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Adverse Cutaneous Drug Reactions in a Tertiary Care Center Patients: a Prospective Analysis

Sandeep Mahapatra[1] and Umashanker Pd Keshri[2]
[1]Department of Dermatology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand.
[2]Department of Pharmacology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand.

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ABSTRACT

In the dermatology department of a tertiary care centre patients were scrutinized for adverse cutaneous drug reaction and 100 cases of certain and probable causality assessment were studied for type of reaction and their causative agent. Most common morphological pattern observed was maculopapular drug reaction (23%), followed by fixed drug eruption and urticaria 14% and 13% each respectively. Stevens-johnson and toxic epidermal necrolysis accounted for 25%. Pityriasiform, lupus erythematosus like eruption, acute generalized exanthematous pustulosis and dapsone syndrome each accounted for 1%. Most common causative agent observed was NSAID (24%) followed by antibiotics and antiepileptic each in (22%) cases. Other drug responsible for ADR were antiretroviral (6%), antiprotozoals (5%); antimalarials, antitubercular and antihypertensive; each were 4%. It is our contention that the use of high risk drug should be carefully prescribed, monitored and awareness should be created by treating physician so that the morbidity and mortality by the use of the drug should be decreased.

INTRODUCTION

Drugs are always related with risk of adverse reactions, no matter how safe and efficacious they are. Adverse drug reaction is a response to a drug that is noxious and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function (WHO. International drug monitoring, 1972). It is an unexpected, undesired, and unintended or a toxic consequence of drug administration. Safe use of the drugs is the responsibility of health care professional and a proper knowledge of adverse cutaneous drug reaction related information may be helpful in prevention of it. It includes various forms of noxious effects of the drugs. The incidence of adverse cutaneous drug reaction (ACDR) varies from 15 to 30% of all adverse drug reaction (Boston collaborative Drug Surveillance Program, 1973). It may be trivial, serious or even fatal. Serious and fatal adverse cutaneous drug reaction is common causes of hospitalization and prolongation of indoor patient stay in hospital. Many of the commonly used drugs have reaction rates above one percent (Roujeau *et al.*., 1994).

Consultation of the patient to the physician due to ACDR comprises approximately 2-3% (Bigby *et al.*., 1986). Prevalence of it may range from 2-5% of the inpatients in Indian hospital settings. There is a wide variance in the spectrum of ACDR ranging from a transient maculopapular rash to fatal toxic epidermal necrolysis (Sharma *et al.*, 1996). Although majority of ACDRs are minor reactions and are self limiting, sometimes severe and potentially life threatening situations (Lee *et al.*, 2001) like steven-johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) can occur, which constitute from 2.6 to 7% of all drug reactions (Roujeau *et al.*, 1995). Although it is so common and 1/3 to ½ of ADR are preventable, (Barbara *et al.*, 2001) only a few prospective studies have been reported to evaluate their prevalence and analyze their features in hospital settings. Therefore we have tried to identify the offending drug and type of adverse cutaneous drug reaction to generate data related to safe use of the drug.

* *Corresponding Author*
Dr. Umashanker Pd Keshri, Rajendra Institute Of Medical Sciences, Ranchi, Jharkhand. Mobile no: 9504006303,

MATERIAL AND METHODS

This study was done in a tertiary care hospital (RIMS, Ranchi) of Jharkhand for a period of one year (September 2008 to august 2009) over 100 patients. Indoor and outdoor patient of the department of dermatology and indoor patient referred from the other wards were scrutinized for cutaneous ADR. Cases were excluded where diagnosis were not clear. Approval from institutional ethics committee was taken before starting the study. Consent from patient was also taken. Causality assessment was done using WHO-Uppsala monitoring center scale, 2002. Detailed clinical history was recorded in a predesigned form. Cases with a certain, probable or likely association were recorded. Relevant laboratory investigations were undertaken to arrive at a clinical diagnosis. Dechallenge was done. Rechallenge was not attempted. The data was compiled and subjected to descriptive statistical analysis.

RESULTS

31024 patients attended in skin OPD in one year in which no. of patients with suspected ACDRs were 670 (2.15%). On the basis of WHO-Uppsala monitoring centre 2002 causality assessment scale certain cases were 16 and probable/likely were 84. Percentage of male and female patient was 44 and 56; and 41-50 years age group were most venerable group (22%). Out of 21 patients sufferings from severe ACDRs 4 cases were from HIV positive patients group. Percentage of maculopapular drug reaction were 23, fixed drug eruption 14, urticaria 13, altogether stevens-johnson and toxic epidermal necrolysis 25.

Detail of cutaneous drug reaction type and drug responsible for ACDR has been mentioned in table no. 1 and table no. 2. Analgesic were the most frequently reported drug showing cutaneous drug reactions (24%), followed by antibiotics and antiepiliptics drugs each in 22% cases and antiretroviral in 6% cases. Out of 100 selected cases 30 were definitely preventable, 68 were probably preventable and 2 cases were not preventable. Antiepileptic was observed as the most common offending agents in causation of severe cutaneous drug reactions. Most common offending drug was carbamazepine which accounted 33% followed by nevirapine and phenytoin. Past history were present in 33.33% cases in severe ACDRs and 10.12% in non severe cases.

P value results between male and female suffering patients and of past history were significant, duration of drug intake before development of rash and mean body surface area involvement were very significant and presence of mucosal involvement, time taken for resolution of lesions and number of complications were highly significant.

Maximum number of complications observed were hematological and temperature dysregulation, followed by hepatic, hypoalbuminemia and renal complications. Mortality occurred in one patient due to septicemia.

