International Journal of Biomedical Research
ISSN: 0976-9633 (Online); 2455-0566 (Print)
Journal DOI: https://doi.org/10.7439/ijbr
CODEN: IJBRFA

Original Research Article

Clinico-aetiological study of cutaneous adverse drug reactions in a tertiary care hospital

B Raghu Kiran, N M Prasad Naik*, and Gautham Krishna Reddy

Department of DVL, Osmania Medical College / NTR University of Health Sciences, India

QR Code

***Correspondence Info:**
Dr. N M Prasad Naik
Department of DVL,
Osmania Medical College, Hyderabad, India
NTR University of Health Sciences, India

***Article History:**
Received: 13/06/2017
Revised: 01/07/2017
Accepted: 02/07/2017
DOI: https://doi.org/10.7439/ijbr.v8i8.4237

Abstract

Background: Healthcare professionals, and indeed patients, face numerous challenges when considering ADRs.
Methods: The objectives of this study are to observe the prevalence, clinico-aetiological patterns and clinical type of drug eruptions. A Prospective observational, Non-invasive study was carried out at Department of Dermatology, Osmania General Hospital, a Tertiary Care Teaching Hospital for a period of 12 months. A total of 100 cases of drug eruptions were randomly selected into the study.
Results: Females seem to be more susceptible to drug reactions than Males. Adults and middle aged people were seems to be more prone for drug reactions. Fixed drug eruption was the commonest reaction followed by Urticaria, Pruritus, Lichenoid eruption and Acneiform eruption in this order. Common offending drugs, in order of frequency are Sulphonamides, NSAIDs, Isoniazid and other antibiotics.
Conclusion: By implementing the ADR reporting, one can promote drug safety and better patient care, among healthcare professionals and be aware of these concerns so that they might be anticipated and addressed in future patients with CADRs.

Keywords: Drug Eruptions, Fixed Drug Eruption, NSAIDs, Sulphonamides.

1. Introduction

A drug is a substance or product that is used by means of ingestion, injection, inhalation, inserted, instilled or topically applied on skin for management or prevention of diseases. Since the times of Homer (950 BC) there are many warnings in the medical literature about the toxic effects of drugs [3]. Drug eruptions are most frequent of all the manifestations of drug sensitivity.[5] The drug eruptions are unwanted and unintended mucocutaneous reactions which occur upon the administration of any diagnostic or therapeutic agents.[1]

The most common morphological pattern of drug eruptions were morbiliform eruptions, exanthematous rash, urticaria, angioedema, fixed drug eruptions, papulosquamous, pustular and bullous eruptions, erythema multiform and Stevens Johnson syndrome, in different cases. The prevalence of drug reactions depends upon many factors including genetic and racial factors. Availability of and usage of drugs varies from region to region in the same, or different countries. Some drugs which are notorious for drug reactions have been banned in developed countries, but they are still in use in India. In addition India is known for its indigenous Medicines since ancient times, which also can be a source of drug eruptions.[1]

The incidence of adverse drug eruptions in US is approximately 2-5% of in patients and, greater in out patients. In our country, it varies in between 6 to 30%and about 3 to 8% of hospital admissions are due to drug eruptions. Internationally drug eruptions occur in approximately 2 to 3% of in-patients.[2]

About, mortality and morbidity, most drug eruptions are mild, self-limited and usually resolves after the drug have been discontinued. Severe and potentially life threatening eruptions occur in approximately 1 in 1000

hospital patients. Mortality rate for erythema multiforme major is significantly high. Stevens Johnson syndrome (SJS) has less than 5% and toxic epidermal necrolysis (TEN) approaches 20-30%, because of sepsis.

Smith *et al* observed an adverse reaction rate of 40% in patients given 16 to 20 drugs. There is direct relation between the rate of occurrence of adverse drug reactions in hospitalized patients and the number of different drugs they are given. Women and increased age, are the more vulnerable group for drug eruptions.[3]

From Boston collaborative surveillance programme, among 39,665 consecutive medical in-patient seen it was found that 2.2% had mild skin reactions. Eg. pruritus, rash, urticaria [4], Overall reaction rate was 3/1000. Penicillins, Sulphonamides and blood products accounted for 2 / 3rd of cutaneous reactions.[4]

Present study is undertaken to explore in detail about the incidence, prevalence and aetiology, clinical patterns of cutaneous eruptions and other systemic association of drug eruptions.

