



Original Research Article

A prospective observational study on drug induced cutaneous eruptions in a tertiary care hospital

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ABSTRACT

Aims: To study the clinical pattern of drug-induced cutaneous eruptions, associate the causality relationship between the suspected drug and the cutaneous reaction observed, also to assess the severity and the preventability criteria of cutaneous reaction.

Subject & Methodology: A hospital-based Prospective, the Observational study was carried out in patients presenting to Department of Dermatology at Osmania General Hospital. Data collection form was designed according to the need of our study. Naranjo scale, Modified Hartwig and Siegal scale, Schumock and Thornton scale was used in the study to assess the causality, severity and the preventability criteria of the observed reactions respectively. After inclusion and exclusion criteria, 147 cases were enrolled in the study.

Results: A total of 147 cutaneous eruptions were identified in which female predominance was observed. The most common clinical pattern observed was Drug-induced rash (17%) followed by Fixed Drug Eruption (13%) and Steroid induced Acne (12%). The drug class responsible for the majority of the reactions were Antibiotics (19.7%) followed by NSAIDs (17.7%). According to Naranjo scale, (17%) cases were Definite ADRs, (46%) were probably ADRs, (35%) were likely to be possible ADRs. Modified Hartwig and Siegal scale revealed (45%) Mild cases, (39%) Moderate cases and (15.6%) were severe cutaneous eruptions. (19.8%) cases were definitely preventable, (27.2%) were likely to be probably preventable and (53%) cases were not preventable, according to Schumock and Thornton assessment scale.

Conclusion: Drug-induced cutaneous eruptions related hospital visit/admissions is a significant problem in the healthcare system. Since the majority of the reactions are Predictable and often preventable, there is a need for greater awareness among the healthcare professionals, regarding not only the potential reactions but also for the prevention or minimization and awareness of ADRs.

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INTRODUCTION

An adverse drug reaction (ADR) has been defined as any noxious, unintended and undesired effects of a drug which occurs at a dose used in humans for prophylaxis, diagnosis, therapy or modification of physiological functions (WHO 1984). Adverse drug reactions account for significant morbidity and mortality in the health sector.

An Adverse Cutaneous Drug Reaction (ACDR) caused by a drug is any undesirable change in the structure and function of the skin, its appendages or mucous membrane and it encompasses all adverse events related to drug events, regardless of the etiology (Nayak et al., 1992). ADRs are rated as the fifth leading cause of death among all diseases. Approximately 5-8% of all

hospitalization worldwide is due to ADR. CADR are the commonest ADRs (30-45%) and responsible for about 2% of hospital admissions (Valeyrie et.al 2000). Approximately 2-7% of these may be severe (Ajayi et al., 2000). In India, CADR account for 2-5% of all inpatients, while it affects 2.6% of outpatients (Chatterjee et al., 2006). Many ADR is commonly known and is present in the literature but some are rare and may present without warning. Cutaneous drug eruptions are one of the most common types of adverse reaction to drug therapy, with an overall incidence rate of 2-3% in hospitalized patients (Wolkenstein et al., 1995).

Almost any medicine can induce skin reaction, certain drug classes such as NSAIDs, Antibiotics (eg. Penicillin, Sulfonamide) and Antiepileptics (eg. Phenytoin) have drug eruption rates approaching 1-5% in previous reports. According to WHO database adverse reactions like rashes, pruritis, urticaria is reported respectively from 4.2%, 2.7% and 2.6% of patients receiving drugs. The hypersensitivity reaction in some patients may be due to over the counter medicine, herbal or homeopathic preparation, vaccine or contrast media or the pharmaceutical excipients.

Assessment and Management:

The recognition or identification of a DISR is often a diagnosis of exclusion. Possible skin cancers, as well as the presence of a virus, disease, or food-related allergy, should be ruled out. A step-by-step approach should be used to identify a possible DISR:

1. Complete a drug history. Reconciliation of all prescription and nonprescription agents, as well as any natural medicines, should be completed. Develop a written drug-exposure timeline in relation to the adverse reaction, with start and stop dates for all drugs/products. Note dates, dosages, and product formulations as soon as possible. Discontinue any suspected drug or product.
2. Physically inspect the affected area, documenting patient signs and symptoms.
3. Determine possible systemic involvement, such as fever, wheezing or difficulty breathing, or skin blistering. Any reaction that involves multiple systemic symptoms or appears to be rapidly worsening should be immediately referred for medical evaluation. Possible DICE include Stevens-Johnson syndrome and toxic epidermal necrolysis.
4. Identify the drug, classify the type of reaction, make treatment recommendations, and provide patient education to avoid future adverse reactions (Adam et al., 2017).

