RESEARCH ARTICLE

Pharmacovigilance Study of Adverse Cutaneous Drug Reactions in a Tertiary Care Hospital

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ABSTRACT

Background: The wide and indiscriminate use of drugs has increased the incidence and the modes of presentation of cutaneous drug reaction. Adverse cutaneous drug reactions are common, comprehensive information about their incidence, severity and ultimate health effects are unavailable.

Objective: To study and evaluate incidence of adverse cutaneous drug reaction (ACDR) at our tertiary care hospital and assess the impact of active surveillance on adverse drug reaction (ADR) reporting.

Materials and Methods: Prospective study involving 29,156 patients was carried out by active observation of patients attending Dermatology department over a period of 21 months. Retrospective study involving 61000 patients attended Dermatology OPD over last 4 years was carried by available data of dermatology department. Both the studies were compared by chi square test.

Results: In prospective study 48 (0.17%) were diagnosed as having ACDR. Acneform eruption (25%) followed by fixed drug eruption (FDE) (22.92%) were the most common morphological forms. The most common drugs responsible were betamethasone, isoniazid and rifampicin for acneform eruption, while metronidazole and paracetamol for FDE. WHO causality assessment showed 13 were certain, 24 were probable and 11 were possible in nature. Hartwig severity assessment revealed 40 were moderate, 07 were mild and 01 was severe. Modified Schomock and Thronton scale showed 37.5% were definitely preventable, 33.33% were probably preventable and 29.17% were not preventable. In retrospective study 63 (0.10%) ACDRs were reported, out of them FDE was most common (28.57%), followed by acneform eruption (11.11%). Antimalarials and metronidazole were most commonly responsible for FDE while systemic steroids were responsible for acneform eruption. There is significant association between both the studies with higher incidence in prospective study ($p<0.05$).

Conclusion: Most common ACDRs were acneform eruptions and FDE in both prospective study and retrospective study. Pharmacovigilance activity is significantly effective in increasing the reporting of ADRs.

KEY WORDS: Adverse cutaneous drug reaction (ACDR); Pharmacovigilance; Causality of Adverse Drug Reactions; Severity of ADR; Preventability of ADR

INTRODUCTION

According to WHO, 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] An Adverse Cutaneous Drug Reaction (ACDR) caused by a drug is any undesirable change in the structure or function of the skin, its appendages or mucous membranes and it encompasses all adverse events related to drug eruption, regardless of the etiology.[2] Drug eruptions are among the most common cutaneous disorders encountered by the dermatologist.[3,4] There is a wide spectrum of ACDRs varying from transient maculopapular rash to fatal toxic epidermal necrolysis (TEN)[5] and acneform eruption[6]. Mode of onset, severity and underlying mechanism varies for different types of ACDRs. The wide and indiscriminate use of drugs has increased the incidence and the modes of presentation of cutaneous drug reaction.[7] The incidence of ACDRs in developed countries range from 1 to 3% among indoor patients,[8-10] whereas in developing countries such as India, some studies have documented it to 2 to 5% of the indoor patients;[11-14] however, there is lack of comprehensive data regarding out-patient department. The inadequacy of data could be attributed to lack of awareness to report Adverse Drug Reaction (ADR). ADR reporting directly helps to drug monitoring and may even guide to Pharmaceutical companies and regulatory authorities for better drug usage. The pattern of cutaneous adverse drug eruptions and the drugs responsible for them keep changing every year.[11] Although such cutaneous reactions are common, comprehensive information about their incidence, severity and ultimate health effects are unavailable.[15] So this study was undertaken to evaluate incidence and causality of ACDRs in dermatology department of our tertiary care centre and to compare it with hospital data to assess the impact of Pharmacovigilance on ADR reporting.

MATERIALS AND METHODS

The study was approved by Institutional 'Human Research Ethics Committee (HREC)', C U Shah Medical College & Hospital, Surendranagar. It was a comparative and observational study, conducted in two parts. Prospective study was conducted during SEPTEMBER 2010 to MAY 2012 by active observation of patients. Retrospective study was done by analyzing the available hospital data from January 2006 up to August 2010.

Prospective study was carried out by observing patients attending Dermatology out Patient Department (OPD) over a period of 21 months to find the incidence of ACDRs. Diagnosis of ACDRs was done by the dermatologists. All the doctors, residents, interns and students were encouraged to notify any suspected ACDRs by either telephonic direct reporting to the Dept. of Pharmacology. Reporting was done according to 'CDSCO ADR Reporting Form'.[16] Reporting form was consisting details like drug history and information like onset and nature of reaction, associated drugs and past history of similar or other allergic reactions.

