Thornton's criteria (Table 4).[13] The data obtained were collected, compared, and

Table 1: Naranjo ADR probability scale—items and score[10]

S. no.	*Question*	*Yes*	*No*	*Do not know*
1	Are there previous conclusion reports on this reaction?	+1	0	0
2	Did the adverse event appear after the suspect drug was administered?	+2	−1	0
3	Did the adverse reaction (AR) improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4	Did the AR reappear when drug was readministered?	+2	−1	0
5	Are there alternate causes (other than the drug) that could solely have caused the reaction?	−1	+2	0
6	Did the reaction reappear when a placebo was given?	−1	+1	0
7	Was the drug detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10	Was the adverse event confirmed by objective evidence?	+1	0	0

Table 2: WHO-UMC causality categories[11]

Causality term	*Assessment criteria (all points should be reasonably compiled)*
Certain	• Event/laboratory test abnormality, with plausible time relationship to drug intake
	• Cannot be explained by disease or other drugs
	• Response to withdrawal plausible (pharmacologically, pathologically)
	• Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon)
	• Rechallenge satisfactory, if necessary
Probable/likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake
	• Unlikely to be attributed to disease or other drugs
	• Response to withdrawal clinically reasonable
	• Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake
	• Could also be explained by disease or other drugs
	• Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
	• Disease or other drugs provide plausible explanation
Conditional/unclassified	• Event or laboratory test abnormality
	• More data for proper assessment needed, or
	• Additional data under examination
Unassessable/unclassifiable	• Report suggesting an adverse reaction
	• Cannot be judged because information is insufficient or contradictory
	• Data cannot be supplemented or verified

Table 3: Hartwig and Siegel severity assessment scale[12]

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 (LOS)
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 LOS
Level 4	Any level 3 ADR which increases the length of stay by at least 1 day or the ADR was the reason for the admission
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

ADR, adverse drug reaction; mild, levels 1 and 2; moderate, levels 3 and 4; severe, levels 5, 6, and 7

reviewed, calculating the percentage to assess their significance and evaluation.

RESULTS

The result of this study on 152 patients attending Dermatology OPD/IPD reported with ADRs is presented in Tables 5 to 8. Sex-wise distribution is given in Table 5. From Table 5, it can be analyzed that the most common incidence (54%) was reported in the age group of 18 to 35 years and the higher incidence rate was observed in males as compared to females (M:F = 1:0.52). The most common age group presenting with ACDRs was 18 to 35 years with 54% having ACDRs, while in the age group of 63 to 80 years, the percentage of ACDRs was

Table 4: Preventability criteria according to the Schumock and Thornton scale[13]

Definitely preventable
1. Was there a history of allergy or previous reactions to the drug?
2. Was the drug involved inappropriate for the patient's clinical condition?
3. Was the dose, route, or frequency of administration inappropriate for the patient's age, weight, or disease state?
4. Was a toxic serum drug concentration (or laboratory monitoring test) documented?
5. Was there a known treatment for the adverse drug reaction?
Probably preventable
6. Was required therapeutic drug monitoring or other necessary laboratory tests not performed?
7. Was a drug interaction involved in the ADR?
8. Was poor compliance involved in the ADR?
9. Were preventative measures not prescribed or administered to the patient?
Not preventable
10. Were all above criteria not fulfilled?

Table 5: Age- and sex-wise distribution of patients who developed ACDRs in the prospective study

Age group (in years)	*Male*	*Female*	*Total (%)*
1–17	17	07	24 (16)
18–35	53	29	82 (54)
36–62	26	13	39 (26)
63–80	04	03	07 (04)
Total	100	52	152

Table 6: Type of reaction seen in patients

S. no.	*Type of reaction*	*No. of patients (%)*	*Drugs/groups responsible*
1	Urticaria	46 (30.2)	NSAIDs, fluoroquinolones
2	Fixed drug eruptions	25 (16.4)	Systemic steroids
4	Angioedema	15 (9.0)	Oral contraceptive pills
5	Erythema multiforme	16 (10.5)	Ampicillin, NSAIDs
6	Steven–Jonson Syndrome	15 (9.0)	Sulfonamides
7	Acneiform/follicular eruption	9 (5.9)	NSAIDs, ACE inhibitors
8	Toxic epidermolytic necrosis	4 (2.6)	Chloroquine
9	Exfoliative dermatitis	4 (2.6)	Ampicillin, chloroquine
10	Photosensitivity drug eruption	6 (3.9)	Isoniazid
11	Swelling of lips	5 (3.2)	Topical creams
12	Serum sickness	2 (1.3)	Systemic steroid
13	Other bullous drug reaction	2 (1.3)	Antimalarial, clofazimine
14	Vasculitis	2 (1.3)	Metronidazole
15	Others	1 (0.6)	Hydroxychloroquine

