Adverse Drug Reaction Monitoring In Dermatology Out - Patient Clinic


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ABSTRACT

Background: Medicines fight against diseases however, dermatological drugs are associated with a higher risk due to the unique characteristics of skin and therapeutic indication that in most of cases gets neglected. So, there is an immense need to monitor the drug therapy and safety.

Objective: The primary objective is to identify frequency and pattern of suspected ADR and secondary objective is to identify causality, severity, and outcome of suspected ADRs in dermatology out-patient clinic.

Method: A Prospective Observational Cross-sectional study conducted at Perfect Skin Care, Gandhinagar, Gujarat from October 2021 to March 2022 with age group 18-59 yr visiting dermatology outpatient clinic.

Results: Out of 33 patients with 36 suspected ADRs, 9 were Male and 24 were Female. Overall incidence rate of Dermatological ADR was 7.95%. Dry Skin, chapped lips, Nausea, and persistent erythema are most found ADRs. The most frequent suspected class of drugs were Retinoids, Steroids, Antibiotics and NSAIDS. 24 reactions were of Probable and 11 reactions were of Possible class. 30 reactions were of mild Class and 6 reactions were of moderate class. Out of 36 ADRs Type A (n=32), Type B (n=1), Type C (n=2) and Type D (n=1). Total number of patients recovered from suspected ADRs were 30.

Conclusion: The Healthcare system should promote the spontaneous reporting of Dermatological ADRs to pharmacovigilance centers for drug safety. Most of ADR gets unreported due to lack of interest in ADR monitoring and reporting at hospital settings. Pharmacist can play a major role in prevention and actively reporting of suspected ADRs.

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INTRODUCTION:
The World Health Organization (WHO) defines an Adverse drug reaction (ADR) as a “reaction which is noxious and unintended and which occurs at doses normally used in human for prophylaxis, diagnosis or therapy of disease or modification of the physiological function.”[1]

Factors which might increase the possibility of the occurrence of ADRs include; extremes of age, gender, multiple drugs, disease state, history of ADR or allergy, genetic factors, large doses, and many other factors. Adverse drug reactions (ADR) are important causes of morbidity and mortality and can occur during hospital admissions or in the community leading to hospital admission. [2] In many countries ADRs rank among the top 10 leading causes of mortality and India is one of them. [3]

The incidence of dermatological ADRs among in-patients in developing countries such as India it is 2–5 %. [4] The burden of dermatological Adverse Drug Reactions (ADRs) is resulting into switching or discontinuation of drug as well as medication non-adherence. Active search is essential for evaluating, managing for post marketed drugs. [5]

Thus, there was an immense need to have a standardized and full-bodied Pharmacovigilance system for the nation. [6] Now with the advent of Pharmacovigilance programme more ADR reporting centers have been established in almost every government health care set up. [7]

MATERIALS AND METHODOLOGY
The study was a Prospective Observational Cross-sectional study carried out after the approval from K.B Independent Ethics Committee of K.B. Institute of Pharmaceutical Education and Research. The study was conducted for a duration of 6 months from October 2021 to March 2022 at Perfect Skin Care, Gandhinagar with the patient visiting dermatology clinic who received drugs and were suspected with ADR.

Consent for study was taken from the patients by signing informed consent form. The suspected ADR were then confirmed by with the physician and relevant information of the patients were collected by interviewing patient, reviewing case file, progress report, laboratory data if any was transcribed in the CDSCO Suspected ADR reporting form (version 1.4) which focuses on following information that is patient Demographics, Suspected drug & observed adverse reactions, concomitant Medications, Relevant History and Laboratory test (if any)

The inclusion criteria of the study were patients of both genders from18-59 years. Pregnant women, Geriatric, Pediatric and Psychotic Patients were excluded. The reported ADRs were assessed for causality using Naranjo’s probability scale. The total score was calculated and it was categorized as certain (score >9), probable (score 5-8) and possible (score 1-4). The severity of ADRs were assessed by using Modified Hartwig’s criteria into seven levels. Level 1 and 2 classified as mild category, level 3 and 4 considered as moderate and level 5, 6 and 7 grouped as severe category. The classification of the reported ADRs were assessed using the Extended Rawlins and Thompson scale which describes result of data as Type A to E. These scales were filled by the investigator under the guidance of physician. Management was performed by the physician based on severity of reaction.