On the basis of collected data, incidence rate was calculated and the ACDRs were classified on the basis of age, sex and most common drug causing them. Causality assessment was done by WHO causality assessment scale[17], classifying ADR in to certain, probable, possible, unlikely, unclassified and unassessible. ACDRs reported under certain, probable and possible were included in study. Severity assessment was done by modified Hartwig and Siegel's scale[18], which classifies severity of ADR as mild, moderate or severe based on factors like necessity of change in treatment, increased duration of hospital stay and disability produced by ADR. Assessment of preventability was done by modified Schomock and Thronton scale.[19] According to this scale detected ACDRs were categorised in to definitely preventable, probably preventable and not preventable.

Simultaneously retrospective study of patients attended Dermatology OPD over last 4 years was carried out from the available data in register of Dermatology department. Patients diagnosed as ACDRs were noted and incidence rate was calculated. Data was classified for most common reaction and most common drugs or drug group causing it. Confidentiality of the patient data was maintained throughout the study.

Statistical Analysis

Results from both the studies were compared for association by chi-square test using MedCalc. Software version 7.6.0.0 ($p < 0.05$ was considered as significant).

RESULTS

In prospective study 29,156 patients attending dermatology OPD were observed. Out of all observed patients 48 (0.17%) were diagnosed as having ACDRs by dermatologists. Most cases had reaction time between 1 to 10 days. The most common age group diagnosed as having ACDRs was 18-35 years and higher incidence rate was observed in male as compared to females (M:F = 1:0.66) [Table 1].

Table-1: Age and Sex wise Distribution of Patients who Developed ACDRs in Prospective Study

Age Group (In Years)	Male	Female	Total
1 – 17	05	00	05
18 – 35	16	12	28
36 – 62	08	07	15
63 – 80	00	00	00
Total	29	19	48

Out of 48 ACDRs reported in prospective study, most common was acneform eruption (25.00%) [Figure-1] followed by fixed drug eruption (FDE) (22.92%). Other reported ACDRs were urticaria (8.33%), Steven Johnson (SJ) syndrome (8.33%), bullous eruption (6.25%), maculopapular rash (6.25%), pellagrous dermatitis (4.17%), hypertrichosis (4.17%), hypopigmentation (4.17%), eczematous drug eruption (2.08%), vesicular eruption (2.08%), swelling of lips (2.08%), acne rosacea (2.08%) and stria (2.08%) [Figure-2].

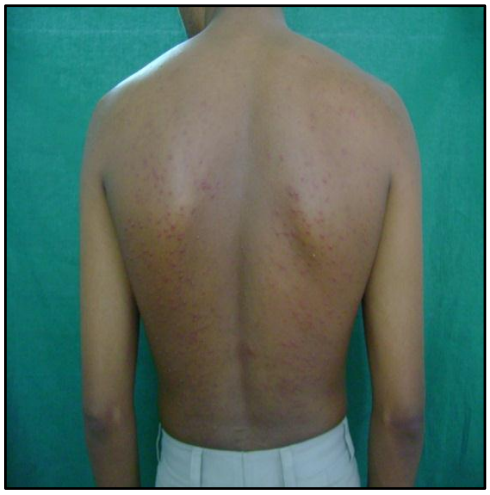

Figure-1: Acneform Eruption

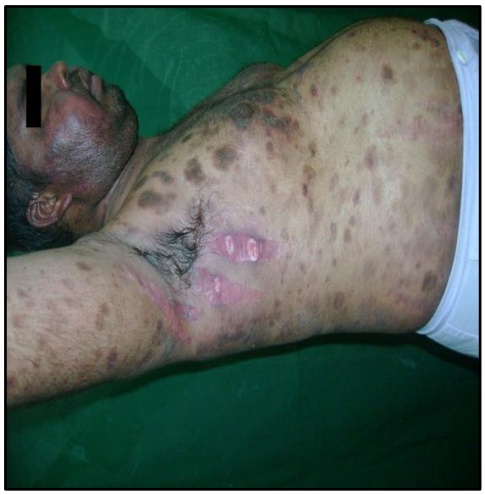

Figure-2: Stria

The most common drugs responsible for ACDRs in prospective study were betamethasone, isoniazid and rifampicin for acneform eruption, while metronidazole and paracetamol for FDE. Antimicrobials (22.92%), other steroids (18.75%) and NSAIDs (10.42%) were responsible for other various ACDRs [Table-2]. According to WHO causality assessment 13 were certain (27.08%), 24 were probable (50%) and 11 were possible (22.92%) in nature. On severity assessment by modified Hartwig and Siegel's scale, out of 48 ACDRs 7 (14.59%) were mild, 40 (83.33%) were moderate and 1 (2.08%) was severe [Table-3].