1.1 Aims and objectives

- To calculate the prevalence of drug eruptions.
- To evaluate the various clinicoaetiological factors leading to drug eruptions.
- To study the various clinical patterns of drug eruptions.

2. Materials and methodology

A hospital based Prospective, Observational; Noninvasive study was carried out on all the inpatients and outpatients attending the Dermatology department, Osmania General Hospital, Hyderabad for a period of 12 months.

2.1 Inclusion Criteria

- Patients of either sex, age 0-60yrs with obvious skin lesions with drug history.

2.2 Exclusion Criteria

- Patients more than 60yrs age.
- Patients on Anti-retroviral medication
- Patients not responding to verbal stimulus.
- If lesions turned out to be disease related (e.g., viral exanthemas, rash of rickettsial infections, and collagen vascular disease,) on closer examination.

The patients of either sex, in Dermatology Department are observed for Cutaneous Adverse events, and are enrolled as per the inclusion and exclusion criteria, with patient's written consent for this study. Current medical history and diagnosis was noted during the first visit. After enrolment into study, follow up was done for the inpatients and outpatients (who were reviewed after a week). At each follow up patients are asked for any new complaints, and examined. Prescriptions, non-prescriptions and previous records are reviewed and Cutaneous Adverse drug reactions were analyzed and recorded in the proforma.

3. Results

The data collected on CADRs form during the study period was analyzed into various parameters viz. Type of CADR, Causality and Severity assessments, clinical patterns of CADRs, detection of the offending drug implicated in the Cutaneous Adverse drug reaction and management of CADRs. During the study period, September 2015 to August 2016, at Department of DVL, Osmania General Hospital, Hyderabad, 100 cases of drug eruption were taken randomly.

3.1 Prevalence

Out of the total attendance of 89968 new cases during, September 2014 to August 2015, there were 100 cases of drug eruptions, which attended DVL Department OP, at OGH, Hyderabad.

Out of total attendance of 89968, there were 100 cases of drug eruptions prevalence of drug eruptions in this study is,

Total number of patients = 89968
Number of drug eruption patients = 100
Percentage of drug eruption = 0.111 %

Table 1: Age and Sex Distribution of Drug Eruptions

Age	Male	Male Percentage	Female	Female Percentage	Total	Total Percentage
0 – 10	4	8.34%	2	3.84%	6	6%
11 – 20	2	4.16%	4	7.7%	6	6%
21 – 30	18	37.5%	27	51.9%	45	45%
31 – 40	13	27.1%	12	23.1%	25	25%
41 – 50	6	12.5%	3	5.76%	9	9%
51 – 60	5	10.4%	4	7.7%	9	9%
Total	48		52		100	

Table 2: Type of Drug Eruption wise Distribution

S. No.	Type of Drug Eruption	No. of Cases	Percentage
1.	FDE	`18	18%
2.	SJ Syndrome	5	5%
3.	Acneiform Eruption	8	8%
4.	Exfoliative Dermatitis	5	5%
5.	Morbiliform Eruption	4	4%
6.	Urticaria	12	12%
7.	Purpura	5	5%
8.	Papulo Squamous rash	6	6%
9.	TEN	3	3%
10.	Erytheme Multiforme	6	6%
11.	Allergic Contact Dermatitis	2	2%
12.	Lichenoid Eruption	9	9%
13.	Bullous Drug Eruption	4	4%
14.	Oral Erosion (only)	1	1%
15.	Eczema	1	1%
16.	Pruritus	11	11%

