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A STUDY ON CUTANEOUS ADVERSE DRUG REACTIONS: CLINICAL PATTERN AND CAUSATIVE AGENTS

Veena DR, Cuckoo Aiyappa*, Anuradha HV, Sumathy TK
Department of Pharmacology & Dermatology, M S Ramaiah Medical College & Teaching Hospital, Bangalore - 560 054, India.

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ABSTRACT
Cutaneous eruptions are the most frequently reported adverse reactions to drugs. The pattern of cutaneous adverse drug reactions (ADRs) and the causative drugs keep changing every year.
The study was designed to ascertain the different clinical pattern of cutaneous ADRs and to determine the causative agents. A prospective hospital based study was carried out over a period of one year. The cutaneous ADRs of outpatients in the Department of Dermatology and inpatients transferred from other departments were recorded. Naranjos algorithm was used to determine the causality assessment. A total of 150 patients diagnosed to have cutaneous ADRs were included in the study. The most common type of cutaneous ADRs were maculopapular rash (34.7%), followed by urticaria (12.7%) and acneiform eruptions (10%). Antimicrobial agents (40.7%) were responsible for majority detected adverse drug reactions, followed by nonsteroidal anti-inflammatory drugs (18.7%), anticonvulsants (12%) and antihypertensives (10.7%). Altogether 146 reactions had probable and 4 reactions had possible causal association with the drug. A wide clinical spectrum of cutaneous ADRs ranging from mild maculopapular rash to serious Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) were observed. Most of these drug eruptions were caused by antimicrobial agents. The occurence of cutaneous ADRs in the present study was in concurrence to various studies conducted in India.

Keywords: *cutaneous; adverse drug reactions; drug eruptions; maculopapular rash.*

INTRODUCTION

Cutaneous Adverse Drug Reactions are the most frequently occurring adverse reactions to drugs. Most commonly used drugs have reaction rates above 1%[1]. The severity of such reactions ranges from mild to fatal ones.

Drug reactions may occur to any prescribed drug, over the counter medications and herbal products. The main drugs implicated are antibiotics and non-steroidal anti-inflammatory drugs[2]. A single drug may elicit more than one type of reaction. The mechanisms responsible for drug reactions are numerous and sometimes more than one mechanism may be operative.

Iatrogenic factors that lead to adverse drug reactions can include inappropriate dosage, inappropriate combination of drugs, and use of drugs not recommended for a particular age group. Most cutaneous adverse drug reactions are not associated with serious morbidity but are important as they are frequently the reason for discontinuation of drug therapy. The present study was undertaken to evaluate the different clinical patterns of cutaneous adverse drug reactions and to determine the causative drugs responsible for the above mentioned reactions.

METHODOLOGY

Source of Data

It was a prospective, hospital based study conducted in the Department of Dermatology at M.S.Ramaiah Medical College and Teaching Hospital, Bangalore after obtaining approval by institutional ethics committee. Inpatients and outpatients with suspected drug eruptions who were referred to the Department of Dermatology for evaluation were considered for the study.

Inclusion criteria

1. Patients with cutaneous adverse drug reactions who have documented evidence of having taken the suspected drug.
2. Patients of either sex.
3. All age groups.

Exclusion criteria

1. Cases associated with vaccines.
2. Over dosage
3. Patients on other systems of medicine- e.g. Homeopathy, Herbal, and Ayurveda.

Study Procedure

A total of 150 patients suspected of having cutaneous drug reactions seen in outpatients and inpatients of various departments were evaluated. In every case a detailed history was elicited regarding drug intake,

***Correspondence :** drcuckooa@yahoo.com

temporal correlation to drug intake and onset of symptoms, duration of reaction, morphology of eruption, associated mucosal or systemic involvement, improvement of lesions after dechallenge and previous allergic history. An informed consent was taken from each patient and a thorough clinical examination was conducted. The data was recorded on a pre-designed proforma.

If more than one drug was thought to be responsible, the most likely offending agent was noted and the impression was confirmed by subsiding of symptoms/ signs on withdrawal of the drug. All the information was carefully recorded in a pre-designed proforma. Naranjo's algorithm was used for causality assessment of adverse drug reactions (Table 1). It is a simple questionnaire that can be easily used bedside to perform causality assessment of adverse drug reactions. The algorithm consists of questions that yield the following associations between total score and causal relationship[3].

Table 1: Naranjo's Algorithm[4]

Sl.no	Question	Yes	No	Do not know
1	Are there previous conclusive reports on this reaction	+1	0	0
2	Did the adverse event appear after suspected drug was administered	+2	-1	0
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered	+1	0	0
4	Did the adverse reaction reappear when the drug was readministered	+2	-1	0
5	Are there alternative causes (other than the drug) that could 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 blood (other fluids) in concentration known to be toxic	+1	0	0
8	Was the reaction more severe when the dose was increased or less severe when dose was decreased	+1	0	0
9	Did the patient have a similar reaction to the same/similar drugs in any previous exposure	+1	0	0

Less than 0 points = doubtful; 1 to 4 points = possible; 5 to 8 points = probable; 9 or more points = definite

Statistical Analysis

The data was subjected to descriptive analysis. Since it is an observational study no statistical test was conducted. Data analysis was carried out using Statistical Package for Social Science (SPSS, V 10.5) package.

