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A STUDY ON EVALUATION OF DERMATOLOGICAL ADVERSE DRUG REACTIONS CAUSALITY, SEVERITY AND PREVENTABILITY

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Abstract:

Background: *The burden of dermatological Adverse Drug Reactions (ADR's) is resulting in switching or discontinuation of the drug as well as medication non-adherence. Active research is essential for evaluating, managing, reporting ADR's and strengthening the activity of pharmacovigilance of the country. The purpose of the study was to evaluate causality, severity, and preventability of Dermatological ADR's.*

Method: *A prospective observational study was carried out over a period of 1 year at the Department of Dermatology in Nellore Government general hospital with diagnosed dermatological ADR's. The suspected ADR's were evaluated for causality by Naranjo's scale and WHO-UMC causality, severity by Hartwig and Siegel scale and preventability by Schumock and Thornton criteria. The agreement between causality scales was obtained by Cohen's Kappa test.*

Result: *Total of 51 patients was enrolled with 74 suspected ADR's. The incidence of dermatological ADR's was 3.78 %. Most commonly manifested ADR's was rash (26.67 %). Total 97 drugs were suspected. Maximum incidence of dermatological ADR's was observed with antimicrobial agents (43.30 %) followed by nonsteroidal anti-inflammatory drugs (NSAIDS) (26.80 %), possible (54.64 %) and 35 (36.08 %) probable ADR's by WHO-UMC scale. Naranjo's scale showed most cases of probable (74.23 %). ADR's were of moderate severity (98.97 %) and definitely preventable (72.16 %). The causality scales showed 'slight agreement' with kappa value 0.012.*

Conclusion: *Dermatological adverse drug reactions were a common occurrence and awareness about them was found to be essential for early detection and prevention. The healthcare system can promote the spontaneous reporting of dermatological ADR's top Pharmacovigilance center's for ensuring safe drug use and patient care.*

Keywords: *Dermatological adverse drug reactions, Pharmacovigilance, slight agreement', kappa value.*

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INTRODUCTION:

Drugs, no matter how safe and efficacious, are coupled with the inescapable risk of adverse reactions. Adverse Drug Reactions (ADRs) are considered as one among the leading causes of morbidity and mortality [1]. Adverse Drug Reactions are major problem of drug therapy. According to WHO, an adverse drug reaction is defined as "a response to a drug that is noxious and unintended and occurs at doses, used in man for prophylaxis, diagnosis or therapy of a disease or for modification of physiological function [2]. Adverse Drug Reactions may also result in diminished quality of life, increased physician visits, hospitalizations and even death. The incidence of dermatological ADRs among inpatients in developed countries ranges from 1–3 % whereas in developing countries such as India it is 2– 5 %. The incidence of drug-induced adverse skin reactions commonly known as dermatological relations is found to be 2–15 % [3].

In many countries, ADRs rank among the top 10 leading causes of mortality and India is one of them. There is a need to study ADRs and ADRs reporting to minimize the risk of medicines. Pharmacovigilance is the study of the safety of drugs marketed drugs examined under the practical conditions of clinical use in large populations [4]. Early detection, evaluation and monitoring of ADRs are essential to reduce patients harm and to improve public health [5]. A clinical pharmacist plays an important role in the field of Pharmacotherapy including in the scientific field dealing with the safety of drugs pharmacovigilance [6]. Hospital/clinical pharmacists also have a greater role to play in the area of pharmacovigilance to strengthen the national pharmacovigilance program [7]. The burden of ADRs is resulting into switching or discontinuation of the drug as well as medication in-adherence. Little information is available about dermatological adverse drug reactions associated and it's reporting in routine clinical practice in Government general hospitals in India. So that the present study was made to explore dermatological ADRs.

MATERIAL AND METHOD:

A prospective observational, non-interventional, cross-sectional study carried out over a period of 1 year at the Department of Dermatology in Nellore Government general hospital with diagnosed dermatological ADR's. The inclusion criteria of the study were patients of all age groups with both genders, any medicines at 1st visit, patients coming for a follow-up visit, patients with any disease and co-morbid condition and patient who had been hospitalized due to dermatological ADR had been enrolled. Pregnant women and nursing mothers were excluded. Demographic data like the patient initial, hospital number, age, sex, marital status, medical history, medication history, surgery history, allergies, herbal and cosmetic use had been recorded. The prescription given to the patient including the drug prescribed, dose, frequency and duration of the treatment had noted. The findings related to ADR also added into CDSCO's ADR reporting form and management of ADR was also recorded. Causality of ADRs was evaluated by Naranjo's scale and WHO-UMC assessment scale. The severity of ADRs was evaluated by Hartwig and Siegel's scale. Preventability of ADRs was evaluated by Schumock and Thornton's criteria. The statistical analysis was carried out by using SPSS Version 22.0. The descriptive analysis had been represented in mean with standard deviation, frequency, percentage, range to present preliminary data. Fisher Exact test was used to test the level of significance at a 95 % confidence interval and 5 % α. The result was considered as significant when $p < 0.05$ obtained. Agreement between WHO-UMC causality assessment and Naranjo's scale was established by Cohen's kappa test.

