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Research Article

An observational study of drug induced cutaneous reactions used in various group of patients

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Abstract: Adverse drug reactions (ADRs) are noxious and unintended response to medicines. The detection and evaluation of ADRs of new drug is often delayed because they have long latency and are unexpected. But now a days pharmacovigilance surveillance system makes it possible for physicians, pharmacist and other health care providers to report suspected ADRs. The objective of this prospective study was to assess clinical pattern of drug induced cutaneous reactions in Dermatology OPD. In our study total of 60 patients with suspected cutaneous adverse drug reactions were recruited. A detailed physical examination was done by a physician including drug intake during 3 weeks preceding reactions and type of drug reactions. Most frequently reported cutaneous drug reactions were Stevens Johnson Syndrome (23%), Maculopapular rash (18%) Toxic Epidermal Necrolysis (15%) and were caused by antiepileptic drugs in 21(35%) patients, followed by antibiotics in 17(28.33%) cases, NSAID's in 7(11.6%) cases, antitubercular drugs in 3(5%) and antiretroviral drugs in 3(5%) cases. A high proportioned of these reaction (50%) were moderate (31%) of these were severe because they require hospitalisation or increased the duration of stay in hospital or were life threatening in (1%). Principal offending drug was phenytoin. So, a good knowledge of ADRs, a careful history taking and watchful approach while prescribing of new drugs can prevent many of the adverse drug reactions. These facts justify the development of an intensive programme of pharmacovigilance.
Keywords: Adverse Drug Reactions, Stevens Johnson Syndrome, Pharmacovigilance, Phenytoin.

INTRODUCTION

Modern medicine has changed the way in which diseases are managed and controlled. However, despite all benefits, evidence continues to mount that adverse drug reactions are common yet preventable cause of illness, disability and even death. Adverse drug reaction constitutes a major clinical problem in terms of increase in morbidity and mortality, as well as an increase in the cost of healthcare. In contrast to systemic ADRs, cutaneous Adverse Drug Reactions are most frequently reported because these are generally easily visible and hence, detected by the patient even if he is symptom free. Cutaneous reactions constitute majority of these ADRs and can range from mild maculopapular rash to severe Toxic Epidermal Necrolysis (TEN).

Epilepsy is one of the most common neurological disorder. ADRs to anti-epileptic drugs significantly impact the quality of life and account for a large number of treatment failures. Adverse effects of AEDs remain a major cause of morbidity and mortality in the course of treatment of epilepsy and hence considerably impact the quality of life of people with epilepsy, perhaps as much as the seizure burden. The exact incidence of adverse effects of AEDs has not been determined as most people with epilepsy are managed as outpatients and are not hospitalized for either the epilepsy or for the adverse effects. The exact incidence of adverse effects of AEDs has not been adequately documented for various reasons.

The advancements in technology may help us improve the ability to predict and hence prevent the occurrence of some of the serious ADRs. One such example is the potential prediction of the risk of severe cutaneous hypersensitivity reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis by testing for expression of HLA-B*1502 allele in patients who are prescribed AEDs (carbamazepine, phenytoin etc.) The association between HLA-B*1502 expression and carbamazepine skin reactions has been documented in India but the role of HLA testing in Indian populations needs to be clarified in larger groups of patients within the country.

Adverse Drug Reaction

Definition

According to WHO, Adverse Drug Reaction(ADR) is defined as- A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or for the modification of physiological function [1]. Another definition of an adverse drug reaction: "An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product'' [2].

The term "adverse effect" is preferable to other terms such as "toxic effect" or "side effect". A toxic effect is one that occurs as an exaggeration of the desired therapeutic effect and which is not common at normal doses. For example, a headache due to a calcium antagonist is a toxic effect—it occurs by the same mechanism as the therapeutic effect (vasodilatation). A toxic effect is always dose-related. On the other hand, an unwanted side effect occurs via some other mechanism and may be dose-related or not. For example, the dose-related anticholinergic effect of a tricyclic antidepressant is a side effect, since this action is not associated with the therapeutic effect; similarly, non dose-related anaphylaxis with penicillin is a side effect. The term "adverse effect" encompasses all unwanted effects; it makes no assumptions about mechanism, evokes no ambiguity, and avoids the risk of misclassification.

The terms "adverse reaction" and "adverse effect" are interchangeable, except that an adverse effect is seen from the point of view of the drug, whereas an adverse reaction is seen from the point of view of the patient. However, the terms "adverse effect" and "adverse reaction" must be distinguished from "adverse event". An adverse effect is an adverse outcome that can be attributed to some action of a drug; an adverse event is an adverse outcome that occurs while a patient is taking a drug, but is motor not necessarily attributable to it.

