*IOSR Journal Of Pharmacy* *www.iosrphr.org*
*(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219*
*Volume 7, Issue 4 Version. 1 (April 2017), PP. 18-22*

# A Study of Cutaneous Adverse Drug Reactions in A Tertiary Care Teaching Hospital

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**Abstract :** Adverse drug reactions (ADR's) are the major cause of morbidity and mortality and most of the adverse drug reactions become evident only when the drug enters into the market, as clinical trials conducted on drugs involve only a limited number of subjects. Cutaneous manifestations of ADR's occur more frequently, hence this study was conducted to detect the morphological pattern, the common drugs causing cutaneous ADR's and to assess the severity of the same using Naranjo's algorithm. This was a prospective study conducted over a period of one year in the department of Dermatology and the department of Pharmacology. All the ADR's reported during the study period were confirmed by a dermatologist and assessed using Naranjo's algorithm. A total of 90 Cutaneous Adverse Drug Reactions (CADR's) were reported during the study period. Fixed drug eruption was the most common morphological pattern of ADR. Antibiotics were the most common drugs involved in causing CADR's. Most of the CADR's belonged to Probable category. Hence this study showed that CADR's are common to the drugs widely used, and the detection of the same will enable the treating physician to withdraw the use of the suspected drug. Also spontaneous reporting of ADR's will strengthen the Indian Pharmacovigilance database.

**Keywords –** *Antimicrobials, Cutaneous Adverse drug reaction, Fixed drug eruption, Naranjo's algorithm Pharmacovigilance*

## I. INTRODUCTION

The world health organization defines an adverse drug reaction as any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for diagnosis, prophylaxis or therapy [1]. Adverse drug reactions (ADR's) constitute one of the most important causes of morbidity, hospitalization, increased health expenditure and even death.[2] Results of a meta-analysis revealed that serious ADR's accounted for 6.7% of hospitalized admissions in USA.[3] ADR's accounted for 0.7% of total admissions and 1.8% of total deaths in a South Indian hospital.[4] Data regarding the safety profile of a drug prior to marketing is essentially based on preclinical and clinical studies and the later involve only a limited number of subjects. However, when drugs are marketed and used extensively, new adverse events come to light. It is estimated that only 50% of the undesirable reactions can be detected during the pre-marketing clinical trials [5], which makes postmarketing surveillance of drugs mandatory even after it obtains approval from the regulatory authorities. The dermatological manifestations of adverse drug reactions are more frequent. Studies have found that the incidence of cutaneous adverse drug reactions (CADR's) in developed countries as 1 to 3 %, while the incidence in developing countries is higher, between 2 to 5% [6] The pattern of cutaneous reactions differs among various drugs. Hence, understanding the precise nature of the drug reactions may help in identifying the offending drug. Clinicians come across many instances of suspected CADR's in different forms. Hence, familiarity with these conditions to enable early diagnosis and prompt withdrawal of the causative drug to prevent mortality[7] Also, knowledge of drugs that can cause cutaneous adverse drug reaction can help physicians in choosing safer drugs and therefore can be helpful to society at-large[8] Hence this study is carried out with the objective of encouraging spontaneous reporting of ADR's by the clinicians, which will strengthen the Indian pharmacovigilance database and to promote rational use of medicines in the future.

## II. MATERIALS AND METHODS

### 2.1. Aims and Objectives

This study was conducted with the main objective of studying the prevalence of cutaneous adverse drug reactions, their morphological patterns, and to identify the suspected medication(s) causing the adverse drug reactions, and to perform causality analysis of the same using Naranjo's algorithm.