Types of Drug-Induced Cutaneous Eruptions

Drug reactions may be classified as immune-related reactions and nonimmune-related reactions. Immune-related reactions include exanthematous drug reactions (type IVb, T lymphocyte-eosinophil-mediated; type IVc, T lymphocyte-cytotoxic-mediated); anaphylaxis (type I, IgE [immunoglobulin E]); angioedema (type 1, IgE); urticaria (type 1, IgE); allergic contact dermatitis (type IVa, T lymphocyte-macrophage-mediated); drug hypersensitivity syndrome (DHS; type IVb, T lymphocyte-eosinophil-mediated); fixed drug eruptions; erythema multiforme; and serum sickness-like reactions. Nonimmune-related reactions include drug-induced nail changes, hyperpigmentation and skin-color changes, pseudoallergy, and selective cutaneous reactions.

The aim of the study was to know the clinical pattern of drug-induced cutaneous eruptions, associate the causality relationship between the suspected drug and the cutaneous reaction observed, also to assess the severity and the preventability criteria of cutaneous reaction.

SUBJECTS AND METHODOLOGY

Plan of Work

The study was conducted to assess the clinical pattern and the drugs responsible for cutaneous eruptions. The patients of either sex in Dermatology department were observed for drug-induced cutaneous reactions. The study was designed to collect the patient's demographic data, medication history, family history to define a causal relationship. A standard data entry format to collect the patient's details was designed according to the need of the study. The prescriptions of outpatients were analyzed for cutaneous drug eruptions. During ward rounds, entire data was recorded for the patients with reference to drug-induced cutaneous eruptions. The first step was to review the patient's complete medication list, including over-the-counter supplements. Document any history of previous adverse reactions to drugs or foods. Consider alternative etiologies, especially viral and bacterial infections.

Naranjo Adverse Drug Reaction Probability Scale was used in the study to associate the causality of the reaction, which classified the reaction as Definite, Possible, Probable or Unknown (Naranjo Adverse Drug Reaction Probability Scale Annexure-III) Modified Hartwig and Siegal scale was used in the study to assess severity of the reaction, which classified the reaction as Mild, Moderate or Severe (Modified Hartwig and Siegal severity scale Annexure -IV). Schumock and Thornton scale was applied to the study to evaluate the

preventability of the reaction as Definitely preventable, Probably preventable or Not preventable (Schumock and Thornton preventability scale Annexure-V).

The study was approved by Ethical Committee of MESCO College of Pharmacy. Permissions for the collection of data was taken from the Head of the Dermatology Department. The authors were permitted to utilize the hospital facilities and make a follow up with prescriptions in the Inpatient department.

Out Patient Department of Dermatology and In patients admitted in a special ward of Dermatology at Osmania General Hospital, Hyderabad.

Study Design

A hospital-based prospective, observational study was carried out on 147 patients presenting to dermatology department. The data was collected which contains patient demographics, date of admission, date of discharge, history of present illness, past medical history, diagnosis, the name of the drug, dosage regimen(form, route, dose, frequency, and duration). The knowledge assessment questionnaire form contains questions to assess the knowledge of patient towards the medication used. After inclusion and exclusion criteria, 147 patients were enrolled in the study.

Patients of either sex visiting the hospital as inpatients or outpatients and also patients with visible skin eruptions, lesions, or rashes were included in the study. Patients above 80 years and patients who could not recall the name of the suspected drug consumed were excluded from the study.

Data collection form was designed according to the need of the study and Naranjo Adverse Drug Reaction Probability. Modified Hartwig and Siegal Severity Assessment Scale; and Schumock and Thornton Preventability Assessment Scale were used as Assessment Scale.

RESULTS

Population Demographics

Figure 1 shows the distribution of patients based on gender. A total of 147 suspected drug induces cutaneous eruptions were observed during the period of study, out of which 70 patients were males and 77 patients were females. Females experienced a significantly higher incidence of drug-induced cutaneous eruptions than males.

Distribution of Subjects in Relation to Age Group

The study population involved the patients of age 0 to 80 years. The youngest patient was of age 7 and the oldest patient was of 78 years. Maximum patients

belonged to the age group of 21-30 (28.5%) followed by the age group of 31-40 (23.9%). Female predominance was seen in the age group of 21-30 (52.3%) and males were predominant in the age group of 31-40 (60.6%) while least number of cases were seen in the age group of 71-80.