Table 1:- Classification of Adverse Drug Reactions[2]

Type of reaction	Mnemonic	Features	Examples	Management
A: Dose-related	Augmented	• Common • Related to a pharmacological action of the drug • Predictable • Low mortality	• Toxic effects: Digoxin toxicity; serotonin syndrome with SSRIs • Side effects: Anticholinergic effects of tricyclic antidepressants	• Reduce dose or withhold • Consider effects of concomitant therapy
B: Non-dose-related	Bizarre	• Uncommon • Not related to a pharmacological action of the drug • Unpredictable • High mortality	• Immunological reactions: Penicillin hypersensitivity • Idiosyncratic reactions: Acute porphyria Malignant hyperthermia Pseudoallergy (eg, ampicillin rash)	• Withhold and avoid in future
C: Dose-related and time-related	Chronic	• Uncommon • Related to the cumulative dose	• Hypothalamic-pituitary-adrenal axis suppression by corticosteroids	• Reduce dose or withhold; withdrawal may have to be prolonged
D: Time-related	Delayed	• Uncommon • Usually dose-related • Occurs or becomes apparent some time after the use of the drug	• Teratogenesis (eg, vaginal adenocarcinoma with diethylstilbestrol) • Carcinogenesis • Tardive dyskinesia	• Often intractable
E: Withdrawal	End of use	• Uncommon • Occurs soon after withdrawal of the drug	• Opiate withdrawal syndrome • Myocardial ischaemia (β-blocker withdrawal)	• Reintroduce and withdraw slowly
F: Unexpected failure of therapy	Failure	• Common • Dose-related • Often caused by drug interactions	• Inadequate dosage of an oral contraceptive, particularly when used with specific enzyme inducers	• Increase dosage • Consider effects of concomitant therapy

SSRIs=serotonin-selective reuptake inhibitors.

Cutaneous adverse drug reactions are responsible for the majority of ADRs in hospitalized patients. Cutaneous Adverse Drug Reaction (CADR) are the commonest ADR (30-45%) and responsible for about 2% of hospital admissions [3]. In India, CADR account for 2-5% of all in patients, while it affects 2.6% of out patients [4]. Many of the commonly used drugs can produce cutaneous ADRs. A wide spectrum of cutaneous manifestations ranging from maculopapular rash to severe Toxic Epidermal Necrolysis (TEN) can be produced by different classes of drug.

MATERIALS AND METHODS

The study was conducted at the Department of Pharmacology, Dr.S.N. Medical College and Dermatology department, Mathura Das Mathur Hospital, Jodhpur (Rajasthan) respectively for around 12 months (January 2014 to December 2014).

1. Institutional ethics approval

The study protocol was approved by the Department of Pharmacology and subsequently by the Institutional Ethics Committee of Dr.S.N. Medical College, Jodhpur, and Rajasthan.

2. Study Population

Mathura Das Mathur hospital is a tertiary care teaching hospital in western Rajasthan. Sixty patients prescriptions were taken once a month on a randomly chosen date and all the patients visiting the dermatology outpatient department between January 2014 to December 2014 with any suspected cutaneous adverse drug reaction were included in this study.

3. Informed consent

Patients were made to understand the entire purpose of the study, their rights and the procedure of the study with the help of the patient information sheet which was available in both Hindi and English. Patients who gave written informed consent were then included in the study.

4. Study design

A prospective cross sectional observational study

5. Methodology

(i) Adverse Drug Reaction Assessment

An observational cross sectional study was undertaken in the Dermatology out Patient Department (OPD) of Mathura Das Mathur Hospital, Jodhpur for a period of 12 months.

All the patients visited the Dermatology Out Patient Department between January 2014 to December 2014 with any suspected cutaneous adverse drug reactions were included in the study. Patients and their accompanying family members were interviewed and previous prescriptions, medicines and case notes, if available, were reviewed and details of the disease and medicines prescribed were noted down.

ADRs were observed and recorded on adverse drug event reporting form for voluntary reporting of adverse drug events by health care professional. This proforma is prepared by Central Drug Standard Control Organization (CDSCO).

Causality assessment: - Naranjo's Scale

Severity Scale: - Modified Hartwig & Siegel Scale of ADRs

Level 1: An ADR occurred but required no change in treatment with the suspected drug.