The outcome of the reaction assessed as a part of ADR analysis was classified as recovered, recovering, continuing, fatal, unknown, and other. The follow up of reported reaction after management was done via telephonic interviews of the patients. The data were subjected to statistical analysis using Microsoft Excel and SPSS software.

All the filled CDSCO suspected ADR reporting forms was verified and documented along with signed informed consent and other data analysis in the prepared study file. A completed copy of CDSCO suspected ADR reporting form was submitted to
Pharmacovigilance Department of GMERS Medical College, Gandhinagar.

**RESULT:**

Total 415 patients were enrolled in the study, in which 36 ADRs were identified. The total number of patients with ADR were 33. Out of which 24 (72.73%) were female and 9 (27.27%) were male. The Incidence rate of ADR was 3.70% in Male and 13.90% in Female. The overall incidence rate of Dermatological ADR was 7.95%. The mean (SD) age of all 33 patients was 27.61 (8.04) years, from 18 to 55 years. The age group of patients between 18-29 years was found to be maximum affected with ADR (72.72%) followed by age Group 30-39 years (18.18%) (Graph 1).

![Graph 1: Age wise Distribution of Patients Experiencing ADR N=33](image)

The Patients with single ADRs and with Two ADRs were 90.90% and 9.09% Respectively. The commonest most ADRs was found in 12 patients which was Dry skin (33.33%), 09 patients with Chapped lips (25%), 03 patients with Nausea and Anorexia (8.33%), 02 patients with persistent erythema (5.55%) (Graph 2). In each patient, Angioedema, weight gain, Skin Tanning, Itching, Swelling on Eye, Hair falls were found (2.77%) (Graph 2). In this study majority of reaction occurred within 15 days of treatment and least number of reactions observe in treatment period of 75 days (Table 1). The maximum number of patients with ADR which was 21 was with medical condition Acne vulgaris (63.64%), 02 patients with Melasma and Headache respectively (6.06%). The least found ADR which is in each patient were with medical condition Acne scar, Alopecia, eruptive lichen planus, Hidradenitis suppurativa, Ring warm infection, urinary tract infection, proteinuria, vitiligo (3.03%). Average number of medicines which is 5.5 were observed in the patient’s prescription. The most frequent suspected drugs were Isotretinoin in 20 (60.61%) Patients, Hydroquinone+ tretinoin+ mometasone cream in 2 (6.06%) of Patients, Diclofenac in 2 (6.06%) of patients followed by s of terbinafine, Betamethasone, methotrexate, clindamycin in each patient (3.03%). (Graph 3)
Graph 2: Frequency of Suspected ADR N=36

- Diarrhoea: 6
- Puffy skin: 3
- Nausea: 3
- Stomach upset: 2
- Skin Tanning: 2
- Weight gain: 1
- Angioedema: 12

Graph 3: Frequency of Suspected Drugs N=33

- Diclofenac: 2
- Amoxicillin +Clavulanate: 1
- Tissot (minerals): 1
- Hydroquinone+ tretinoin+ mometasone: 2
- Clindamycin: 1
- Methotrexate: 1
- Norfloxacin/ ofloxacin: 1
- Betamethasone: 1
- Terbinafine: 1
- Cyclophosphamide: 1
- N-acetyl cysteine inositol: 1
- Isotretinoin: 20

Graph 4: Frequency of therapeutic class of suspected ADR N=36

- combination: Depigmenting…: 5.55%
- Minerals: 2.77%
- Antibiotics: 5.55%
- Corticosteroids: 2.77%
- Anti-fungal: 2.77%
- Immunosuppressive: 5.55%
- Quinolones: 2.77%
- Pseudovitamin: 2.77%
- Retinoids: 63.89%
- NSAIDS: 5.55%
Table 1: Descriptive Analysis of Onset of ADRs with timescale of occurrences