Table 3: Drug wise Distribution of Eruptions

S. No.	Name of Drug	Type of Eruption	Total No. of cases	Percentage
1.	NSAIDs	Pruritus FDE Lichenoid Eruption Papulosquamous Urticaria EMF SJ. Syndrome TEN Purpuric rash Oral mucosal erosion	6 11 4 3 2 2 1 1 1 1	32%
2.	Tab. Sulphonamides	Urticaria Bullous FDE Purpuric Rash FDE Pruritus Exfoliative Dermatitis Lichenoid Eruption TEN	4 2 2 4 2 2 2 1	19%
3.	Tab. Carbamazepin	Exfoliative Dermatitis TEN	1 1	2%
4.	Tab. INH	Acneiform Eruptions Pruritus Morbilliform Eruption Papulosquamous	4 2 1 1	8%
5.	Neomycin ointment	Eczematous drug eruption	1	1%
6.	Zandu Balm	Allergic contact Dermatitis	1	1%
7.	Tab. Furoxone	Urticaria	3	3%
8.	Herbal leaf	Allergic contact Dermatitis	1	1%
9.	Tab. Progestin	SJ Syndrome Acneiform Eruptions	1 1	2%
10.	Inj. Penicillin	Purpuric rash	1	1%
11.	Tab. Estrogen	Purpura Acneiform Eruptions	1 1	2%
12.	Steriod inhalation	Acneiform Eruptions	2	2%
13.	Inj. Streptomycin	SJ Syndrome	1	1%
14.	Cap. Tetracycline	Bullous FDE	2	2%
15.	Tab. Cetrizine	Urticaria	1	1%

S. No.	Name of Drug	Type of Eruption	Total No. of cases	Percentage
16.	Cap. Ampicillin	Erythema Multiforme	3	3%
17.	Amoxycillin syrup	Morbilliform rash	1	1%
18.	Topical Camphor	Lichenoid Eruption	3	3%
19.	Tab. Cifran	Morbilliform rash	1	1%
20.	Unknown	EMF FDE SJ Syndrome Exfoliative dermatitis	1 2 1 1	5%
21.	Tab. Ranitidine	Gaint Urticaria	1	1%
22.	Inj. Gentamycin	Morbilliform eruption	1	1%
23.	Cap. Rifampicin	Exfoliative dermatitis SJ Syndrome	1 1	2%
24.	Tab. Metronidazole	Pruritus Urticaria FDE	1 1 1	3%
25.	Tab. Dapsone	Papulosquamous	2	2%

4. Discussion

Adverse drug reactions (ADRs) constitute a major problem in society and in drug therapy, both as a health care problem and as an economic burden on society. They are a common cause of short-term hospitalization, prolonged hospitalization and death, especially among the elderly. Cutaneous ADRs have a varied presentation in clinical patterns, distribution of age and gender, Causality assessment and drug response because of variant geographical representation.

100 cases of Drug Eruptions were studied in the Department of Dermatology during 2014-15. Depending on severity, few of them were hospitalized. In most of the cases careful history revealed the offending drug. In hospitalized patients the offending drug was identified either by dechallenge or rechallenge.

Prevalence of drug eruptions in this study is 0.111%. According to Rook *et al*, the incidence of drug eruption is difficult to determine because many mild and transitory eruptions are not reported.[5]

In the present study out of 100 patients 48 were Males and 52 were Females, with a Male: Female ratio of 1: 1.08. In Kauppinens study from Finland the Male: Female ratio was 1: 2; Mehta *et al* (1971) and Mary Mathew (1983) on the contrary reported drug eruptions to be more common in Males, the Male: Female ratio being 2.3: 1 and 1.5: 1 respectively. The present ratio is in agreement with the findings of Kauppinens study.[6-8]

The commonest age group affected in both the males and females was 21-40 years. Least prevalence was seen between 11-20 years in males and between 0-10 years in females.

Fixed drug eruption was the commonest drug eruption we could come across in this study, with a prevalence of 14%. In Kauppinen's series in 1972, Finland FDE was only third in order of frequency and was less common than exanthematous and urticarial eruption. Mehta and Marquis and Mary Mathew *et al* (1971) reported the prevalence of 24.2% and 26.6% fixed drug eruption cases respectively.[6-8] Urticaria and Pruritus were next common drug eruption constituting 12% and 11% respectively.

4.1 Fixed Drug Eruption

Sulphonamides were responsible for 3 out of 7 cases. According to Sehgal V.N. sulphonamides alone is responsible for large number of FDE patients throughout world [9]. In our study NSAIDs were major cause for FDE.

4.2 Urticaria

Kauppinen's series and Fitz Patrick *et al* found urticaria as second most common eruption.[4,6] Mehta *et al* reported 12.8% and Mary Mathews reported 9.6% of cases of urticaria in their studies.[7,8] In our study the prevalence was 8%. Bigby M, found pencillins as the most common cause of urticaria[10]. We found sulphonamides, paracetomol, furoxane, Tab. citirizine as the responsible drugs.

