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Original Article

DRUG-INDUCED CUTANEOUS REACTIONS: A PHARMACOVIGILANCE STUDY

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ABSTRACT

Objective: Drug-induced cutaneous reactions are common problem in our country and can range from simple rash to severe reactions. Early recognition of these reactions enables early identification and withdrawal of offending drugs, thereby reducing morbidity and mortality. So present study aimed to assess clinical pattern of drug-induced cutaneous reactions in Dermatology OPD.

Methods: This study was an open, non-comparative, non-interventional, observational study conducted on patients visiting dermatology department to see the clinical pattern of drug-induced cutaneous reactions. A 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 w preceding reactions and type of drug reactions.

Results: 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 reactions (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.

Conclusion: A good knowledge of ADRs, a careful history taking and watchful approach while prescribing of drugs can prevent many of adverse drug reactions. These facts justify the development of an intensive programme of pharmacovigilance.

Keywords: Adverse drug reactions, Pharmacovigilance, Antiepileptic drugs

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INTRODUCTION

The pharmaceutical industry has the main responsibility for the safety of medicines, from the beginning of drug development and thereafter throughout its life cycle. Modern medicine has changed the way in which disease is managed and controlled. However, despite all the benefits, evidence continues to show that adverse drug reactions are common but preventable cause of illness, disability and even death. Adverse drug reaction constitutes a major clinical problem in terms of an 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 in asymptomatic patient. Cutaneous reactions accounted for the majority of these adverse effects and can range from mild maculopapular rash to severe Toxic Epidermal Necrolysis (TEN). Epilepsy is one of the most common neurological disease. Adverse effects of antiepileptic drugs have a major impact on patient's quality of life and are responsible for a large number of treatment failures. Adverse effects of antiepileptic drugs (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 established as most people with epilepsy are treated as outpatients and are not hospitalized for either the epilepsy or for the adverse effects [1]. The exact incidence of adverse effects of AEDs has not been adequately documented for various reasons. The advances in technology may help us in improving the ability to predict and hence prevent the occurrence of some of the serious ADRs. One such example is the predicting 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 cases who are prescribed AEDs (carbamazepine, phenytoin etc.) The association between HLA-B*1502 expression and carbamazepine skin responses has been documented in India but the role of HLA testing in Indian populations needs to be clarified in larger groups of cases within the country [2].

According to the 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. Another description 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 pullout 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 boluses. For illustration, 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 goods, 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. 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 cases [4]. So present study aimed to assess clinical pattern of drug-induced cutaneous reactions in Dermatology OPD.

MATERIALS AND METHODS

This study was an open, non-comparative, non-interventional, observational study conducted on the patients visiting the dermatology outpatient department with any suspected cutaneous adverse drug reaction by the Department of Pharmacology, in collaboration Dermatology department, at Dr. S. N. Medical College, Jodhpur (Rajasthan) respectively for around 12 mo. Patients who do not gave written informed consent were then excluded in the study. This study protocol having approval number No. F.1/Acad/MC/JU/14/8339 dated 06-06-2014 was approved by the Department of Pharmacology and subsequently by the Institutional Ethics Committee of Dr. S. N. Medical College, Jodhpur, Rajasthan. Sixty patients prescriptions were taken on a randomly chosen date and all the patients visiting the dermatology outpatient department with any suspected cutaneous adverse drug reaction were included in this study. 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. ADRs were observed and recorded on adverse drug event reporting form for voluntary reporting of adverse drug events by healthcare professional. The proforma we used was prepared by Central Drug Standard Control Organization (CDSCO). Causality assessment was done according to Naranjo's Scale [5] and Severity assessment was done according to Modified Hartwig and Siegel Scale [6] of ADRs as shown in fig. 1 and 2.

Question	Yes	No	Don't Know
1. Are there previous conclusive reports on this reaction?	1	0	0
2. Did the adverse reaction appear after the suspected drug was administered?	2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonists was administered?	1	0	0
4. Did the adverse reaction reappear when the drug was readministered?	2	-1	0
5. Are there alternative causes that could on their own have caused the reaction?	-1	2	0
6. Did the reaction reappear when a placebo was given?	-1	1	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	1	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	1	0	0
9. Did the patient have a similar reaction to the same or similar drug in any previous exposure?	1	0	0
10. Was the adverse event confirmed by any objective evidence?	1	0	0

*Scoring: ≧9: definite, 5-8: probable, 1-4: possible, ≦0: doubtful

Fig. 1: Naranjo's scale

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

Fig. 2: Modified hartwig and siegel scale, *Mild= level 1 and 2, moderate= level 3 and 4, severe= 5, 6 and 7