RESULT:

51 patients with 74 suspected Adverse Drug Reactions were screened and enrolled for the study based on inclusion and exclusion criteria. From these 28 (54.90 %) males and 23 (45.09 %) females as a sample with a ratio of male: female 1.21:1. The incidence of dermatological ADR was 3.78 %. The mean age of the sample was 38 ± 19.73 years ranging from 0.8 to 85 years. The most commonly reported dermatological ADRs were rash (n=20, 26.67 %) cases followed by pruritus is (n= 8, 10.67 %), urticaria (n=8, 10.67 %) (Table 1). The most common suspected drug class showing highest numbers of ADR were antimicrobial agents (n=42, 43.30 %), followed by (n=26, 26.80 %) of NSAIDs (Table 2).

Table 1: Total numbers of suspected dermatological ADRs

Sl. No.	Suspected dermatological ADR's	Frequency (%)
1.	Rash	**19**
2.	Pruritis	**05**
3.	Angioedema	**03**
4.	Facial edema	**02**
5.	Urticaria	**08**
6.	Maculopapular rash	**05**
7.	Fixed Drug Eruption	**02**
8.	Itching	**01**
9.	Oral lesions	**02**

Table 2: Therapeutic class of suspected drug

SL. NO.	Therapeutic class of suspected drug	Frequency (%)
1.	Antimicrobial agents	42 (44 %)
2.	NSAIDs	26 (27 %)
3.	Corticosteroids	9 (9 %)
4.	Antiepileptic	5 (5%)
5.	Antipsychotics	3 (3 %)
6.	Antihistamines	3 (3 %)
7.	Antihypertensives	3 (3 %)
8.	Antiasthamatic	2 (2 %)
9.	Antidepressants	2 (2 %)
10.	Vitamin B_{12}	1 (1 %)
11.	Antidiabetic	1 (1 %)

From the total 97 suspected drug, the most frequent suspected drugs were Paracetamol (n=15, 15.46 %), amoxicillin (n=9, 9.28 %), diclofenac sodium (n=6, 6.19 %), Cefixime (n=5, 5.15 %). 4 individual cases of ibuprofen, nevirapine, phenytoin, prednisolone. 3 (3.09 %) cases of gentamicin, pyrazinamide, 2 (2.06 %) cases of azithromycin. The Paracetamol showed highest number of suspected ADRs followed by amoxicillin (Table 3). There were 4 different actions taken against the suspected drug which were drug discontinuation, drug replaced, dose reduction and medication given for the management of ADRs (Table 4).

Table 3: Most common suspected drug with reaction details

SL. NO.	Suspected Drug	Reaction details	Frequency (%)
1.	Paracetamol (NSAIDs)	Rash (8), Pruritis (3), Angioedema (2), Facial edema (1), Urticaria (1)	15 (15.46%)
2.	Amoxicillin (Antimicrobial)	Urticaria (3), Rash (2), Maculopapular rash (2), Pruritis (1), Fixed Drug Eruption (1)	9 (9.28 %)
3.	Diclofenac (NSAIDs)	Urticaria (2), Rash (2), Maculopapular rash (1), Itching (1)	6 (6.19 %)
4.	Cefixime (Antimicrobial)	Rash (2), Pruritis (1), Urticaria (1), Facial edema (1)	5 (5.15 %)
5.	Ibuprofen (NSAIDs)	Angioedema (1), Fixed Drug Eruption (1), Urticaria (1), Rash (1)	4 (4.12 %)
6.	Nevirapine (Antimicrobial)	Oral lesions (2), Rash (1), Maculopapular rash (1)	4 (4.12 %)
7.	Phenytoin (Antiepileptic)	Rash (3), Maculopapular Rash (1)	4 (4.12 %)

Table 4: Action taken against suspected drug

SL. NO.	Action against suspected drug		Frequency (n %)
1.	Drug discontinuation	Yes	65 (67.01 %)
		No	32 (32.99 %)
2.	Drug replacement	Yes	94 (96.91%)
		No	3 (3.09%)
3.	Dose reduction	Yes	95 (97.94%)
		No	2 (2.06%)
4.	Medication was given for ADR	Yes	4 (4.12%)
		No	89 (95.88%)