4.3 Acneiform Eruptions

This also like Stevens Johnson Syndrome contributed 10% of cases. INH was the main culprit. Mary Mathew reported 7.8% prevalence for Acneiform eruption.[8]

4.4 Exfoliative Dermatitis

The incidence of Exfoliative Dermatitis was akin to Stevens Johnson Syndrome and Acneiform eruption with 10% of prevalence. Prevalence of 2.3% and 1.4% were reported by Mary Mathew *et al* and Mehta *et al* respectively. 3 out of 5 Exfoliative Dermatitis were due to sulphonamides in this study.[7,8]

4.5 Purpura

In our study 8% of cases were purpura coinciding with report of Mehta Marquis [7]. This differs with Mary Mathews study which reported prevalence of 0.5% only.[8]

4.6 Stevens Johnson Syndrome

10% of total cases were of Stevens Johnson Syndrome. Most of these cases were due to Anti Tuberculous Therapy. Mehta *et al* reported 4.2% and Mary Mathew reported 5.5% of prevalence.[7,8]

4.7 Pruritus

In the present study the prevalence of Pruritus was 11%.

4.8 Toxic Epidermal Necrolysis

In the present study the prevalence of Toxic Epidermal Necrolysis was 6% differing with that of Mehta *et al* (2.8%) and Mary Mathrew (3.3%). According to Sen *et al* and Muthuswamy 40% of toxic epidermal necrolysis were due to thiacetazone, 10% being fatal. NSAIDs and sulphonamides are responsible for Toxic Epidermal Necrolysis in our study. [7,8,11].

4.9 Exanthematous Eruptions

Kauppinen (1972) Davies (1981) Fitz Patrick (1979) and Rook *et al* (1979) observed exanthematous reactions to be most frequent of all the drug eruptions. In this study only 8% of cases were reported. [4-6,12].

4.10 Erythema Multiforme

Erythema multiforme contributed 4% of cases in this study. This is in agreement with Mehta *et al* (4.2%) but differs with Mary Mathew's (50%) report.[7,8]

4.11 Vesiculo Bullous Eruptions

2% cases of vesiculo bullous eruptions were reported here. Mehta *et al* (5.6%), Mary Mathew (4.6%) both reported higher prevalence.[7,8]

4.12 Allergic Contact Dermatitis

It is a common dermatological problem and Type-IV delayed type hypersensitivity response. Simple chemicals or haptens become complete antigens on combining with a carrier, generally epidermal protein. Site of lesion is important for suspecting the causal agent. Air borne contactants, textile dermatitis, shoe dermatitis, occupational dermatitis, metal dermatitis, due to local medication and plant dermatitis.

E.g.: Herbal leaf and Zandu Balm (Composition: Menthol 20% w/w, oil gautheria 10% w/w base) in this study.

4.13 Eczematous Drug Eruptions

A patient of allergic contact dermatitis due to drug may develop an eczematous reaction, when that drug is administered systemically. In some patients, allergens which are immunologically related to sensitizing allergens can also product eczematous contact type of dermatitis.

E.g.: Neomycin sulphate topically; streptomycin, kanamycin and gentamycin systemically, will give rise to eczematous eruptions.

4.14 Eruptions according to drugs used

Availability and usage of drugs differ from region to region. India being developing country certain of the banned drugs are still in use in addition to usage of indigenous medicines further complicating adverse drug reactions.

4.15 Drugs

Mode of administration of drugs will play a role in causing drug reactions. Reactions are more common with orally administered drugs because of ease of administration. In our study, 88% of drug reactions were due to oral medication, 6% by topical therapy and 6% by parental therapy and other modalities of administration.

If single drug is administered the offending drug can be identified easily. But often multiple drugs are taken simultaneously by patients especially for Tuberculosis and Hansens diseases. In our study 34 cases of drug eruptions followed administration of single drug alone. But in 16 cases multiple drugs were used.

In this study most of the drug reactions were due to Sulphonamides, Dapsone, Co-trimoxazle Group NSAIDs and I.N.H, in that order. In Mehta's 1971 series sulphanamides, aspirin, and penicillin were common responsible drugs with 36%, 21 % and 9% respectively. Mathews 1983 reported higher incidence of drug eruption with Antituberculosis drugs followed by Sulphonamides and Antimalarials. Dapsone was responsible for 3 cases of exfoliative dermatitis though Rook *et al* claim that this reaction was rare. Since Tuberculosis is common in India reactions with Antituberculosis drugs like Isoniazid and Rifampicin are more frequently seen. [5,7,8]

Analgesics are available as 'over the counter drugs' (OTC) enabling the self medication by the patients causing various drug eruptions.