Level 2: The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in Length of Stay (LOS)

Level 3: The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR An Antidote or other treatment was required. No increase in Length of Stay (LOS)

Level 4: Any level 3 ADR which increases length of stay by at least 1 day. OR The ADR was the reason for the admission

Level 5: Any level 4 ADR which requires intensive medical care

Level 6: The adverse reaction caused permanent harm to the patient

Level 7: The adverse reaction either directly or indirectly led to the death of the patient

*Mild= level 1 and 2, moderate= level 3 and 4, severe= 5, 6 and 7.

RESULTS

Adverse Drug Reaction Study

A total of 60 patients with suspected cutaneous adverse drug reactions were recruited during the study period from January 2014 to December 2014.

Majority of patients in whom cutaneous ADRs were observed belonged to age group 16-30 years (45%) followed by 31-45 years (30%), >45years (20%) and 0-15 years (5%) respectively (Figure1). Out of total of 60 patients 38(63.33%) were males and 22(36.66%) were females (Figure2).

The most common drug groups implicated and the common cutaneous ADRs are shown in figure 3 to 5.Most frequently reported cutaneous drug reactions were caused by antiepileptic drugs in 21(35%) patients, followed by antibiotics in 17(28.33%) cases, NSAID's in 7(11.6%) cases antitubercular drugs in 3(5%) cases and antiretroviral drugs in 3(5%) cases. Some of the other drugs involved were enalapril, losartan, glibenclimide, isotretinoin, allopurinol and herbal dugs.

Table 2:- Drug group causing cutaneous ADRs

Drug group	No.of patients	Percentage
Antiepileptics	21	35%
Antibiotics	17	28.33%
NSAIDS	7	11.6%
ATT	3	5%
ART	3	5%
Anti hypertensive	2	3.33%
Other	7	11.6%

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs, ART: Antiretroviral Therapy.ATT: Antitubercular Therapy

Table 3:-Types of cutaneous ADR

Types of ADR	**No.of patients**	Percentage
Maculopapular rash	11	18.33%
Urticaria	6	10%
Fixed drug eruption	6	10%
Acneiform eruption	1	1.6%
Photo allergic reaction	5	8.33%
SJS	14	23.3%
TEN	9	15.5%
DRESS	1	1.6%
Erythema	2	3.33%
DHS	5	8.33%

[MPR-Maculopapular rash URT-Urticaria FDE- Fixed drug eruption AFE-Acneiform eruptions PAR-Photo allergic reactions SJS-Steven Johnson syndrome TEN-Toxic epidermal necrolysis DRESS- Drug reaction with eosinophilia and systemic symptoms EM-Erythema multiforme DHS-Drug Hypersensitivity syndrome.]

Table 4:-Spectrum of cutaneous ADR

Types of ADR	Antiepileptic	Antibiotic	NSAID	ATT	ART	AHT	Others
MPR	1	4	3	1	0	1	1
Urticaria	0	3	0	0	0	0	3
FDE	0	4	2	0	0	0	0
AE	0	0	0	0	0	0	1
PAR	0	4	0	0	0	0	1
SJS	11	0	1	1	1	0	0
TEN	4	0	1	0	2	1	1
DRESS	1	0	0	0	0	0	0
Erythema	1	0	1	0	0	0	0
DHS	3	2	0	0	0	0	0

Causality assessment scale:-

Table 5:- Naranjo's causality scale

No. Of patients	**ADR Probability classification**	**Naranjo's scale**	**Percentage**
1	Definite	>9	1.6%
46	Probable	5-8	76.67%
13	Possible	1-4	21.67%
0	Doubtful	O	0

Severity Assessment scale:-

Table 6:-Modified Hartwig & Siegel scaling

Levels	No. of ADRs	Percentage(n=60)
MILD		
Level 1	5	8.33%
Level 2	6	10%
MODERATE		
Level 3	11	18.33
Level 4(a)	10	16.66%
Level 4(b)	9	15%
SEVERE		
Level 5,6,7	19	31.66%

DISCUSSION

Adverse Drug Reaction Study

Adverse drug reactions may affect any organ and the skin is a common site of presentation [5]. Adverse Cutaneous Drug Reactions (ACDR) are common, and some can be lethal with 0.2 - 29.3% of all ACDR requiring hospitalization. Adverse cutaneous drug reactions are distressing to both the patient and

physician. Mortality can occur in severe reactions but even without this, quality of life could be significantly diminished due to hospitalization, prolongation of hospital stay and increased morbidity [6]. Moreover, the development of a skin eruption is frequently cited as a reason for discontinuation of the treatment without completing therapeutic course [7]. Also, probability of developing adverse drug reactions to new drugs is increasing as more and more new drugs are available in the market.

