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Cutaneous adverse drug reactions in a tertiary care hospital

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ABSTRACT

Introduction: Adverse drug reactions (ADRs) are major problem in drug therapy. Cutaneous ADRs are the most common ADRs.; Aim: To study drug induced Cutaneous adverse reactions and to establish the causal relationship.; Materials and methods: In the present study, 30 cutaneous ADRs were included, over a period of 8 months. Both outpatients and inpatients were included. Causal relationship was assessed by Naranjo algorithm. ADRs were categorized as definite, probable, possible and doubtful. All values were expressed in percentages.; Results: Out of total 30 patients, 20 were inpatients and 10 were outpatients. Common types of ADRs observed were Stevens-Johnson syndrome (26.6%) followed by fixed drug eruption (20%), and erythema multiforme (20%). More ADRs were noted with antimicrobial agents (53.33%) followed by anticonvulsants (16.6%), NSAIDS (13.33%), herbal drugs (13.33%) and food additives (3.3%).; Conclusion: Majority of ADRs were seen with antimicrobial agents, belonging to sulphonamide and quinolone group. Severe type of reactions observed were Stevens-Johnson Syndrome and erythema multiforme which occurred with antibiotics and anticonvulsant drug (phenytoin sodium).

Keywords: Cutaneous adverse drug reactions, antimicrobial agents, Stevens-Johnson Syndrome, fixed drug eruption.

INTRODUCTION

Adverse drug reactions (ADRs) are major problem in drug therapy. According to WHO, an adverse drug reaction is defined as “a response to a drug that is noxious and unintended and occurs at doses, used in man for prophylaxis, diagnosis, or therapy of a disease or for modification of physiological function [1]. Cutaneous ADRs are the most common ADRs and have become very common in recent times [2]. They are thought to occur up to 3% of medical inpatients [3].

There are several important predisposing factors for ADRs. Genetic factors may have an important role and patients who have a reliable history of drug allergy always need to be carefully monitored on the initiation of any drug, but particularly, those drugs which are commonly implicated in skin reaction. Hepatic disease, renal disease, systemic lupus erythematosus (SLE) and acute immunodeficiency syndrome (AIDS) are some of the disease states, associated with an increased risk of skin reactions [4].

In some cases, determination of serum or blood levels of drug may be useful to confirm the over dose of drug, at the time of ADR. Dechallenge (improvement after stopping of drug) and rechallenge (recurrence or exacerbation of reaction after reexposure to the offending drug) are also important to document. If no ADR occurs upon rechallenge, the drug can be continued, if clinically indicated. If an ADR does occur, both the severity of reaction and the need for the drug use should be assessed before a decision is made about its continuation or discontinuation [5,6].

A wide clinical spectrum of cutaneous ADRs, ranging from mild purpura to serious Stevens-Johnson syndrome (SJS) can be produced by many drugs. The incidence of developing cutaneous ADR increases with the number of drugs taken and some drug interactions may also contribute to the development of skin eruptions [7]. ADRs can also occur with herbal drugs. The use of herbal supplements has increased dramatically in recent years [8]. The centre for disease control and prevention reported that in 1999, 10% of adults used herbal medicines [9].

Administration of drug and occurrence of reaction should be assessed by causality assessment, by using various scales. The traditional approach by grading – definite, probable, possible, conditional, unlikely or doubtful remains useful. The time relation between the use of drug and occurrence of reaction should be done by causality assessment. There are decision aids available in the form of questionnaire or computerized spread sheet, which may be utilized as a database, to deal with the problem of ADRs [10,11,12].

A large number of new drugs are launched every year. Further there is limited information on the market penetration of new drugs and on their rational and safety prescribing. This study was designed to monitor drug induced cutaneous adverse reactions in patients in dermatology department and establish the causal link between the drug and reaction.

MATERIALS AND METHODS

The present study was conducted for a period of 8 months in the Department of Dermatology in collaboration with Clinical Pharmacology department at Osmania General Hospital, Hyderabad, Andhra Pradesh, India. Both inpatients and outpatients were included in the study. Informed consent was taken from the study subjects. Present and past history of drug intake, past history of allergic reactions, previous drug interactions, type of drug reactions, investigations and the treatment given to the patients were recorded in the case record form.

Degree of causality assessment was done by using Naranjo Algorithm Scale [12]. The scale consists of 10 questions. Each question was given a score and the total score was recorded for each patient and graded definite, probable, possible or doubtful (Table 1).
All values were expressed in percentages.

Table 1: Naranjo Algorithm (Causality Assessment Scale)

S. No		Yes	No	Do not know	Score
1	Are there previous conclusive reports on this reaction?	+1	0	0	
2	Did the adverse event appear after the 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 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 the 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 drugs in any previous exposure?	+1	0	0	
10	Was the adverse event confirmed by any objective evidence?	+1	0	0	
Total Score					

Causality assessment; 0 - Doubtful; 1-4 - Possible ; 5-8 - Probable; >9 - Definite

RESULTS

A total number of 30 patients with cutaneous ADRs were included in the study. There were 14 males and 16 females. Mean age of males was 35±17yrs and females was 29±17yrs. There were 20 inpatients and 10 outpatients in our study.

