



PHARMACOVIGILANCE PROFILE OF DERMATOLOGICAL ADVERSE DRUG REACTION REPORTS COLLECTED FROM A TERTIARY CARE TEACHING HOSPITAL OF BANARAS HINDU UNIVERSITY, VARANASI

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ABSTRACT

Introduction: Drugs can cure, suppress or prevent a disease and are usually beneficial to humans. However, they can also produce undesirable / harmful effects, which are known as adverse drug reactions. These are important cause of morbidity, hospitalization, increased health expenditure and even death. Cutaneous adverse drug reactions are among the most frequent adverse drug reactions. Active search is essential for identification of these, as patients may tend to downplay the causal association between drug use and the subsequent cutaneous manifestation. **Objective:** To observe the types of drug induced dermatological drug reactions in the patients attending to out patients department of Dermatology in a tertiary care teaching hospital, Banaras Hindu University, Varanasi, and find out the incidence, causal relationship with final outcome of skin drug reactions. **Patients and Methods:** A prospective study involved 200 patients attending to the Dermatology Outpatient department was observed during the period of one year to find the patients with Dermatological ADRs using self-reporting method for selection of cases in the adverse drug reaction monitoring form by CDSCO, India. Causality was assessed using WHO-UMC Causality assessment Scale. Results were analysed using suitable statistical methods. **Results and Discussions:** Skin reactions are the most common manifestations of adverse drug reactions. The pattern of adverse drug reactions and the drugs causing them is remarkably different in our population. Knowledge of these drug eruptions, the causative drugs and the prognostic indicators is essential for clinicians for diagnosis and prevention of adverse drug reactions. It is recommended to advise patients to carry a card or an emergency identification of offending drugs in their wallets that list the drug allergies and/or intolerances.

KEYWORDS: Pharmacovigilance, Dermatological reactions, spontaneous reactions, WHO-UMC causality assessment.

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.^[1] It is an unexpected, undesired, and unintended or a toxic consequence of drug administration. Cutaneous drug eruptions are most common types of adverse reaction to drug therapy, with an overall incidence rate of 2%–3% in hospitalized patients.^[2] Any medicine can induce skin reactions, and certain drug classes, such as non-steroidal anti-inflammatory drugs, antibiotics and antiepileptics have drug eruption rates approaching 1%–

5%.^[2] It was seen that most drug eruptions are serious, some are even severe life threatening. Serious reactions include angio-oedema, erythroderma, Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).^[3] The incidence of the these drug eruptions is directly proportional to the number of drugs prescribed.^[4] The history- taking for drug intake is very important, which includes questioning direct, indirect and suggestive. It takes time, but answers are golden in case of cutaneous drug reactions and drug- induced dermatitis.^{[5], [6], [7]} 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.

SUBJECTS AND METHODS

A prospective study spread over 1 year duration, from May 2014 to April 2015 was carried out in the Dermatology OPD in collaboration with Dept. of Pharmacology, IMS-BHU, Varanasi.

200 patients were enrolled for this study using self-reporting method for selection of cases using ADR reporting form by CDSCO.

Following patients were excluded.

- (i) Patients not willing to take part in the study,
- (ii) Patients dropping out the study at any stage at their will
- (iii) Patients lost to follow up.

Inclusion criteria are.

- (i) Patients of all age groups & either sex
- (ii) Developing a suspected adverse cutaneous drug reactions following use of any medication were included in the study.

Detailed clinical history was taken in a predesigned proforma. History of drug ingestion, self-administration & H/O symptoms, other previous skin and systemic diseases, or any other illness was taken. Thorough clinical examination was carried out. Skin, hair, nail and mucosa (eye, oral and genital) were examined. Diagnosis was confirmed by Dechallenge test (disappearance of signs and symptoms after discontinuation of offending drugs). Data of suspected cutaneous adverse drug reactions was entered in CDSCO adverse drug reactions

reporting form, India. Patients' consent was obtained to take photos. WHO definition and classifications of adverse drug reactions were followed. The initial history included a recording of all prescriptions and non-prescription drugs taken within the last one month, including dates of administration and dosage and also the history of previous drug exposure and reactions, family history of drug reactions, features and severity of adverse drug reactions etc.

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. Cases with a certain, probable or possible 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

200 patients among whom 144 males and 56 females were included in this study (table no 1). The time required to develop cutaneous lesions between 1-45 days after intake of drug were considered. Sex distribution of drug eruption indicates patients belong to the 41-50 years age group which is 32% of the study population which is maximum followed by 21-30 years (28%) and 31-40 years (20%) of the study population (table no 1). The youngest patient of our study belongs to 1 year old & the oldest was 80years old.

Table 1: Age & sex distribution of drug eruption in present study.

Age group In years	Male	Female	Total	Percentage (%)
0-10	4	0	4	2
11-20	10	6	16	8
21-30	40	16	56	28
31-40	32	8	40	20
41-50	52	12	64	32
51-60	10	2	12	6
61-70	4	2	6	3
71-80	2	0	2	1
T0tal	144	56	200	

Table 2: Clinical pattern of drug eruption in present study.