RESULTS

Out of 150 patients suspected of having cutaneous drug reactions majority of patients (28%) were in the age group of 21-30years. The mean age of patients was 34.5 years (range: 5– 77years) as depicted in Table 2. In this study, antimicrobial agents contributed to the largest number of cutaneous ADRs (40.7%), followed by NSAIDs (18.7%), anticonvulsants (12.0%) and antihypertensives (10.7%) as depicted in Table 3. Significant past history was present in 8 out of 150 cases (5.3%).

Maculopapular rash (34.7%) was the most common cutaneous ADR, followed by urticaria (12.7%) and acneiform eruptions (11.3%) as shown in Table 4.The most common drugs associated with maculopapular rash were the antimicrobial agents (61%) as shown in Fig 1. NSAIDs were associated with most of the drug induced urticaria as shown in Table 5.

Table 2: Age distribution of Cases

Age	Frequency	Percent
1-10 yrs	2	1.3
11-20 yrs	29	19.3
21-30 yrs	42	28.0
31-40 yrs	30	20.0
41-50 yrs	21	14.0
51-60 yrs	13	8.7
61-70 yrs	11	7.3
>70 yrs	2	1.3
Total	150	100.0

Table 3: Commonly Incriminated Drugs in Drug Eruptions

Drug	Frequency	Percent
Antimicrobials	61	40.7
NSAIDs	28	18.7
Anticonvulsants	18	12.0
Antihypertensives	16	10.7
Sulfonylureas	11	7.3
Corticosteroids	07	4.7
Oral contraceptive pills	05	3.3
Antipsychotics	02	1.3
Antineoplastic drugs	02	1.3
Total	150	100.0

Causality assessment with Naranjo's scale revealed that 146 cases had probable, 4 cases had possible causal relationship with the drug as shown in Fig 2.

Table 4: Types of drug Eruptions

Type of reaction	Frequency	Percent
Maculopapular reaction	52	34.66
Urticaria	19	12.66
Acneiform eruption	17	11.33
Drug hypersensitivity syndrome	14	9.33
Hyperpigmentation	13	8.66
Fixed Drug Eruptions	09	6.0
Photosensitivity	08	5.33
Oral Ulcers	08	5.3
Stevens- Johnson syndrome	04	2.66
Psoriasiform reaction	02	1.33
Toxic Epidermal Necrolysis	01	0.66
Purpura	01	0.66
Erythema multiforme	01	0.66
Vasculitis	01	0.66
Total	150	100

Table 5: Morphological types of cutaneous ADRs and suspected drugs

Types of cutaneous ADRs	Suspected drugs with frequency of occurrence	Total number of cases	Percent (%)
Maculopapular rash	Fluoroquinolones(21) β lactam antibiotics (10) NSAIDs (13) ACE inhibitors (5) anticonvulsants (1) nevirapine (1) antipsychotics (1)	52	34.66
Urticaria	NSAIDs (8), βblockers (5), macrolides (2), sulfonylureas(2), ACE inhibitors (2)	19	12.66
Acneiform eruptions	Corticosteroids (7), ATT (4), NSAIDs (3), OCPs (1), macrolides (1), antipsychotics (1)	17	11.3
SJS,TEN and DHS	Anticonvulsants (15), nevirapine (1), Piperacillin- tazobactam (1), ATT(1), fluoroquinolones (1)	19	12.66
Erythema multiforme	Amoxicillin (1)	01	0.66
Others- photosensitivity, FDE, vasculitis, hyperpigmentation, lichenoid eruptions, oral ulcers	Sulfonylureas (9), clotrimazine (5), NSAIDs (4), OCPs (4), fluoroquinolones (4), β lactam antibiotics (4), methotrexate (2), anticonvulsants (2), βblockers (2), tetracyclines (1), chloroquine (1), macrolides (1), ACE inhibitors (1), thiazides (1)	42	28.0
TOTAL		150	100

Fig. 1: Drugs causing maculopapular rashes

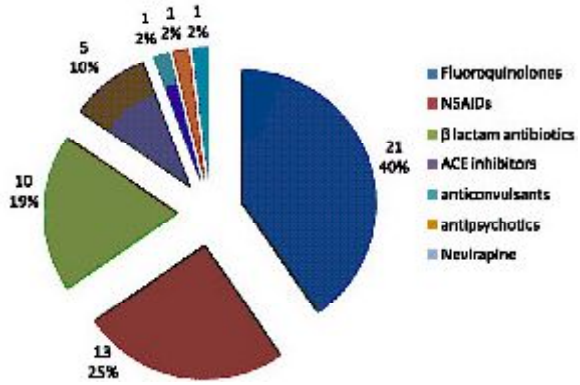
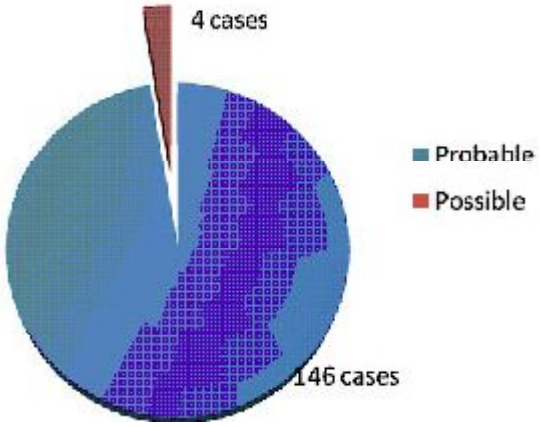