### 2.2. Methodology

The study was a single center, prospective, observational, clinical study conducted over a period of one year in a tertiary care teaching hospital, in collaboration with the Department of Dermatology, Department of Pharmacology and Research Cell. The study included all cutaneous adverse drug reactions reported to the department of Dermatology during the study period, after confirmation by a dermatologist. The adverse drug reaction reports were excluded if the patients had no visible skin lesions, or patients whose lesions are disease related after close examination. The patients who were unable to recall the name of the medication consumed were also excluded from the study. The adverse drug reports with incomplete information like lack of details about the suspected medication(s),absence of the date of starting and stopping the drug, lack of information about dechallenge, lack of information about concomitant drug intake etc; were excluded. The patients who reported to the Department of Dermatology with cutaneous adverse drug reactions or referred to the department of Dermatology from other departments with cutaneous adverse drug reactions were included in the study, after fulfilling the inclusion and exclusion criteria. Prior to the enrollment, an informed written consent was obtained from the patient or caretaker in a language which they can best understand. A detailed history was obtained from the patient with regards to age, sex, body weight, past history, history of allergy to any drugs, pregnancy, smoking, alcohol, and history of liver or renal impairment. The details of the adverse drug reaction regarding the date of reaction started, the date of recovery, and a detailed description of the reaction was obtained. The information whether the reaction stopped after the drug was discontinued and whether the drug was reintroduced was obtained. The detailed history of concomitant drug intake, herbal or alternative systems of medicine intake, with date of therapy were taken. The details of the suspected medication(s) like name, batch number, manufacturer, expiry date, dose, duration, frequency, route of administration, date of starting and stopping the drug, and the reason for which it is prescribed was noted. The relevant clinical, biochemical and hematological investigations was done. The causality assessment was performed using Naranjo Algorithm (TABLE 1) and the adverse drug reactions were graded based on the score as Certain, Probable, Possible, Unlikely or Unclassified. The adverse drug reactions were treated with necessary drugs. The data was analyzed using appropriate statistical tests.

## III. RESULTS

The study was conducted in 90 patients who fulfilled the inclusion and exclusion criteria. The mean age of the patients was 39.88±15.06 years. Of the total study population, 77.7% (n=70) were males and 22.3% (n=20) were females. Among the morphological patterns, Fixed drug eruptions were the most common (n=60, 66.7%) followed by maculopapular rash (n=20, 22.2%) and drug induced exfoliation (n=10,11.1%).The common groups of drugs responsible for causing the CADR's are shown in Fig 1.The common antimicrobials causing CADR's are shown in Fig 2.Among the anti-epileptics, Phenytoin was the most common drug responsible for the cutaneous drug reaction (n=20,66.7%), followed by Levetiracetam (n=10, 33.3%) Among the Non Steroidal Anti Inflammatory Drugs (NSAID's), Aspirin was the most common NSAID causing cutaneous adverse drug reaction (n=10, 11%). The adverse drug reactions were assessed using Naranjo's algorithm. Of the total 90 adverse drug reactions reported, 5 (5.5%) of them were Certain, 60 (66.7%) of them were Probable and 25 (27.8%) of them were Possible.

## IV. DISCUSSION

This study was conducted in 90 patients who attended the department of Dermatology during the study period. The cutaneous adverse drug reactions were analyzed after confirmation by a dermatologist. The study revealed the male preponderance (n=70) in the occurrence of adverse drug reactions. This was similar to the study conducted by Saritha et al (2015) [9] However, a similar study conducted by Ruchika et al (2011) showed that the incidence of CADR's were more in females (n=47) than males (n=44) [10].The study revealed that fixed drug eruption was the most common morphological pattern, followed by maculopapular rash. A similar study conducted by Rohini Sharma et al(2015) showed that fixed drug eruptions are the most common pattern of cutaneous adverse drug reaction (n=50, 33.3%)[11]. However, a study conducted by Punit Kumar Singh et al (2015) showed that morbilliform rash was the most common pattern of cutaneous adverse drug reaction (n=27, 42.85%) followed by fixed drug eruption[12].Antibiotics were the most common drugs causing cutaneous

adverse drug reactions (CADR's) followed by antiepileptics and NSAID's. This was consistent with a study conducted by Ghosh S et al (2006) showed that antibiotics were the most common drugs causing CADR's (n = 16, 30%) , followed by antiepileptics (n= 13, 25%) , antitubercular drugs (n = 6 , 11%) , and antipyretics (n= 5, 9%).[13]However, a study conducted by Mithali dua et al showed that antiepileptic drugs were the most common cause of CADR's(n=21,35%) , followed by antibiotics (n=17,28.33%) , NSAID's (n=7, 11.6%) , antitubercular drugs (n = 3, 5%) and antiretroviral drugs (n= 3, 5%) [14]. Among the antibiotics, Ciprofloxacin was the most common drug, followed by Levofloxacin and Sulphonamides. However, a study conducted by Shamna et al, (2014) showed that Cephalosporins were the most accounted antibiotic class involved in CADR's (n=17, 34.69%) followed by Fluoroquinolones (n= 15, 30.61%), and Penicillins (n=7, 14.28%) [15].Among the antiepileptics, Phenytoin was the most common drug implicated, followed by Levetiracetam. This is consistent with a study conducted by Sudharani et al (2016) which showed that Phenytoin was the most common drug implicated in the causation of CADR's (n= 22) followed by Carbamazepine (n=7) and Sodium Valproate (n=1).[16]Among the NSAID's, Aspirin was the most common drug involved in the causation of CADR's..However, in a study conducted by Faiza et al(2008)[17] showed that NSAID's are the most common cause of CADR's, and the NSAID's responsible included Mefenamic acid, Diclofenac, Ibuprofen, Meloxicam and Tenoxicam, whereas in our study, Aspirin remained the most common cause of NSAID induced CADR's. This could probably be explained by the fact that Aspirin is widely used, not only as an NSAID but also for secondary prevention of coronary vascular disease. The causality analysis was performed using Naranjo's algorithm for all the reported CADR's, and most of the CADR's were found to be of Probable in nature. This is consistent with a systematic review performed by Tejas Patel et al (2014), wherein the distribution of CADR's in "certain"/"definite", "probable" and "possible categories were 34.25%, 58.59%,and 7.15%,respectively[18].