Preventability assessment by modified Schomock and Thronton scale revealed that out of 48 ACDRs 18 (37.5%) were definitely probable, 16 (33.33%) were probably preventable and 14 (29.17%) were not preventable [Table-4].

Table-2: Drugs Responsible for ACDRs in Prospective Study (n=48)

Sr. No.	Type of Reaction	No. of Patients	Drugs Responsible
1	Acneform eruption	3	Betamethasone
		3	Isoniazid, Rifampicin
		1	Chlorpromazine
		2	Prednisolone
		1	Multivitamin
		1	Clobetasol
		1	Testosterone
2	Fixed drug eruption	2	Metronidazole
		2	Paracetamol
		1	Mefenemic acid + Paracetamol
		1	Diclofenac
		1	Levofloxacin
		1	Fluconazole
		1	Cotrimoxazole
		1	Quinine
		1	Sparfloxacin
3	Urticaria	2	Cephalosporin
		1	Propofol
		1	Aceclofenac + Paracetamol
4	SJ syndrome	2	Carbamazepine
		1	Ciprofloxacin
		1	Septran
5	Bullous eruption	1	Furosemide
		1	Ibuprofen + Paracetamol
		1	Ofloxacin
6	Maculopapular rash	1	Isoniazid
		1	Levofloxacin
		1	Diclofenac
7	Pellagrous dermatitis	2	Isoniazid
8	Hypertrichosis	2	Betamethasone
9	Hypo-pigmentation	2	Betamethasone
10	Eczematous drug eruption	1	Indomethacin
11	Vesicular eruption	1	Levofloxacin
12	Swelling of lips	1	Ceftriaxone
13	Acne rosacea	1	Clobetasol
14	Stria	1	Prednisolone

Table-3: WHO Causality and Hartwig and Siegel's Severity Assessment of ACDRs Detected in Prospective Study (n=48)

Sr. No.	Assessment	Category	No. of ADRs	Percentage
1	Causality	Certain	13	27.08%
		Probable	24	50%
		Possible	11	22.92%
2	Severity	Mild	07	14.59%
		Moderate	40	83.33%
		Severe	01	02.08%

Table-4: Assessment of Preventability of ACDRs by Modified Schumock and Thornton Scale (n=48)

Preventability	No. of Patients	Percentage
Definitely preventable	18	37.50%
Probably preventable	16	33.33%
Not preventable	14	29.17%

Table-5: Drugs Responsible for ACDRs in Retrospective Study (n=63)

Sr. No.	Type of reaction	No. of Patients	Drugs / Groups Responsible
1	Fixed drug eruption	18	Antimalarial, Fluroquinolones
2	Acneform eruption	7	Systemic Steroids
3	SJ syndrome	6	Isoniazid, phenytoin, Carbamazepine, Septran
4	Melasma	5	Oral contraceptive pills
5	Angioedema	4	Penicillin, Salicylates
6	Erythema multiformae	4	Sulfonamides
7	Urticaria	3	NSAIDs,ACE inhibitors
8	Drug induced Erythroderma	3	Chloroquine
9	Maculopapular exanthema	3	Ampicillin, Chloroquine
10	Pellagrous dermatitis	3	Isoniazid
11	Hypertrichosis	2	Systemic Steroid
12	Stria	2	Systemic Steroid
13	Hyperpigmentation	1	Clofazamine
14	Bullous FDR	1	Metronidazole
15	Phototoxic reaction	1	Hydroxychloroquine

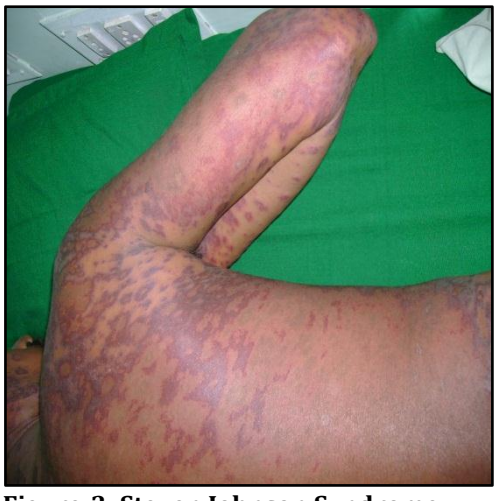

Figure-3: Steven Johnson Syndrome

In retrospective study according to hospital data 61,000 patient attended Dermatology OPD during above duration. Out of 61000 63 (0.10%) patients were documented as having ACDRs by Dermatologists. Most common was FDE (28.57%) followed by Acneform eruption (11.11%). Other documented ACDRs were SJ

syndrome [Figure-3], melasma, angioedema, erythema multiformae, urticaria, drug induced erythroderma, maculopapular exanthema, pellagrous dermatitis, hypertrichosis, stria, hyperpigmentation, bullous FDE and phototoxic reaction in descending order.