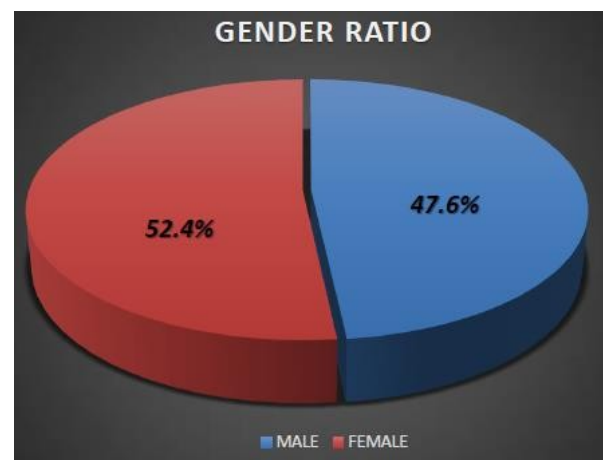


Figure 1. Distribution of subjects based upon gender.

Dice Based on RMP / OTC Medication

Among the 147 cases studied, the offending drug in the majority of the cases is 68.7% contributed to the prescriptions of the Registered Medical Practitioner, while 31.3% cases were due to self-medication which was purchased over the counter without the prescription of any RMP.

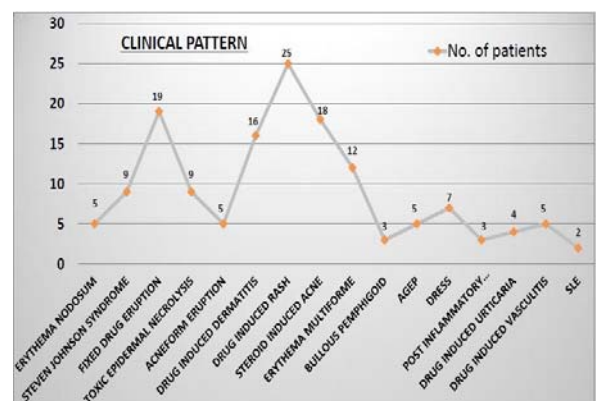


Figure 2. Clinical pattern of cutaneous eruption in the study population.

Clinical Pattern

Figure 2 shows clinical pattern observed in drug-induced cutaneous eruptions. The most common clinical pattern was Drug induced rashes (14.9%) followed by Fixed drug eruptions (14.2%) other types of cutaneous eruptions noted were Steroid induced acne (12.2%), Drug induced dermatitis (10.8%), Erythema Multiforme (8.16%) followed by Toxic Epidermal Necrolysis (6.1%), Steven Johnson syndrome (6.1%), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (4.7%), Erythema Nodosum (3.4%), Acneiform eruptions (3.4%), Acute Generalised Exanthematous Pustulosis (3.4%), Drug Induced

vasculitis (3.4%), Drug induced urticaria (2.7%) Post inflammatory hyperpigmentation (2%), Bullous Pemphigoid (2%) and Systemic Lupus Erythromatosus (1.3%)

Drugs responsible for drug induced cutaneous eruptions:

Figure 3 shows the most common class of drugs responsible for drug induced cutaneous eruptions. Majority were by Antibiotics 29 cases followed by NSAIDS 26 cases and steroids 25 cases. Other class of drugs which were associated with the causality of cutaneous eruptions were Anti-convulsants 23 cases, Sulfa drugs 7 cases, Anti-tubercular drugs 6 cases, Anti-hypertensives 4 cases, Anti-psychotics 4 cases, Anti-fungal 3 cases, Anti-viral 2 cases, Others 14 cases.