Table . 1: Incidence of various morphological patterns in adverse cutaneous drug reactions .

Serial no.	Types of drug reactions	Number of cases in percentage
1	Maculopapular/Exanthematous	23
2	Fixed drug eruption (FDE)	14
3	Urticaria / Angioedema	13
4	Erythema Multiforme(EM)	06
5	Stevens- Johnson Syndrome (SJS)	10
6	SJS-TEN Overlap syndrome	09
7	Toxic Epidermal Necrolysis (TEN)	06
8	Vasculitis / Purpura	06
9	Lichenoid Eruption	03
10	Exfoliative Dermatitis	02
11	Oral Ulcers	02
12	Acneiform	02
13	Pityriasiform	01
14	Lupus Erythematosus like eruption	01
15	Acute Generalized Exanthematous Pustulosis (AGEP)	01
16	Dapsone Syndrome (DDS)	01

Table. 2: Drugs incriminated in adverse cutaneous drug reactions.

Serial no	Drug classification	Drugs incriminated in cutaneous ADRs.
1	NSAIDs	Aspirin (4), Diclofenac (1), Nimesulide (8), Ibuprofen (2), Acelofenac (3), Paracetamol(2), Piroxicam (1),Naproxen (1),Rofecoxib (1), Celecoxib (1)
2	Antibiotics	Cotrimoxazole (10),Ampicillin(2), Cephadroxil (1), ,Amoxycillin (1), Ciprofloxacin (4),Amoxy-Clauv (1), Norfloxacin (1), Sparfloxacin (1) ,Cepalexin (1)
3	Antiepiepilitics	Carbamazepine (12), Phenytoin (8), Oxcarbazepine (1), Olanzapine (1)
4	Antimalarials	Chloroquine (3), Quinine (1)
5	Antiprotozoals	Tinidazole (2), Metronidazole (2), Ornidazole (1)
6	Antituberculous	Isoniazid (2), Rifampicin (2)
7	Antihypertensives	Propranolol (2), Ramipril (1), Nifedipine (1)
8	Antiretrovials	Nevirapine (6)
9	Antifungals	Griseofulvin (1), Fluconazole (1)
10	Miscellaneous	Dapsone (2), Allopurinol (1), Ferrous Sulfate (1), Methotrexate (1), Oral Steroids (2)

NSAIDS: non steroidal anti-inflammatory drugs

DISCUSSION

In our study no. of patients with suspected ACDRs was 2.15%. ACDRs in other studies were observed in 2-3% of the hospitalized patients (Mani *et al.*, 1983). It is probably due to the frequency of ADR related admissions depends on the detection method, department specialty and frequency of urgently admitted patients. On the basis of WHO-Uppsala monitoring centre 2002 casualty assessment scale certain cases were 16% and probable/likely were 84%. There is no gold standard investigation for confirmation of a drug-induced reaction. Instead diagnosis and assessment of a drug cause involve analysis of features; such as timing of drug exposure and reaction time, course of reaction with drug withdrawal/ discontinuation, timing and nature of a recurrent eruption on rechallenge, a history of similar reaction to the suspected drug and previous reports of similar reactions to the same drug. (Shear *et al.*, 2003). In our study Percentage of female patient suffering from ACDR is more than male patient. It is different from a study done in a North-Indian tertiary care center which reported male preponderance (Sharma *et al.*, 2001). In some study reports female preponderance also has been found. One possibility to explain the gender difference may be due to their genetic makeup or adherence to the drug more due to variability in the number of the male and female patient attending in different center and so frequently attending patient has higher chances of ADR. In this study among various age group 41-50 years age group had preponderance but in some other Indian studies the young adults had the preponderance (Barbara *et al.*, 2001). A wide clinical spectrum of cutaneous ADRs was noticed in this study. Maculopapular rash was the commonest reaction found in this study which encountered as cited in the literature (Puavilai *et al.*, 1989). Altogether stevens-johnson and toxic epidermal necrolysis accounted for 25% of total cases.

A high incidence of TEN and SJS has also been reported from a North-Indian hospital, (Uppal *et al.*, 2000) while western studies have shown very low incidence (Naldi *et al.*, 1999; Hunziker *et al.*, 1997). Despite having scientific data on drugs, one can't be sure how the patient will respond to the drug. Genomic research will help in attaining safety and efficacy of the drug treatment. In this study a very high percentage of cases were preventable. Patient education and having an information chart related to drug reaction may be helpful in reducing this number. Antiepileptic was observed as the most common offending agents in causation of severe cutaneous drug reactions. Most common offending drug was carbamazepine followed by nevirapine and phenytoin. A similar study done in St. John's Medical College, Bangalore revealed antiepileptics, (mainly phenytoin and carbamazepine) responsible for the majority of the ADRs among the etiological drugs (Noel *et al.*, 2004). Nevirapine was detected as causative agent for severe ACDRs in HIV positive patients group. Cutaneous diseases, including drug reactions, are extremely common in patient with HIV infection, and there incidence increases as immune function deteriorates (Serge et el, 1993). Serious CADRs were also detected by some newer drugs like celecoxib, rofecoxib, and oxcarbazepine. Periodical study related to ADR is therefore essential due to emergence of newer drugs.

CONCLUSION

It is concluded from the above study that by knowing the incidence, morphological patterns and causative agents of various adverse cutaneous drug reactions, many common and serious adverse affects due to drugs can be avoided. Due to lack of interest in ADR monitoring and poor response of the clinician for pharmacovigilance many of them go unreported. It is our contention that the use of high risk drug should be carefully monitored for ADR and awareness should be created in patients by treating physician so that the morbidity and mortality by the use of the drug should be decreased.

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