The most common drug groups responsible were antimalarial and fluroquinolones for FDE [Figure-4], while acneform eruption was mainly caused by systemic steroids. Drug groups responsible for other ACDRs were anti-tuberculer, antipsychotics, antibiotics and NSAIDs [Table-5].

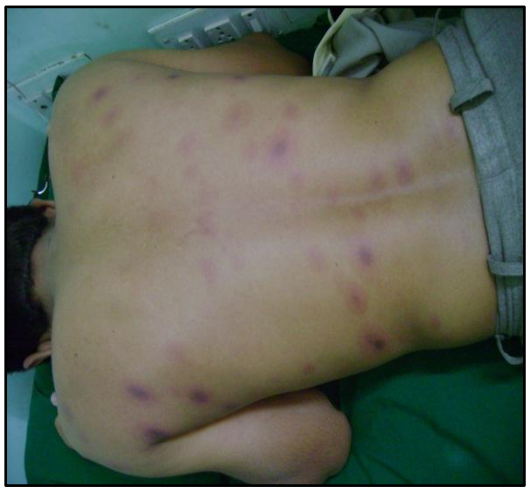

Figure-4: Fixed Drug Eruption

Comparison between Prospective and retrospective study was carried out by chi-square test. Analysis showed that comparison was significant (x^2 =6.03) ($p< 0.05$). It suggests that there was significant association between prospective study and retrospective study with higher incidence rate of ACDRs in prospective study.

DISCUSSION

This study was carried out with an approach to reveal pattern of ACDRs with simultaneous vision of establishing impact of Pharmacovigilance activity in our tertiary care centre. The ACDRs reported was 0.17% of the observed patients in prospective study analysis, while in retrospective study analysis it was documented in 0.10% of the observed patients. In a study conducted by chatterjee at el.[15] (2006) the incidence of drug induced adverse skin reaction was found to be 2 to 6 % at dermatology out patient setting. The fewer incidences in our study might be due to better drug prescribing method or still lack of awareness regarding ADR reporting, but incidence rate in prospective study was higher as compared to retrospective study data. There was significant association between both the studies suggesting impact of Pharmacovigilance on reporting of ACDRs.

Pudukadan D et al.[11] (2004) revealed that most common age group was 20-39 years followed by 40-59 years with higher incidence in female (M:F = 0.87:1), similarly in our study most common age group was 18-35 years followed by 36-62 years, but with male preponderance (M:F = 1:0.66), However other studies have been reported with high male female ratio.[3,5]

A broad clinical spectrum of ACDRs was observed in this study. FDE (28.57% & 22.92%) and acneform eruption (25% & 11.11%) were the most common ACDRs in prospective study and retrospective study. Others have noted maculopapular rash and FDE as the most common ACDRs.[5,6,15]

Analysis of results showed that in prospective study metronidazole and paracetamol, while in retrospective study antimalarial and fluroquinolones were the most common drugs responsible for FDE, which has already been reported.[4] Other studies[5,9] have documented sulfonamides and tetracycline as the most common causative agent.

In consonance with earlier study[6] steroids and anti-tuberculer drugs were responsible for acneform eruption in this study. Causative agents for SJ syndrome in this study were antipsychotics, which is supported by other studies.[5,12,15]

Other causative agents for ACDRs revealed by this study were antimicrobials (22.92%), steroids (18.75%) and NSAIDs (10.42%), which is in concordance to results of other studies.[5,15]

Causality assessment revealed 27.08% were certain, 50% were probable and 22.92% were possible which was comparable to Chatterjee et al.[15] (2006). As supported by literature[2] Hartwig severity assessment showed 2% of total reported ACDRs were severe. Importantly, in this study preventability assessment was done by modified Schomock and Thronton scale which was lacking in other studies done on ACDRs. In retrospective study causality, severity and preventability assessment was not possible due to lack of sufficient data. This shows importance of Pharmacovigilance activity in proper assessment of ADR. Interesting part of this study was detection of some rare ACDRs such as pellagrous dermatitis and hypertrichosis. Our hospital is situated in Surendranagar district of Gujarat, which has flow of patients who belongs to poor socioeconomic class, so major limitation of this study was that it could not reveal pattern of ACDRs in higher socioeconomic class. This study can be further carried out on wide basis for better evaluation of ACDRs.

CONCLUSION

Fixed drug eruption and acneform eruption are the most commonly encountered ACDRs at our tertiary care centre. Most common drugs responsible were corticosteroids, isoniazid, rifampicin, metronidazole, fluroquinolone and antimalarial drugs. Pharmacovigilance activity is significantly effective in increasing the reporting of ADRs.

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