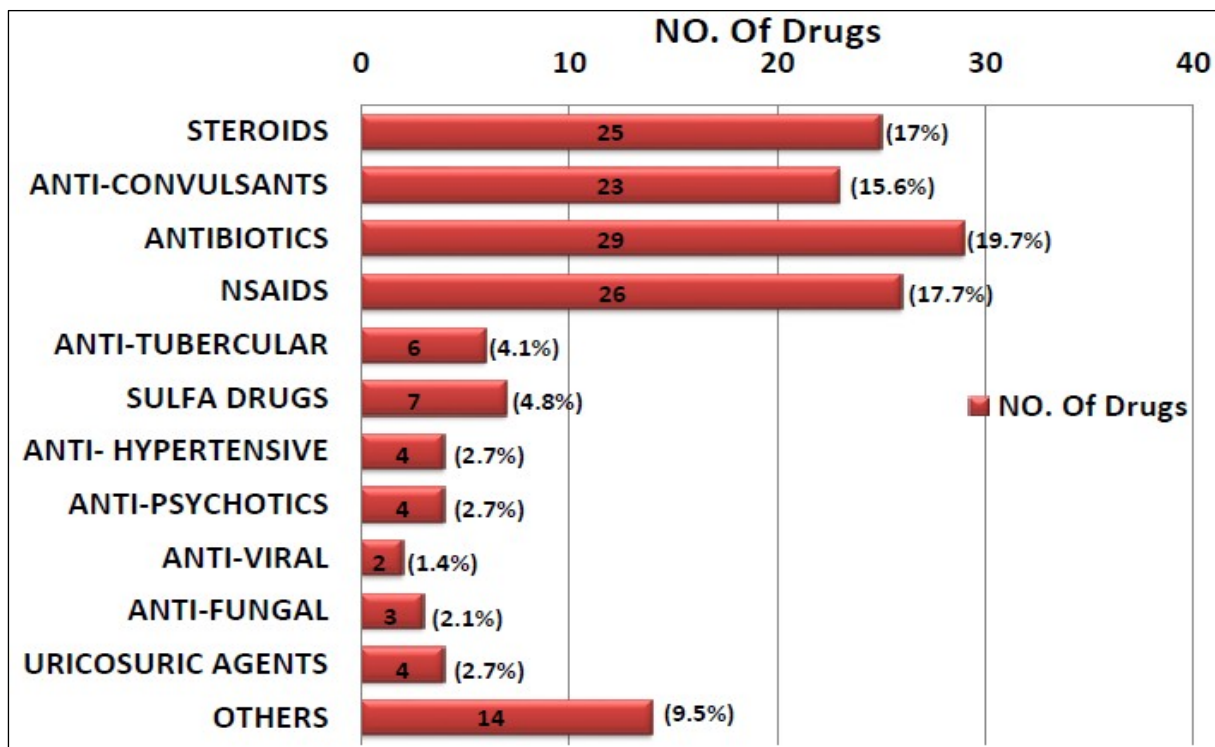


Figure 3. Percentage of suspected class of drugs.

Among Antibiotics, Penicillins 11 cases (38%) constituted for the majority of the cases preceded by fluoroquinolones 8 cases (27.6%), tetracyclines 4 cases (13.8%), cephalosporines 5 cases (17.2%), chloramphenicol 1 case (3.4%).

NSAIDs are more commonly used as the OTC drugs or usually drug of choice for selfmedication. Among them Diclofenac accounted for 10 cases (38.5%), Combiflam 3 cases (11.5%), Paracetamol 8 cases (30.8%), Ibuprofen 3 cases (11.5%) and Naproxen 2 cases (7.7%). Among Anti-convulsants, Phenytoin contributed to 60.8% of the cases followed by Carbamazepine which caused 39.2% of the cases.

Causality assessment (NARANJO scale)

Table 1 shows percentage of causality assessment of adverse drug reaction. 147 cases of drug induced cutaneous eruptions were analyzed. After assessment 25 cases (17%) scored Definite, 67 cases (46%) were of Probable score, whereas 51 cases (35%) were in Possible score category and 4 cases (3%) were doubtful in the Naranjo scale.

Table 1. Percentage of causality assessment of ADR's using NARANJO scale

S. No.	Causality Assessment	No. of Patients	Percentage
1	Definite ADR	25	17%
2	Probable ADR	67	46%
3	Possible ADR	51	35%
4	Doubtful ADR	4	3%

Abbreviation: ADR- Adverse drug reaction

Severity Assessment

Table 2 shows percentage of severity assessment of drug induced cutaneous eruption using Modified Hartwig-Siegal Severity Assessment scale which is the gold standard for severity assessment for cutaneous ADRs. Analysis revealed 67 cases (45.5%) of Mild grading, 57 cases (38.9%) of Moderate and 23 cases (15.6%) of Severity grading.