Table 7: WHO causality and Hartwig and Siegel severity assessment of ACDRs

S. no.	*Assessment*	*Category*	*No. of ADRs*	*Percentage*
1	Causality	Certain	19	13.0
		Probable	85	56.1
		Possible	47	30.7
2	Severity	Mild	110	72.3
		Moderate	38	25
		Severe	04	2.6

Table 8: Assessment of the preventability of ACDRs by the modified Schumock and Thornton scale

S. no.	*Preventability*	*No. of patients*	*Percentage*
1	Definitely preventable	105	69.1
2	Probably preventable	26	17.1
3	Not preventable	21	13.8

least (4%). Out of 152 ACDRs reported in this retrospective study, the most common was urticaria (30.2%) followed by fixed drug eruptions (16.4%). Other reported ACDRs were angioedema (9.0%), erythema multiforme (10.5%), Steven–Johnson syndrome (SJS) (9%), acneiform/follicular eruption (5.9%), toxic epidermolytic necrosis (2.6%), exfoliative dermatitis (2.6%), photosensitivity drug eruption (3.9%), hypersensitivity syndrome (3.2%), serum sickness (1.3%), vasculitis (1.3%), and others (0.6%). As is evident from Table 6, the most common drugs responsible for ACDRs in this prospective study were NSAIDs and fluoroquinolones followed by systemic steroids, oral contraceptive pills, ampicillin, ACE inhibitors, and so on. According to WHO causality assessment, 19/52 cases were certain (13.0%), 85/152 were probable (56.1%), and 47/152 were possible (30.7%) in nature. On severity assessment by the modified Hartwig and Siegel

scale, 110/152 (72.3%) ACDRs were mild, 38/152 (25%) were moderate, and 4/152 (2.05%) cases were of severe type. Preventability assessment by the modified Schumock and Thornton scale[13] revealed that 105/152 ACDRs (69.1%) were definitely probable, 26/152 (20.51%) were probably preventable, and 21/152 (13.8%) were not preventable.