Davies (1991) claims that drug reactions are more common in debilitated and poorly nourished patients. In our study the general condition was poor in 6% of the cases at the time of developing drug reactions. This shows that general condition of the patient is not a factor-in developing reactions.[3]

According to Davies (1981) kidney and liver diseases predisposes to drug toxicity. In our study, a sixty year old patient died of renal failure.

In most of the patients the offending drug was withdrawn immediately. Severe reactional states like Stevens Johnson Syndrome, Toxic Epidermal Necrolysis and Acute Urticaria and Exfoliative dermatitis were hospitalised and managed with carticosteroids and other drugs depending upon the situation. All the patients recovered but for one who died of renal failure.

In conclusion as Rook rightly said every drug should be viewed with suspicion and the physician should follow conservative rather aggressive methods of treatment.[5]

It is suggested that a warning card be issued to all patients showing drug hypersensitivity reactions and a close relative should be explained about such drug reactions. This step is urgently required to be taken in our country where illiteracy, ignorance and indescriminate use of several drugs are still widely prevalent.

In these cases for identifying the exact incriminating drug the dechallenge and rechallenge tests were done.

5. Conclusion

The study has demonstrated that Cutaneous Adverse drug reactions have significant burden in terms of their impact on patient's lives, considering that there is relatively a high incidence of CADRs, therefore CADRs monitoring is of great clinical significance to prevent patient from unwanted exposure to drug toxicity. Females seem to be more susceptible to drug reactions than Males. Adults and middle aged people were seems to be more prone for drug reactions. Fixed drug eruption was the commonest reaction followed by Urticaria, Pruritus, Lichenoid eruption and Acneiform eruption in this order. Common offending drugs, in order of frequency are Sulphonamides, NSAIDs, Isoniazid and other antibiotics. Religion, socioeconomic Status and occupation have no role on drug eruptions. Every drug should be viewed with suspicion and conservative method of prescription will at least lessen the drug eruption. More elaborate studies with larger groups of patients utilizing modern investigative facilities are necessary to have a better etiological evaluation of newer drug eruptions. It can be used to guide the healthcare professionals to communicate more effectively regarding the management of such conditions. This helps in prevention and early detection of CADRs. The aim of the study was achieved by assessing the prevalence, causality and severity assessment, offending drugs involved in CADRs, clinical patterns recorded during the course of study. By implementing the ADR reporting, one can promote drug safety and better patient care, among healthcare professionals.

Declarations

Funding: None

Conflict of interest: None.

References

[1]. Valia *et al*. Drug Reactions; IADVL Textbook of dermatology, 3rd Edition, 2013; 2:1633.

[2]. Breathnach SM, Hintner H. Adverse drug reactions and skin, London, England: Blackwell Scientific, 1992.

[3]. Davis DM. Textbook of Adverse Drug Reactions 3rd edition Oxford University Press, 1985; 1-11.

[4]. Fitz Patrick Thomas B. *et al*; Dematology in Internal Medicine 4th Edition MC Grew Hill, 1984.

[5]. Rook *et al*, Wilkinson D.S. & Ebling F.J.G. Text book of Dermatology, fifth edition 2961-2979.

[6]. Kauppinen K. Cutaneous reaction of drugs. *Acta Derm Venereology* 1972; 52 (Suppl 68):1-89.

[7]. Mehta TK, Marquis L, Shelty JN. A study of 70 cases of drug eruptions. *Indian Journal of Dermatology Venereology & Leprology* 1971; 37:1-5.

[8]. Mary Mathews and Mani: A study of 218 drug eruptions. *Ind. Journ Derm Venerol Lep*. 1983; 49: 109.

[9]. Sehgal V.N. & Srivastava-FDE changing scenerio. *IJD* 2006, 45: 897-908.

[10]. Bigby M. rates of cutaneous reactions to drugs. *Arch. Dermatol.* 2001; 137: 765-770.

[11]. Muthuswamy S. Proceedings of the 24th National Conference on Tuberculosis and Chest diseases *P.B.A.* 1969; 1: 235.

[12]. Davies C.M. Drug Induced SLE, *Br. Med. J.* 1966; iii: 682.