## V. FIGURES AND TABLES

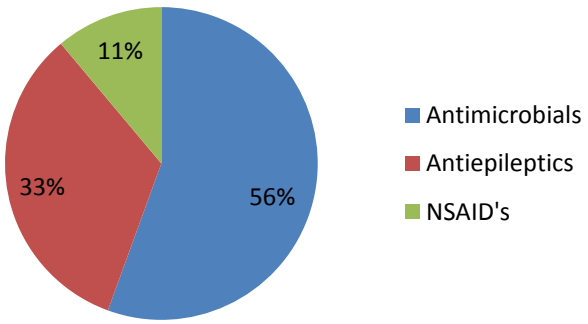


Fig 1: Common groups of drugs causing cutaneous adverse drug reactions.

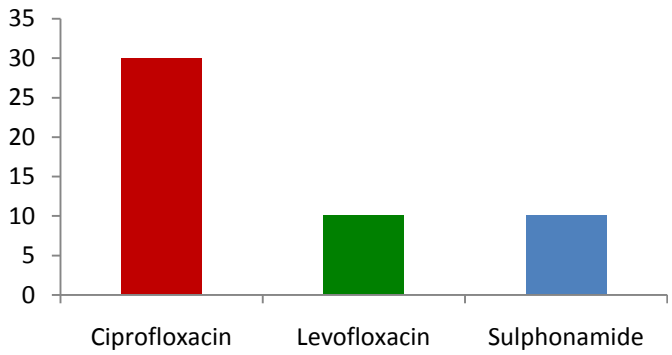


Fig 2: Common antimicrobials causing cutaneous adverse drug reactions

**TABLE 1: Naranjo's algorithm**

| S.NO | Question | Yes | No | Don't Know |
|---|---|---|---|---|
| 1 | Are there any previous conclusive reports on this reaction? | +1 | 0 | 0 |
| 2 | Did the adverse event appear after the suspected drug was administered? | +2 | -1 | 0 |
| 3 | Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered? | +1 | 0 | 0 |
| 4 | Did the adverse event reappear when the drug was readministered? | +2 | -1 | 0 |
| 5 | Are there alternative causes (other than the drug) that could on their own 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 blood (or other fluids) in concentrations 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 any objective evidence? | +1 | 0 | 0 |

## VI. CONCLUSION

This study showed that cutaneous ADR's occurred more frequently and that antibiotics were the most common drugs causing CADR's. The strength of the study included confirmation of the diagnosis by a dermatologist and the application of strict inclusion and exclusion criteria. However, a small sample size and lack of adequate documentation of all the CADR's occurred were the probable limitations. This could be overcome by creating proper awareness among the reporting doctors about the need for reporting ADR's through frequent sensitization programmes about pharmacovigilance, which will encourage the healthcare professionals to report adverse reaction to drugs, vaccines, medical devices and biological products.This practice of spontaneous reporting, in the long run, will generate evidence based information on safety of medicines. However, further studies on the area of pharmacovigilance are needed to promote rational use of medicines and to generate an Indian database of adverse drug reactions, which is consistent with the population of India.

## VII. ACKNOWLEDGEMENTS

The authors would like to acknowledge the Research Cell of Chennai Medical College for their able guidance and support and the entire teaching and non teaching faculty of the departments of Pharmacology and Dermatology for their cooperation.

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