Pattern of Adverse Drug Reactions

In our study the clinical spectrum of cutaneous ADRs with the implicated drugs was observed. The cutaneous adverse drug reactions manifested with varied and diverse morphological pattern ranging from trivial urticaria and maculopapular rash to severe reactions like Steven Johnson Syndrome and Toxic Epidermal Necrolysis. Steven Johnson Syndrome was the most common manifestation among cutaneous ADRs accounting for 23.33% patients, followed by maculopapular rash in 18.33% urticaria in 10%, toxic epidermal necrolysis 15.5%fixed drug eruption 10% and photo allergic reaction in 8.33% of the patients. A high incidence of TEN and SJS has also been reported from various other Indian studies conducted by Saha *et al.;* [8] Padukadan and Thappa [9]. However, the incidence of SJS and TEN was found to be lower in Western studies [10]. This might be due to the close surveillance, and the tendency to withdraw suspected drugs even in cases of minor skin reactions in Western countries. Other factors that could result in the above observation are different ethnic group characteristics, disease prevalence and hence different drug prescription pattern. Moreover, another reason may be due to better reporting of these serious drug reactions in tertiary care hospitals where these Indian studies were conducted. In contrast to our finding where Steven Johnson syndrome was found to be most common cutaneous ADR a study conducted by Ghosh *et al.;* [11] in Manipal, India reported that maculopapular rash is the most common CADR.

Antiepileptic were the most common drug group which caused cutaneous ADRs (35.41%) followed by antibiotic (28.33%) and NSAIDs (11.6%) which was consistent with the findings of other studies done in India and China [8, 12]. In our study, antibiotics were mainly implicated in mild to moderate cutaneous ADRs like maculopapular rash, urticaria, fixed dose eruptions and photo allergic reactions. Antibiotics mainly responsible for these ADRs were amoxicillin, cotrimoxazole, doxycycline and amoxicillin+clavulanic acid. Phenytoin and carbamazepine caused a wide spectrum.

Cutaneous ADRs among antiepileptics, these two drugs were responsible for most of the severe cutaneous ADRs like SJS, TEN and DHS. Carbamazepine has been approved for epilepsy, trigeminal neuralgia, and post herpetic neuralgia. But in our patients carbamazepine and phenytoin were predominantly used for seizure disorders. The next major group of drugs implicated was NSAIDs mainly paracetamol and ibuprofen. Moreover, it was interesting to note that a severe CADR like Toxic Epidermal Necrolysis was caused by ibuprofen which is very commonly prescribed drug drug in our hospital settings. In our study, allopurinol, drug used for gouty arthritis caused urticaria and maculopapular rash in one each of the patients.

Our study showed that the reaction time for various cutaneous ADRs ranged from few hours to 70 days with a mean reaction time of 14.53 days. Some of the ADRs occurred within few hours of taking the medicines. The reaction time is the time interval between drug intake and first appearance of cutaneous lesions. The reaction time for maculopapular rash, fixed drug eruptions acneiform eruptions and urticaria varied 1 to 10 days and reaction time for SJS and TEN ranged from 8 to 70 days whereas drug hypersensitivity reactions occurred after 10 to 38 days of taking the suspected medicines. This profile of reaction time is similar to the study by Sushma *et al.;* [13] (1-3 weeks) but slightly different from the study by Sharma *et al.;* (few hrs to 1 week) [14].

Taking into account the different drugs and their respective reaction times, it appears that antibiotics and NSAIDs tend to have short reaction time whereas antiepileptics and allopurinol have longer latency period. This shows that not only doctor need to enquire about recent medications but also it is important that doctor should be vigilant about CADR even to drugs patients is taking from long period (especially for phenytoin, carbamazepine and allopurinol). The reaction time can also be helpful in suggesting the offending drug in cases of polypharmacy which in turn will prevent unnecessary withdrawal of harmless medicines

In the present study, dechallenge was done in 54 cases out of total of 60. Five patients had already completed the drug treatment at the time of presenting to Dermatology OPD with cutaneous ADR. In one patient of acne vulgaris, who presented with photosensitivity treatment with tretinoin was continued with precautions to avoid sunlight and was advised to use sunscreen lotion.

In our study, rechallenge was not attempted in any of the patients because of the possible associated risks of more severe reaction after rechallange with the suspected drug. But in two of the cases, patient did not give history of previous cutaneous adverse drug reaction and was accidently advised same drug (phenytoin). In one case patient had Steven Johnson Syndrome 4 years back which he did not told to his prescribing doctor. In 2nd case patient had a mild

cutaneous reaction for which he was adviced to stop the offending medication and patient condition improved, but after few days he again continued the same medicine and then developed severe skin reaction and was diagnosed as drug hypersensitivity syndrome.