Clinical pattern of eruption	Present study, n=200	
	Number	Percentage (%)
Fixed drug eruption	122	61
Maculopapular rash	52	26
Acne form eruption	6	3
Erythema multiforme	4	2
SJS	12	6
TEN	4	2

Table 3: Drugs responsible for fixed drug eruption.

Offending drug	Number (n=61)	Percentage (%)
Antipyretic, analgesic	32	52.46
Antimicrobials	20	32.78
Antiepileptics	8	13.11
Unknown	1	1.63

Table 4: Drugs responsible for maculopapular rash.

Offending drug	Number (n=26)	Percentage (%)
Antimicrobials	12	46.15
Analgesic, antipyretics	8	30.7
Antiepileptics	3	11.53
Others	3	11.53

It was seen that cutaneous drug eruption which is commonest in our study was fixed drug eruption which was 61% of study population followed by maculopapular rashes 26% (table no: 2). Fixed drug eruption most commonly occurs due to non steroidal anti inflammatory drugs (NSAIDs) around 52% of all fixed drug eruption patients followed by antimicrobials 32% (table no:3). Other drugs like antiepileptics are also responsible for the fixed drug eruption i.e only 13.11%. one case of fixed drug eruption was found due to unknown drug in our study population. The most common NSAIDs to produce fixed drug eruption is Nimisulide whereas common antimicrobials were Fluoroquinolones, Azithromycine and Cephalosporins.

Maculopapular rashes were the 2nd most common cutaneous drug eruption for which the most important & common offending drug was antimicrobials followed by analgesics & antipyretics (table no: 4). some other drugs like antiepileptics, antimalarials, antitubercular drugs were also responsible for development of maculopapular rashes.

In our study 6 patients presented with acne form eruptions out of which 4 were due to antitubercular drugs (INH, Rifampicin, Pyrazinamide, Ethambutol) & one was due to Ampicillin. 2 cases of erythema multiforme were seen because of Ibuprofen.

There were 12 cases of Stevens–Johnson syndrome out of which Ibuprofen induced were three in number, two were due to antimicrobials (Levofloxacin, Cefixime) (Table no :2, figure no:5), one was due to unknown drug. Amongst these two were severe which were managed in intensive care with positive result. There were 4 cases of toxic epidermal necrolysis, out of which two case was due to Rifampicin which was severe but responded well to immediate management. Another one was due to unknown drug which was proved fatal.

DISCUSSIONS

Among 200 patients of our study population, 144 were male & 56 were female. So percentage of male patients

was more affected by cutaneous drug eruptions than females in our study population. The ratio of male to female patients comes out as 2.57. It is similar as a study done in a North-Indian tertiary care center which reported male preponderance.^[8] 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 adverse drug reactions.

Next component of the study was to find out whether there is any association between different age groups of the patients and the incidence of cutaneous drug eruptions. 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.^[9]

The commonest pattern was fixed drug eruption (61%), followed by maculopapular rashes (26%) and Stevens–Johnson syndrome (6%). According to Pudukadan D et al study, the pattern of cutaneous drug eruption which was commonest was fixed drug eruption (31.1%), followed by maculopapular rash (12.2%) which was similar to our study.^[4] Malhotra et al study reported morbilliform rash (29.63%), and urticaria in (9.26%) as common patterns of reaction.^[10] Jhaj et al. reported morbilliform rashes commonest pattern followed by, urticaria (21%).^[5] Most important reason for intake of the above drugs are pain, fever and infection. The commonest culprit of fixed drug eruption in our study were NSAIDs, differ from the study by Singh et al where cotrimoxazole was the commonest cause^[6] NSAIDs and cotrimoxazole were the common cause of drug eruption in the study by Shrivastava et. Al.^{[7][11]}

Quinolones were a common cause of maculopapular rash and photosensitivity in our study which indicates increased use of quinolones.^[12] Ibuprofen was the commonest cause of erythema multiforme (EM) and Stevens Johnson's syndrome (SJS) in our study. From the report of Halevi et al Stevens Johnson's syndrome is due to acetaminophen,^[12] while in the study by Devik et al carbamazepine was the commonest offending drug.^[13] The incidence of isoniazide induced acneiform eruptions (0.53%) described in a study by Sharma PP,^[14] while we had 3 cases of acne form eruptions due to isoniazide. A high incidence of toxic epidermal necrolysis and Stevens Johnson's syndrome has also been reported from a North-Indian hospital,^[15] while western studies have shown very low incidence.^[16]

Study lacunae: Small sample size, confined to the outpatient department (OPD) of the skin & VD department only & a short period of six months & unable to do the rechallenge. Yet the study clearly provides the baseline data for comparing with other similar studies at the level of state, country and the

world. It also provided the information regarding the management of the cutaneous adverse drug reactions and their outcome thus making the drug therapy safer and more rational. This study has been a further step in the direction of strengthening the activity of pharmacovigilance in this part of the country.

CONCLUSIONS

It's the responsibility of clinicians and clinical pharmacists to recognize clinically important ADRs and report them to strengthen the pharmacovigilance activity. This was a prospective and observational study for detection of DADRS and analyzing various facets of the same. The study has revealed many interesting points and has given us insight to carry out further studies of similar type in future so as to derive better information. 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 effects 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 ADRs 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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