DISCUSSION

Drugs are used for the treatment and prophylaxis of various disease conditions and are considered as safe when used rationally. Drugs show some ADRs in various patients. ADR monitoring is an essential aspect of therapeutics. However, most of the time, it is overlooked and not considered important. Even when observed, many would not document and report voluntarily. Establishing pharmacovigilance units in hospitals has facilitated this activity to a great extent. This study focused on the pattern of dermatological ADRs of drug class in the post-marketing surveillance studies to find out the effects in a large and diverse population. This study was carried out with an approach to reveal the pattern of ACDRs with simultaneous vision of establishing the impact of pharmacovigilance activity in our tertiary care center. In a study conducted by Chatterjee et al.,[14] it was concluded that the incidence of the drug-induced adverse skin reaction was found to be 2 to 6% at the dermatology outpatient setting. The present study has revealed that higher numbers of ADRs were reported in males. Similar results were seen in other studies showing higher male preponderance; however, a female preponderance was seen in other studies as well.[15] The reason for higher incidence in the present study could be that males are more aware and are more mobile and, hence, have access to treatment before ADRs become severe. In the present study, the most suspected ADRs were urticaria (46%) cases, followed by fixed drug eruptions (16.4%), angioedema (9%), acne (5.9%), and SJS (5.9%), followed by toxic epidermal necrolysis, swelling of lips, and others. Highly occurring ADR in the present study was urticarial rash, which is similar to results obtained in other studies.[16] There were studies conducted in the past,[17] which showed that the most common suspected ADR was rash followed by urticaria and/or fixed drug eruptions (FDE), which were also observed in the present study, and microbial agents, NSAIDs, corticosteroids, and antiepileptics. Chatterjee et al.[14] showed the same higher incidence of the suspected drug classes, which were antimicrobial agents, antiepileptics, and NSAIDs. This is quite consistent with the present study in which the most offended drug classes were NSAIDs, corticosteroids, hormonal preparations, etc. In a study by Suthar et al.,[18] NSAIDs, antibiotics, and antiepileptics were reported to produce a higher incidence rate, in which the development of ADRs in two-thirds of the patients was due to NSAIDs and antibiotics. In our study, 4 (2.4%) cases of toxic epidermal necrosis (TEN) and 15 (9%) cases of SJS were reported. In a study conducted by Lihite et al.,[19] 2 cases of TEN and 1 case of SJS were reported out of 108 cases over a period of 5 months, whereas Sushma et al.[21] have shown 11.4% fatal cases of TEN and SJS. However, Sharma et al.[20] reported that there is a change in cutaneous ADR patterns and the possible reason for this change can be attributed to the emergence of newer drugs/molecules and changing trends in the prescribing pattern of drugs by clinicians. In the present study, most of the ADRs in our study were designated as possible (30.7%) or probable (56.1%) and 13% as certain as per WHO-UMC (Uppsala Monitoring Centre) causality assessment. These findings are consistent with a study conducted by Sushma et al.[21] showing the similar effects in patients. Among them, possible ADRs were highly observed. A study by Suthar et al. have shown that commonly incriminated drugs causing CADR (cutaneous adverse drug reaction) were antimicrobial agents i.e. ciprofloxacin (21.57%) followed by phenytoin (9.8%), diclofenac sodium (6.86%), anti-snake venom (6.86%) and vancomycin (3.92%), respectively.[18] The percentage of dermatological ADRs falling in the category of definitely preventable is very high (69.1%), probably preventable (17.1%), and not preventable (13.8%) (Table 8). According to United States-Food and Drug Administration (US-FDA) criteria,[22] any adverse reaction is denoted as serious when the patient outcome falls within categories, such as death, life-threatening, hospitalization (initial or prolonged), disability or permanent damage, congenital or birth defect, or required intervention to prevent permanent damage to patient. However, in our study, causality assessment revealed that 13.0% cases were certain, 56.1% were probable, and 30.7% were possible, which were comparable to those reported by Chatterjee et al.[14] Analysis of the results showed that in this prospective study, NSAIDs and fluoroquinolones were the most common drugs responsible for FDE. Other studies[23] have documented sulfonamides and tetracycline as the most common causative agents. Hartwig severity assessment showed that 04/152 (2.6%) of the total reported ACDRs were severe, 38/152 (25%) cases were moderate, and 110/152 (72.3%) cases were mild. Similarly, from Table 8 of the present study, it can be concluded that 105/152 (69.1%), 26/152(17%), and 21/152 (13.8%) of ACDRs were definitively preventable, probably preventable, and not preventable, respectively, as has been evaluated by the modified Schumock and Thornton scale. Polypharmacy is a recognized risk factor for ADRs particularly in the elderly and is likely to increase

the incidence of ADRs, since therapeutic guidelines indicate that multiple therapies are used to treat various diseases.[24] Similarly, patients with multiple diseases and patients with impaired hepatic or renal status are at an increased risk of developing ADRs due to the use of multiple drugs for their multiple diseases. In an Indian study conducted by Jose et al.,[25] polypharmacy and the multiple disease state (52.9%) were revealed as the most prevalent predisposing factors for the development of ADRs (93.1 and 52.9%, respectively). Another Indian study by Sriram et al.[26] showed that multiple drug therapies (68%), advanced age (56%), and comorbid diseases (42%) were the major risk factors for developing ADRs.

CONCLUSION

Urticaria, fixed drug eruption, and acneiform eruption are the most commonly encountered ACDRs at our tertiary care center. The most common drugs responsible were NSAIDs, fluoroquinolones, corticosteroids, isoniazid, rifampicin, metronidazole, and antimalarial drugs. Polypharmacy and allergy are important risk factors, which can be prevented by taking proper history, prescribing alternative drugs, and educating the patients about the risk of self-medication. There are gaps between knowledge and ADR reporting among doctors working in hospitals, which need to be addressed by improved training in pharmacovigilance and risk perceptions of drugs.

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