Fig. 2: Causality assessment



DISCUSSION

In the present study, polypharmacy was observed in 8% cases. In such cases, the most likely agents responsible for the reaction were noted and the impression was further confirmed by the subsiding of the rash on withdrawal of the drug. Polypharmacy can lead to drug interactions and thereby increase the rate of ADRs. Of the 150 cases, 8 patients had a similar cutaneous reaction in the past and 3 patients were prescribed the same drug despite the known past history.

Cutaneous ADRs can assume various morphological patterns. In the present study, maculopapular rash (34.7%) was the most common cutaneous ADR, followed by urticaria (12.7%) and acneiform eruptions (10.0%). A study from North India also reported maculopapular rash to be the most common type of cutaneous ADR[5].

Majority of the cutaneous ADRs were associated with oral administration of drugs (95.3%), followed by parenteral route (4.6%). The incubation period for all types of rashes ranged from one day to 3 months. The incubation period was 1-3 days for fixed drug eruption, 1-5 days for maculopapular rash, 1-2 weeks for SJS and TEN, 1-3 weeks for drug hypersensitivity syndrome (DHS), 3-8 weeks for photodermatitis and 4-10 weeks for hyperpigmentation. This is in accordance with the previous reports, which further confirm the causality of the drug[6].

The largest number of cutaneous ADRs were associated with the use of antimicrobial agents(AMAs) (40.7%), followed by NSAIDs (18.7%), anticonvulsants (12.0%) and antihypertensives (10.7%). A large study done in Italy also reported that AMAs were the most common cause of cutaneous ADRs[7]. Previous studies in India also have shown that AMAs are the major causative agents for cutaneous ADRs[7, 8].

Among the AMAs, cutaneous ADRs were commonly associated with fluoroquinolones (34.4%), followed by β lactam antibiotics (26.2%). But according to a report from Boston Collaborative Drug Surveillance Program, amoxicillin, trimethoprim-sulfamethoxazole and ampicillin had the highest reaction rates[9]. This could be attributed to wide spread use of fluoroquinolones or different trends in the use of AMAs in various regions. The most common drugs associated with maculopapular rash were the antimicrobial agents (61.5%). This finding is similar with another study done in India[10]. NSAIDs were associated with most of the drug induced urticaria (42%). This is in conformity with the findings of a study done in U.K[11]. According to Naranjo's algorithm 146 cases had probable, 4 cases had possible causal relationship with the drug.

Serious cutaneous ADRs (SJS, TEN, DHS) were recorded in 19(12.6%) cases. The incubation period varied from 2 days to one week. Most of these reactions (78.9%) were associated with anticonvulsants. One out of the 3 HIV positive patients, on therapy with nevirapine developed SJS.

Liver function abnormalities were present in most of the patients with DHS. Abnormal liver function tests also have been described as an independent indicator of the severity of a drug-induced cutaneous eruption[12].
Cutaneous drug reactions are a challenging diagnostic problem since they can mimic a large variety of skin diseases like viral exanthema, collagen vascular disease, psoriasis, etc. Furthermore, if a patient is on multiple drugs, the identification of the causative drug becomes much more complex. In most patients, the suspected drug was withdrawn and the skin lesions subsided within ten days. The development of skin eruptions is frequently cited as a reason for discontinuation of treatment. Rechallenge was not done in any of the cases due to ethical reasons.

Thus in this study, a wide clinical spectrum of cutaneous ADRs ranging from mild maculopapular rash to serious SJS and TEN was observed. New drugs associated with a high risk of such reactions can be identified, relabeled or withdrawn from the market only if clinicians recognize and report severe reactions to regulatory authorities and manufacturers[13].

Hence it is recommended that more studies are essential to create an awareness of possible ADRs, and to assist in the early recognition which in turn aids in the implementation of effective drug safety measures.

CONCLUSION

In this study, maculopapular rash was the most common cutaneous ADR and most of these drug eruptions were caused by AMAs. Amongst the AMAs, cutaneous ADRs were commonly seen with fluoroquinolones. Most of the serious ADRs were associated with anticonvulsant therapy. This study has provided baseline information about the prevalence of cutaneous ADRs and their morphological distribution amongst different age group, genders and causative drugs. It emphasizes the need for more extensive ADR monitoring in the hospital and will be useful in framing policies towards rational use of drugs.

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