<table>
<thead>
<tr>
<th>Within 7 days</th>
<th>Within 15 days</th>
<th>Within 30 Days</th>
<th>Within 45 Days</th>
<th>Within 60 Days</th>
<th>Within 75 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioedema (1)</td>
<td>Chapped lips (4)</td>
<td>chapped lips (2)</td>
<td>Dry skin (2)</td>
<td>Hair fall (1)</td>
<td>Weight gain (1)</td>
</tr>
<tr>
<td>Diarrhea (1)</td>
<td>Dry skin (5)</td>
<td>Rashes (2)</td>
<td>Skin tanning (1)</td>
<td>Dry skin (1)</td>
<td></td>
</tr>
<tr>
<td>Nausea (2)</td>
<td>Sweating on Eye (1)</td>
<td></td>
<td>Rashes (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry skin (3)</td>
<td>Nausea (1)</td>
<td></td>
<td>Chapped Lips (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chapped lips (2)</td>
<td>Itching (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent Erythema (2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Causality Assessment of the suspected ADR was Assessed for its likelihood with the drug using Naranjo’s causality Algorithm. Most of the reactions observed were of Probable in 24 patients (69.44%) followed by Possible in 11 patients (30.54%) (Graph 4). The Severity of Suspected ADR was Assessed using Hartwig and Seigel’s Severity Assessment. The maximum number of ADRs Found were Mild in 30 patients (83.33%) and 6 Moderate ADR were found (Graph 4). The Suspected ADR Was Classified using Extended Rawlins and Thompsons Classifications. Out of the 36 ADR obtained 32(88.88%) reaction were of type A, 01 (2.77%) reaction were type B (bizarre), 02(5.55%) reaction were type C (continuous) and 01(2.77%) reaction were Type D (Dose related).

In 6 patients (16.67%) suspected drugs were withheld, in 01 patient (2.77%) ADRs and Drug Frequency was changed. Some patients didn’t require any interventions, so same drug was continued for 6 ADR patients (16.67%) (Graph 5). In 17 patients, (47.22%) systematic treatment was required based on the reaction. Among the 36 ADRs, 30(83.33%) reactions were totally recovered and 6, (16.67%) reaction were still unknown in study period (Graph 5).
Graph 5: Management and Outcome of suspected ADR N=36

Table 2: Assessment and Management of suspected ADRs N=36

<table>
<thead>
<tr>
<th>Severity of suspected ADR</th>
<th>Type of suspected ADR</th>
<th>Suspected Drugs N=33</th>
<th>Suspected ADRs N=36</th>
<th>Action taken for Suspected ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Suspected Drugs N=33</td>
<td>Suspected ADRs N=36</td>
<td>Action taken for Suspected ADR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Possible causality</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dry skin (1), chapped lips (1), Rashes (1)</td>
<td>No treatment or no withdrawal</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Type A</td>
<td>isotretinoin (7)</td>
<td>Dry skin (2), Chapped lips (2)</td>
<td>Lip balm and moisturizer given respectively without drug withdrawal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dry skin (1), Chapped lips (1)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Moderate</td>
<td>Type A</td>
<td>cyclophosphamide (1)</td>
<td>Hair fall (1)</td>
<td>withdrawal</td>
</tr>
<tr>
<td></td>
<td>Type D</td>
<td>Terbinafine (1)</td>
<td>skin rash (1)</td>
<td>unknown</td>
</tr>
</tbody>
</table>

Probable causality

| Mild                     | Type A                | Isotretinoin (13)   | Dry Skin (1), Skin tanning (1) | No treatment or no withdrawal |
|                          |                       |                     | Dry skin (7), chapped lips (4) | Lip balm and moisturizer given respectively without drug withdrawal |
|                          |                       |                     | Chapped lips (1) | Withdrawal |
|                          | Amoxycillin + clavulanate (1) | Diarrhea (1) | Tablet Sporolac given without Drug withdrawal |