In our study we found that the patterns of the cutaneous adverse drug reactions and the drugs implicated varied in our study according to the pattern of the drug intake, the associated illness and the susceptibility of the patients. A good knowledge of the adverse drugs reactions, a careful history taking and a watchful approach while prescribing of new drugs can prevent many of the adverse drug reactions. As newer drugs are entering the market promptly special attention must be given to monitor and report the cutaneous adverse drug reactions.

CONCLUSION

This present study was mainly focused on the clinical pattern of drug induced cutaneous reactions pattern in Dermatology out Patient department of Mathura Das Mathur hospital. The pattern of cutaneous ADRs in our study was similar in many ways to the other studies conducted in India. A wide spectrum of cutaneous ADRs was observed ranging from trivial urticaria and maculopapular rash to severe reactions like Steven Johnson Syndrome and Toxic Epidermal Necrolysis. The commonest type of cutaneous ADR observed was Steven Johnson Syndrome (20.8%) followed by maculopapular rash (18.75%).

Antiepileptic drugs (35. %) were the most common drugs which were implicated for cutaneous ADRs in our study, followed by antibiotic (28%) and NSAIDs (11.6%). Most of the drug reactions were caused by phenytoin, carbamazepine and amoxicillin. Phenytoin and carbamazepine were responsible for most of the severe cutaneous ADRs like SJS, TEN and drug hypersensitivity syndrome. The reaction time for various ADRs ranged from few hrs to 70 days. In our study, dechallenge was done in 54 cases out of 60 cases and rechallenge was not attempted in any of the patients because of ethical reasons. A high proportioned these reaction (50%) were moderate, (31%) of these were severe because they require hospitalisation or increased the duration of stay in hospital or were life threatening in 1%. Principal offending drug is phenytoin. So, a good knowledge of the adverse drugs reactions, a careful history taking and a watchful approach while prescribing of new drugs can prevent many of the adverse drug reactions these facts justify the development of an intensive programme of pharmacovigilance.

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REFERENCES

1. WHO. International drug monitoring: The role of national centres. Tech rep ser WHO1972, no 498. Avaliable on internet at [http://www.who-umc.org/graphics/24756.pdf]
2. Edwards IR, Aronson JK; Adverse drug reactions: definitions, diagnosis, and management Lancet 2000; 356:1255–59.
3. Valeyrie-Allanore L, Sassolas B, Roujeau JC; Drug-induced skin, nail and hair disorders. Drug Saf 2007; 30:1011-30.
4. Ajayi FO, Sun H, Perry J; Adverse drug reactions: a review of relevant factors. J Clin Pharmacol 2000; 40:1093-101.
5. Ives TJ, Bentz EJ, Gwyther RE; Drug-related admissions to a family medicine inpatient service. Arch Intern Med 1987; 147:1117-20.
6. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ *et al.;* Adverse drug reactions as cause of admission to hospital: Prospective analysis of 18,820 patients. British Medical J 2004; 329:15-19.
7. Svensson CK, Cowen EW, Gaspari AA; Cutaneous drug reactions. Pharmacol Rev 2001; 53:357-7
8. Saha A, Das NK, Hazra A, Gharami RC, Chowdhury SN, Datta PK; Cutaneous adverse drug reaction profile in a tertiary care outpatient setting in Eastern India. Indian J Pharmacol 2012; 44:792-97.
9. Pudukadan D, Thappa DM; Adverse cutaneous drug reactions: Clinical pattern and causative agents in a tertiary care centre in South India. Indian J Dermatol Venereol Leprol 2004; 70:20-24.
10. Hunziker T, Künzi UP, Braunschweig S, Zehnder D, Hoigné R; Comprehensive hospital drug monitoring. Adverse skin reactions, a 20-year survey. Allergy.1997; 52:388-93.
11. Ghosh S, Leelavathi D, Padma GM Rao; Study and evaluation of the various cutaneous adverse drug reactions in kasturba hospital, Manipal. Indian J Pharma Sci 2006;68:212-14
12. Thong BY, Leong KP, Tang CY, Chng HH; Drug allergy in a general hospital: results of a prospective inpatient reporting system. Ann Allergy Asthma Immunol 2003;90:342-47
13. Sushma M, Noel MV, Ritika MC, James J, Guido S; Cutaneous adverse drug reactions: A 9-year study from a South Indian Hospital. Pharmacoepidemiol Drug Saf 2005; 14:567-70.
14. Sharma VK, Sethuraman G, Kumar B; Cutaneous adverse drug reactions: Clinical pattern and causative agents - a 6 year series from Chandigarh, India. J Postgrad Med 2001; 47:95-9.