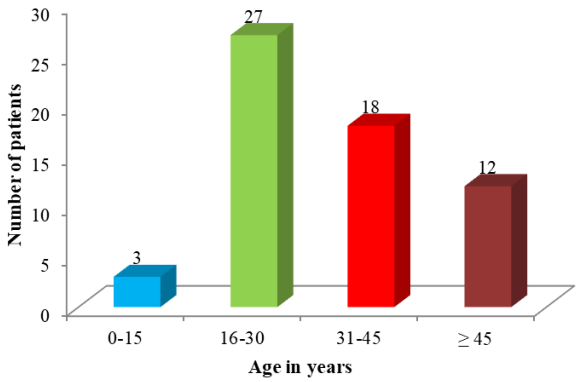

Fig. 3: Showing age distribution

STATISTICAL ANALYSIS

The data was entered Microsoft Excel and analysed using statistical Package for the Social Sciences software (SPSS 17.0). The number of ADRs observed and the prescribed drugs with which these ADRs were seen were expressed in percentages using chi square test.

RESULTS

A total of 60 patients with suspected cutaneous adverse drug reactions were recruited in this study period. Majority of patients in whom cutaneous ADRs were observed belonged to age group 16-30 y (45%) followed by 31-45 y (30%),>45 y (20%) and 0-15 y (5%), respectively (fig. 3). Out of total of 60 patients 38(63.33%) were males and 22(36.66%) were females (fig. 4).

The most common drug groups implicated and the common cutaneous ADRs are shown in fig. 5 to 6. 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, whereas different spectrum of cutaneous ADRs is shown in fig. 7

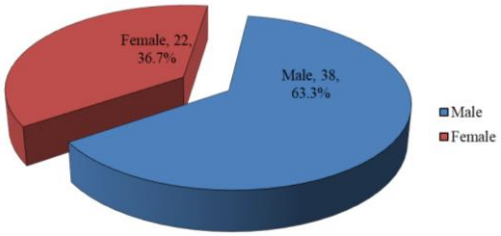

Fig. 4: Showing sex distribution

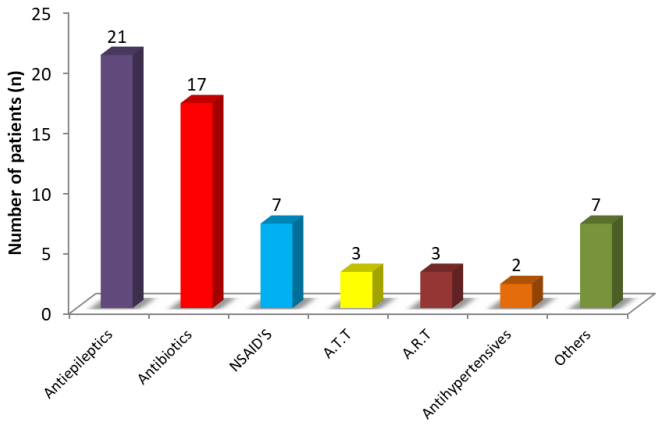

Fig. 5: Showing different drugs groups causing cutaneous ADRs: NSAIDs: Non-steroidal anti-inflammatory drugs, ART: Antiretroviral therapy. ATT: Antitubercular therapy

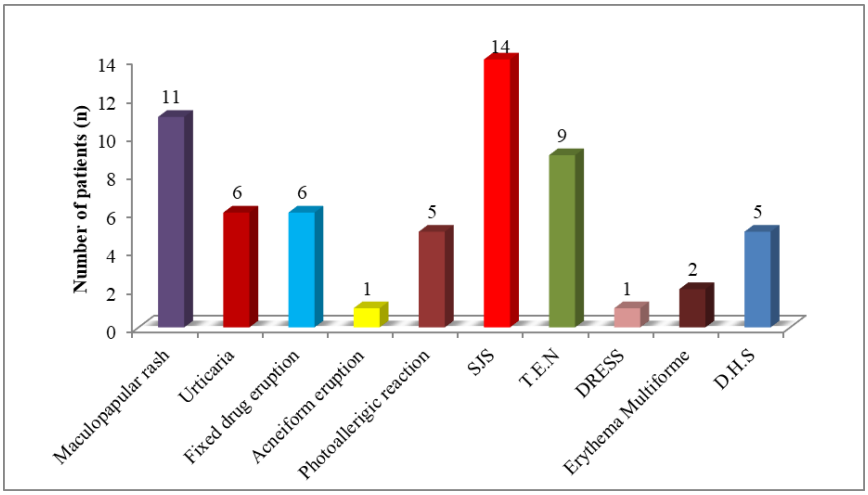

Fig. 6: Showing different types of cutaneous ADRs: MPR-Maculopapular rash URT-Urticaria FDE-Fixed drug eruption AFE-Acneiform eruptions PAR-Photo allergic reactions SJS-Steven Johnson syndrome TEN-Toxic epidermal necrolysis DRESS-Drug reaction with eosinophilia and systemic symptoms EM-Erythema multiforme DHS-Drug Hypersensitivity syndrome