DISCUSSION

Drugs are used for the treatment and prophylaxis of various disease conditions and are considered as safe when used rationally. Drugs can exhibit many ADRs in various patients. It may also result in diminished quality of life, increased physician visits, hospitalizations, and even death. Which may ultimately get burden on Pharmacoeconomics of patients. Health professionals play their respective role in patient care and already burdened with diagnosing and treating the patient so the drug related problem is often neglected. When observed, many would not document and report voluntarily; reason include lack of time and knowledge. [8]

This present study revealed incidence of dermatological ADRs in out-patients is 7.95%. This is due to there are limited treatment option for certain dermatological condition which can lead to use of certain drugs, most preferable route of administration is topical which led to direct contact of skin. This observation shows higher incidence rate with studies conducted by Gohel et al which was 3.78%. [9] Similar data were shown in study conducted by Chatterjee et al., [10] concluded that the incidence of the drug induced adverse skin reaction was found to be 2 to 6% at the dermatology outpatient setting. Some of previous studies showed incidences of dermatological ADRs in out-patients were 3.78%, 1.6%, 7.02% and 9% respectively. [5,10,11,12]

The present study has found that higher numbers of ADRs were reported in Females than Male. This is due to hormonal difference, Skin structure and function, differences in drug metabolism, use of different cosmetic products and under reporting of ADR in male. This is in accordance with Murshida Parvin et al. 2019, [5] Ajay Borah et al.2016 [12] who also found similar results. Moreover, other two studies showed female preponderance. [13,14]

In present study, higher incidence of ADR was present in the patients who belong to the age group of 18-29 years (younger Adults) then other age groups. The reason for higher incidence in our study is because number of changes takes place like hormonal changes, genetic and life style changes (Stress, diet etc.) and environmental triggers which leads to ADR in the body. The similar outcome is found in some studies having higher incidence of ADR in patients who belong to the age of 18-35 years. [12,15,16,17]

The frequency distribution of different dermatological ADR is unique. The majority of ADRs occur often
due to the substantial variability in the pharmacokinetics and pharmacodynamics of medicine seen among patients. In present study maximum number of Dermatological ADR of dry skin followed by chapped lips. Data found in our study is same with results obtained in other two studies. [10,19] Two other studies conducted in past concluded Angioedema (0.97%) and Dry skin (1.94%) [20] as most suspected ADR. Which were also observed in the present study. So, this analysis concluded that the spectrum of dermatological ADR remain the same and only frequency is changed. In present study rare onset of action was presented with NSAIDS class (Diclofenac), swelling on eye and angioedema were reactions caused. weight gain and hair fall were seen as long-term adverse drug reaction after use of steroids. Period of the duration of medication, Immunological, genetic factor may play a role in the reaction of the body. Particularly allergic reaction, appear to have an immunological and pharmacogenetic etiology. 
The higher number of ADRs were presented with the treatment given for acne vulgaris and melasma with the use of retinoid class of drugs. Due to hormonal issues and environmental factors in younger patients they are more prone to Acne.

In this presented study, the most common suspected drug class showing steroids, antibiotics, and immunosuppressive agents. Same results were also shown in study conducted by Chatterjee et al. [10] explored the same higher incidence of the suspected drug classes. Other some studies also support that the most class of drug causing ADR were NSAIDS and Antibiotics. [11,12,15] Analysis of the results showed that in one of the studies, NSAIDs and fluoroquinolones were the most common drugs responsible for allergic reactions. [5,17] Particularly allergic reaction, appear to have an immunological and pharmacogenetic etiology.