The total numbers of medicines given for management of ADR were 238. Among them, a most common drug prescribed was chlorpheniramine in 51 cases, followed by calamine lotion in 22 cases, ranitidine in 18 cases, Azithromycin in 16 cases, liquid paraffin on 14 cases. Out of 72 dermatological ADRs, the 53 cases found to be possible by WHO-UMC assessment scale (Table 5), whereas 72 cases found to be probable by Naranjo's scale (Table 6). 2 dermatological ADRs were classified as mild while 95 dermatological ADRs were found to be moderate (Table 7). In the case of preventability of dermatological ADRs, 70 were definitely preventable whereas 27 were probably preventable (Table 8). Comparison of WHO-UMC and Naranjo's causality had shown 'slight agreement' with kappa value 0.012.

Table 5: WHO-UMC causality of dermatological ADRs

SL. NO.	WHO-UMC scale	No. of ADRs	(%)
1.	Certain	5	5.15
2.	Probable	35	36.08
3.	Possible	53	54.64
4.	Unlikely	04	4.12

Table 6: Naranjo's causality of dermatological ADRs

SL. NO.	Naranjo's causality scale	No. of ADRs	(%)
1.	Possible	21	21.65
2.	Probable	72	74.23
3.	Definite	04	4.12

Table 7: Severity of dermatological ADRs by Hartwig and Siegel's scale

SL. NO.	Severity	Frequency of ADRs	(%)
1.	Definitely	02	2.06
2.	Probably	95	97.94

Table 8: Preventability of dermatological ADRs by Schumock and Thornton's criteria

SL. NO.	Severity	Frequency of ADRs	(%)
1.	Definitely	70	72.16
2.	Probably	27	27.84

DISCUSSION:

Drugs are used for treatment and prophylaxis of various disease conditions and are considered as safer drugs when used rationally. Drugs show some Adverse Drug Reactions in various patient conditions. Adverse Drug Reaction monitoring is an essential aspect of therapeutics. However most of the time it is overlooked and not considered as important. Even when observed, many would not document and report voluntarily. Establishing pharmacovigilance units in the hospitals has facilitated this activity to a great extent.

This study focused on the pattern of dermatological Adverse Drug Reactions of drug class in the post-marketing surveillance studies to find out the effects in a large and diverse population. The suspected ADRs were also notified into National

Pharmacovigilance Programme of India. The direct reporting is also helpful for suspecting dermatological ADRs. This study revealed the incidence of dermatological ADRs was 3.78 % when comparing to previous studies showed incidences of dermatological ADRs were 2.6 %, 2.85 %, 1.6 %, 7.02 % respectively [1,3,8,9].

The present study finding shows that higher numbers of cases found in males. The same outcome found in some studied having higher male preponderance [10-13]. Moreover, many studies showed female preponderance [2,3,9,13,15]. There is no big difference between the numbers of male and female. The reason for the higher incidence in the present study could be that males are more conscious of any dermatological reaction and treatment of ADR before it gets severe.

In our work, the most suspected ADR were rashes in 20 (26.67 %) cases followed by pruritus is in 8 (10.67 %) cases, urticaria in 8 (10.67 %), acne in 6 (08.00 %), Fixed Drug Eruption (FDE) in 3 (4 %) cases. Highly occurring ADR in our study was rashes, which is similar to results obtained in other studies [1,16]. There were studies conducted in past showing that most common suspected ADR was rash followed by urticaria and/or FDE which are were also observed in the present study [2,11,15-18].

Number of ADRs was suspected of patients due to the more number of drugs prescribed. It is obvious that the dermatological ADR patterns and the drugs causing various reactions are changing every year which may be due to the emergence of newer molecules and changing trends in the use of drugs. The current study showed 72 non-serious and 2 serious dermatological ADRs, which is deviating from Shah et al at., the study showed 40 non-serious and 2 serious dermatological ADR.[10] The nature of these drugs remained unknown because either the patients brought the drugs in loose, unidentified packs or had consumed them as self-medication.

The most common offending drug classes were anti-microbial agents 42 (43.30 %) followed by 26 (26.80 %) NSAIDs, 9 (26.80 %) were of corticosteroids, 5 (5.15 %) were of antiepileptic, similarly Chatterjee et al. showed the same higher incidence of suspected drug class which were antimicrobial agents (34.10 %), antiepileptic (32.88 %) and NSAIDs (21.51 %) [3]. In the present study, Paracetamol was highly suspected drug followed by amoxicillin. The same findings also found in a study conducted by Ghosh S et al.[1] Probability of the higher incidence of ADR due to these 2 drugs could be due to self-medication of such medication without physician consult as it is common among local population or common prescribing pattern.