Table 1: Naranjo's causality scale

No. of patients	ADR probability calassification	Naranjo's scale	Percentage
1	Definite	>9	1.6%
46	Probable	5-8	76.67%
13	Possibie	1-4	21.67%
0	Doubtful	0	0

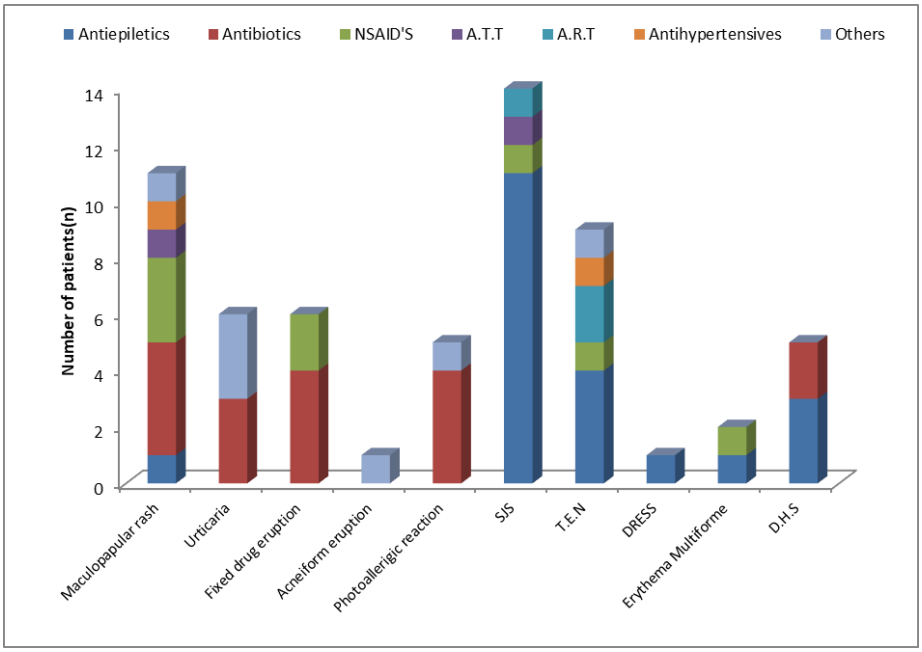

Fig. 7: Showing spectrum of cutaneous ADRs

Table 2: Modified hartwig and 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 reactions may affect any organ and the skin is a common site of presentation [7]. 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 [8]. Moreover, the development of a skin eruption is frequently cited as a reason for discontinuation of the treatment without completing therapeutic course [9]. 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 much higher incidence of TEN and SJS has also been reported from various other Indian studies conducted by Saha *et al.;* [10] Padukadan and Thappa [11]. However, the incidence of SJS and TEN was found to be lower in Western studies [12]. 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.* [13] in Manipal, India reported that maculopapular rash is the most common CADR. Antiepileptics were the most commonest 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 [10, 14]. In our study, antibiotics were mainly implicated in mild to moderate cutaneous ADRs like maculopapular rash, urticaria, fixed-dose eruptions and photoallergic reactions. Main antibiotics responsible for these ADRs were amoxicillin, cotrimoxazole, doxycycline and amoxicillin+clavulanic acid. Phenytoin and carbamazepine causes a wide spectrum of cutaneous ADRs among antiepileptics and 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 d with a mean reaction time of 14.53 d. 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 d and reaction time for SJS and TEN ranged from 8 to 70 d, whereas drug hypersensitivity reactions occurred after 10 to 38 d of taking the suspected medicines. This profile of reaction time is similar to the study by Sushma *et al.;* [15] (1-3 w) but slightly different from the study by Sharma *et al.;* (few hrs to 1 w) [16]. Considering 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 physician need to enquire about new drug but also it is important that doctor should be vigilant about CADR even to drugs which patients is taking from long time (especially for phenytoin, carbamazepine and allopurinol). In our study, dechallenge was done in 54 cases out of 60 cases and rechallenge was not attempted in any patient for ethical reasons. A few shortcomings of this observational study were also there as only a very limited number of patients were included in study, secondly drugs are prescribed in every department OPD so in future we can include other departments also to study the drug-induced cutaneous reactions.

CONCLUSION

Our study was mainly focused on the clinical pattern of drug induced cutaneous reactions pattern in Dermatology out Patient department. 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. A good knowledge of the adverse drugs reactions, a careful history taking and a watchful approach while prescribing of drugs can prevent many of the adverse drug reactions; these facts justify the development of an intensive programme of pharmacovigilance.

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AUTHORS CONTRIBUTIONS

All the authors Dr Arvind Narwat, Dr Mitali Dua, Dr Abhinav have equally made a substantial contribution in data collection, interpretation, drafting the article and finalizing the topic.

CONFLICT OF INTERESTS

Declared none

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