Majority of the drugs experiencing ADR found in our study were Isotretinoin, HMT cream and Diclofenac followed by amoxicillin + clavulanate, Methotrexate and Betamethasone. Drugs utilization habit, co-morbidities, immunological and pharmacogenetic traits influence the frequency of ADR caused. Immune system may play a vital role in this occurrence of ADR. Similar studies showed same data with Amoxicillin and Diclofenac were the maximum number of drugs causing ADR. [20] 

Causality Assessment of ADRs is a method used for estimating the strength of relationship between drugs exposure and occurrences of ADR. One of the most widely used causality assessment objective scale is the Naranjo ADR probability scale . [10,11] As per the Naranjo causality assessment we found that majority of ADR were probable (69.44%) and possible (30.54%). These results are comparable to the previous study carried out by Murshid Parvin et.al, ADR were probable and possible. Rechallenge was not performed so definite association could not be made. Moreover, laboratory investigation such as drug plasma level was not carried out in most of the cases.

In this present study assessed by modified Hartwig Seigel scale majority of the ADR found was of mild category (83.33%) and moderate category (16.66%). Any intervention was not necessary for the treatment of majority of suspected ADRs. History of allergy and high concentration of drug responsible for moderate reactions. In dermatological ADR, mostly hospitalization stay not needed for any drug reaction so no one reaction fall under severe category in this present study. In comparison with previous study carried out by Rahat Kumar et.al mild ADR (72.3%) and moderate (25%) which is in parallel with presented study. Some other study finding revealed contradictory results. [11,12]

The Suspected ADR Was Classified using extended Rawlins and Thompsons Classifications scale. In this present study most of the suspected reactions was common, predictable which were classify Type A. The reason for that is most of the drugs which are used, is a preferable class of drugs for treatment for the dermatological indication. ADR In comparison with previous study carried out by Chatterjee S et.al. [10] revealed contradictory results. In this Present study, most of reactions were managed without drug withdrawal or no change in the treatment, because the ADRs were of mild or moderate category. Some of ADR was treated with drug withheld and one of the ADR treated with another drug of same class with decreased dose. In a
previous study which was conducted shows contradict results. Out of 18 ADRs, in 16 cases drug was withdrawn (88.9%), 1 case dose was altered (5.6%), and in another case no change (5.6%)\textsuperscript{[12]}. Reason behind contrary results in this is that mostly symptomatic management given for ADRs. The outcomes of suspected ADRs were mostly recovered because they were less severe and needed to managed by without any major changes in treatment. Outcome for other remaining ADR were not known till the end period of study because dermatological conditions need treatment for longer period of time depending upon symptoms of disease and follow ups for every patient was not possible due to shorter study period. Sriram\textit{et al.} observed consistent results on the outcome of management of ADRs. Other study conducted in which the treatment outcomes of ADRs was majority of the ADRs were recovered followed by 11.1%,\textsuperscript{[20]}

**CONCLUSION:**

This present study concludes ADRs are essential in order to determine dermatological incidence in medical practice, characterize the types and severity of observed ADRs, determine predisposing risk factors, estimate the causality of ADRs and awareness about dermatological ADRs to health care professional and its reporting. This can improve the outcome of therapy and optimize patient safety. The most common class of drugs responsible were topical steroids, retinoids, NSAIDS, Anti-biotics. Mortality rate is very less in dermatological treatment but the frequency is high in numbers so monitoring and reporting is very essential. It is important establishing pharmacovigilance units in hospitals has facilitated this activity to a great extent to analyses the benefit-risk ratio of marketed medications and to generate the evidence-based information on safety of medicine.

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**REFERENCES:**

4. Jamie.J. coleman, Adverse Drug Reaction, clinical Medicine, 2016 oct; 16(5)
8. Rahat Kumar et al, Dermatological Adverse Drug Reactions in a Tertiary Care Teaching Hospital of Punjab, India—A Pharmacovigilance Study, AMEI's Current Trends in Diagnosis& Treatment, July-December 2018;2(2):71-76
12. Murshida P , Mateti U, Tonita Noronha. Evaluation of Adverse Drug Reactions in Dermatology Department of a Charitable Hospital in India. Libyan Journal of Medical Sciences
18. Shweta S, Dhanya J, Dhanya S. Pharmacovigilance of Cutaneous Adverse Drug Reactions among Patients Attending Dermatology Department at a Tertiary Care Hospital, Indian Dermatol Online Journal 2019;10:547-54

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