Table 2. Percentage of severity assessment among study population

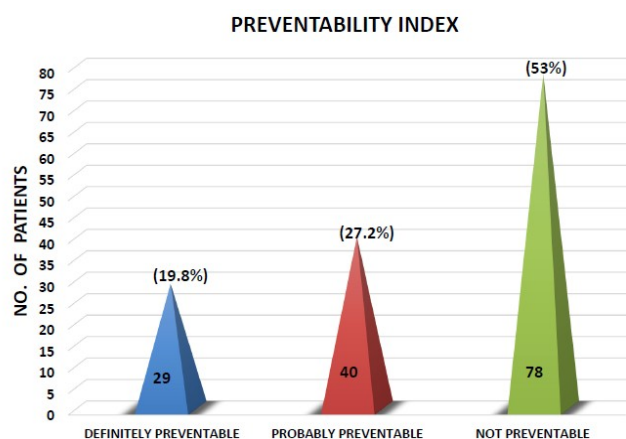
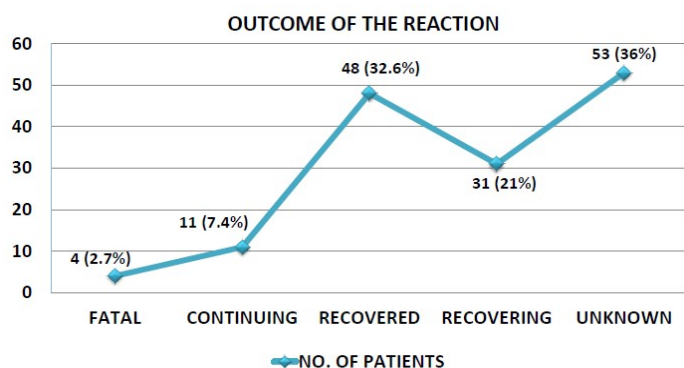
S. No.	Severity Assessment	No. of Patients	Percentage
1	Mild	67	45.5%
2	Moderate	57	38.9%
3	Severe	23	15.6%

Preventability Assessment Using Schumock and Thornton Scale

Figure 4 shows preventability assessment of drug induced cutaneous eruption. Out of 147 cases, 29 cases were Definitely Preventable, 40 cases were Probably Preventable and 78 were Not Preventable.

Outcome of the Reaction

Considering 147 cases, 4 (2.7%) cases were Fatal, 11 cases (7.4%) were Continuing, 48 (32.6%) cases were Recovered, 31 (21%) were Recovering and due to poor review of the patients 53 cases (36%) were left Unknown.

**Figure 4.** Percentage of preventability assessment among study population.**Figure 5** shows outcome of reaction in the study population.

DISCUSSION

Our study was carried out with an objective of revealing the types of drug-induced cutaneous

eruptions of the patients attending Dermatology department. Drug history is mandatory for the diagnosis. Polypharmacy is the main risk for drug-induced cutaneous eruptions in the study. In most of the cases, the suspected drug was withdrawn. In cases where the drugs were absolutely necessary and were not easily modified, the drugs were continued under supervision.

A total of 147 cases were collected during our study period. We observed a slight predominance of female patients which is in accordance with the study performed by Um et al (2010) and contradictory with the study conducted by Raut et al (2015).

Among the various types of drug-induced cutaneous eruptions seen in the study, drug-induced rash were most common followed by fixed drug eruptions which is in accordance with the study conducted by Rajaram et al. (2015) and which is contradictory to study performed by Pudukadan et al (2004) followed by Steroid Induced Acne, Drug-Induced Dermatitis, Erythema Multiforme, Steven Johnsons Syndrome, Toxic Epidermal Necrolysis.

Out of 147 cases, Antibiotics are responsible for the major portion of drug-induced cutaneous eruptions, followed by NSAIDS, Steroids, Anti-convulsants, which is in accordance with the study conducted by Rajaram et al. (2015) and Raut et al. (2015).

According to Naranjo assessment Scale, 25 cases were likely to be Definite ADR's, 67 cases were Probably ADR's, 51 cases were possible ADR's and 4 cases were doubtful ADR's which is in accordance with Noel et al (2004).

Hartwig's and Siegal severity assessment Scale showed 67 Mild cases, 57 Moderate cases, 23 Severe cutaneous eruptions which are in correspondence with the study performed by Verma et al (2014).

Shumock and Thornton Preventability assessment scale showed 29 cases were likely to be Definitely Preventable, 40 cases likely to be Probably Preventable and 78 cases were Not Preventable, which is in accordance with the study performed by Verma et al (2014).

The outcome of the reaction was evaluated, which revealed 4 cases to be fatal, 11 cases to be continuing, 48 cases were recovered, 31 cases were recovering and due to the poor review of the patients, 53 cases were left unknown.

CONCLUSION

Skin reactions may be caused by exposure to certain medications. Patient signs and symptoms help the healthcare professional identify the specific type of DISR. Additionally, the association can be made with the use of a medication history, medication reconciliation, and drug-exposure timeline. After identification, the offending agent should be discontinued, treatment recommendations should be made, and patient education should be provided to prevent future adverse reactions. There is a need to engage health care professionals in a well-framed program to build synergies for monitoring ADRs to ensure maximum benefits for public health and safety.

Awareness should be created among the population regarding drug induce cutaneous eruption and they should be discouraged for inappropriate use of OTC drugs which may contribute to a reduction of most prevalent cutaneous eruptions.

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