In the present study, 1 case was atenolol-induced psoriasis and 1 case is of hydroxychloroquine induced psoriasis was found out. One of the studies also proved that long-term use of these medications can produce psoriasis.[20,21] In our study, 1 case of Toxic Epidermal Necrosis (TEN) and 1 case of Steven Johnson Syndrome (SJS) were reported. In a study conducted by Lihite et al., out of 22, 2 cases of TEN and 1 case of SJS were reported whereas Sharma et al., has shown 11.4 % fatal cases of TEN and SJS [11].

After suspecting ADR, suspected drugs were discontinued or replaced or dose was reduced or medications are given for management of ADR. Withdrawal of the suspected drug and antidote such as the use of systemic and topical steroids, antipruritic agents, and oral antihistamines were given most commonly for ADR management. The similar finding also presented in studies where the drug was being discontinued[1,9] and higher incidence same class of antidote were given [16]. It was the dermatologist's discretion, whether the benefit of the drug overweighed the existing ADR and given a line of treatment for ADR.

In the present study, most of the ADRs in our study were designated as possible (54.64 %) or probable (36.08 %) in WHO-UMC causality assessment which is quite consistent with Shah et al (69 %). Among them, possible ADRs were highly observed. Few studies showed higher cases of probable 73.2 %, 80.35 % respectively.[3,9] The percentage of dermatological ADRs falling in the category of definite (certain) is very low (5.15 %) comparing to another category which is also found low in few studies (11.42 %, 1.7% respectively) [9,12]. In our study according to WHO-UMC causality assessment, NSAIDs caused a certain type of ADR compared to another type of ADR. In the present study according to Naranjo's causality scale, 4 ADRs were definite, 72 ADRs were probable and 21 ADRs were possible. The study by Lihite et al., showed higher cases of probable ADRs similar to the present study [8].

Comparison of the strength of agreement between different scales of causality assessment (WHO-UMC causality assessment and Naranjo's causality scale) is done by using Cohen's kappa test. It showed that full agreement was not found between any of the 2 scales of causality assessment. A positive but poor agreement based on kappa values was seen between

WHO and Naranjo's causality comparison. This was due to different definitions of causality criteria for assessing adverse drug reactions.

In the present study, only 2 ADRs were of mild severity and the rest of all 95 ADRs were of moderate severity. A majority of ADRs were categorized as moderately severe while few cases of severe in nature and similar findings are reported in other studies [1,10]. When ADRs were suspected at dermatology, the medications were always given for the management of ADRs. Despite these, in 2 cases of mild severity, the drugs were only discontinued. The result of the present study showed most of the ADRs was definitely preventable. These findings were similar to study conducted in past [8,11].

On the evaluation of chances of preventability of ADRs, all the ADRs may have been preventable, if proper precaution were taken like patients should carry drug list indicating which drugs they are allergic to at the time of hospital visit to avoid reactions again. Preventability of ADR with the unlikely WHO-UMC causality of ADR showed definitely preventable ADR compared to probably preventable ADR of another category of WHO-UMC causality terms. The limitations of the study were the exact incidence of dermatological ADRs which may be difficult to obtain owing to the fact that the researcher must rely on the patient for reporting of ADR and drug details. In our study reports from dermatology OPD was considered, excluding dermatological ADRs reported from other departments of the hospital, small sample size, confined to the Outpatient the Department of Dermatology for a short period of 3 months. Due to lack of follow-up, exact outcome of ADR was not obtained in all patients. Moreover, the ADRs of recently introduced drugs could also not be generated. Dechallenge and Rechallenge was not done in many cases after identification of ADRs until happened naturally.

There are few recommendations for work in this area is for determination of exact incidence; study may carry out for a longer duration of time with large patient population. Further studies are required to determine the prevalence, predictors and risk factors of the dermatological ADRs in order to improve the drug safety. For patients who don't come back for follow up, some steps should be taken to consider them and give more attention for better patient care. Patient's awareness regarding OTC drugs and self-medication should also be strengthened.

CONCLUSION:

The present study concluded that dermatological Adverse Drug Reactions was a common occurrence and awareness for them is essential for diagnosis and prevention. The dermatological ADR varied in their appearance, duration, causality, severity, and preventability. Antimicrobial agents and NSAIDs were the most commonly implicated drug class. Depending upon nature of ADR, actions against suspected drug along with symptomatic treatments were given whenever found significant. Most ADRs gets unreported due to lack of interest in ADR monitoring and reporting at hospital settings. By a present piece of work, pharmacist contributed patient safety and rational use of the drug by assessing, reporting and treating ADRs. The healthcare system should promote the spontaneous reporting of dermatological adverse drug reaction to pharmacovigilance centers for ensuring drug safety.

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