The number of cutaneous ADRs associated with individual drug groups were antimicrobials 16 (53.3%), anticonvulsants 5 (16.6%), non-steroidal anti-inflammatory drugs (NSAIDS) 4 (13.3%), herbal drugs 4 (13.3%) and food additives 1 (3.3%) (Table 2). Percentage of cutaneous ADRs occurred were Stevens-Johnson Syndrome (SJS) in 8 patients (26.6%), fixed drug eruption (FDE) in 6 patients (20%), erythema multiforme (EM) in 6 patients (20%), exfoliative dermatitis (ED) in 3 patients (10%), purpura in 2 patients (6.6%), drug induced hypersensitivity syndrome (DHS) in 2 patients (6.6%) , lichenoid eruption (3.3%), acneiform eruption (3.3%) and drug induced pemphigus (DIP) (3.3%) in one patient each respectively (Table 3).

Antibiotics: Majority of cutaneous ADRs were observed with antibiotics (53.3%).

Two patients on co-trimoxazole therapy presented with Stevens-Johnson Syndrome. One patient with exfoliative dermatitis and one with fixed drug eruption. One patient developed erythema multiforme with oral sulfadiazine.

Among fluoroquinolones, 5 patients developed ADRs. ADRs with ciprofloxacin were reported in 4 patients, which included erythema multiforme in 2 patients, SJS in 1 patient and exfoliative dermatitis in 1 patient. One case of erythema multiforme was noted with oral ofloxacin.

Cephalosporin induced ADRs were observed in 2 cases. One patient presented with erythema multiforme with cephalexin and SJS with cefotaxime was seen in one patient.

Furazolidone produced fixed drug eruption in one patient.

Table 2: Groups of Drugs involved in Cutaneous Adverse Drug Reactions (n=30)

S.No	Drug	Number of cases	Total	Percentage %
1	Fluoroquinolones a. Ciprofloxacin b. ofloxacin	 4 1	5	16.62
2	Sulfonamides a. Sulphadiazine b. Co-trimoxazole	 1 4	5	16.6
3	Anticonvulsants Phenytoin sodium	5	5	16.6
4	Herbal drugs	4	4	13.3
5	NSAIDS a. Nimesulide b. Diclofenac sodium	 2 2	4	13.3
6	Cephalosporin a. Cephalexin b. Cefotaxime	 1 1	2	6.6
7	Anti-tubercular drugs a. Streptomycin b. INH	 1 1	2	6.6
8	Antilepra drugs Dapsone	1	1	3.3
9	Food additive	1	1	3.3
10	Antidiarrhoeal Furazolidone	1	1	3.3

Table 3: Clinical Spectrum of cutaneous ADRs with implicated drugs (n=30)

Drugs	SJS	ED	Purpura	DHS	EM	FDE	LE	AE	DIP	Total	%
Chemotherapeutic agents										16	53.33%
Co-trimoxazole	2	1				1				4	
Cefotaxime	1									1	
Ciprofloxacin	1	1			2					4	
Dapsone				1						1	
Sulphadiazine					1					1	
Ofloxacin					1					1	
cephalexin					1					1	
Furazolidone						1				1	
streptomycin							1			1	
INH								1		1	
Anticonvulsants Phenytoin Sodium	3			1		1				5	16.6%
NSAIDS										4	13.33%
Nimesulide			1			1				2	
Diclofenac Sodium			1			1				2	
Others										5	13.33%
Herbal Drug	1	1			1				1	4	
Food additive						1				1	
Total	8	3	2	2	6	6	1	1	1	30	
%	26.6%	10%	6.6%	6.6%	20%	20%	3.33%	3.33%	3.33%		

SJS – Stevens-Johnson syndrome; ED – Exfoliative dermatitis; DHS – Drug hypersensitivity syndrome; EM – Erythema multiforme; FDE – Fixed drug eruption; LE – Lichenoid eruption; AE – Acneiform eruption; DIP – Drug induced pemphigus.

Anticonvulsants: Cutaneous ADRs with phenytoin sodium accounted for 16.6% (5 patients) in our study. It caused SJS in 3 patients, drug hypersensitivity syndrome in one patient and fixed drug eruption in one patient.

NSAIDS: They produced 13.3% (4 patients) of cutaneous ADRs in our study. Nimesulide caused purpura and fixed drug eruption in one patient each, respectively. Purpura in one patient and FDE in another patient were observed with diclofenac sodium.
Anti-tubercular drugs: ADRs with anti-tubercular drugs were 6.6% (2 patients). Streptomycin(SM) and Isoniazid (INH) produced lichenoid eruption in one patient and acneiform eruption in another patient, respectively.

Anti-lepra drugs: Drug hypersensitivity syndrome was detected in one patient (3.3%) with dapsone.

Herbal drugs: These constituted 13.3% of total cases. Four patients were presented with cutaneous ADRs, which included SJS, exfoliative dermatitis, erythema multiforme and drug induced pemphigus in one patient each.

Food additive: There was one case (3.3%) of FDE with food additive.

DISCUSSION

In the present study, all age groups were affected with cutaneous ADRs, with higher incidence in adult age group between 21-30 years. Higher incidence of cutaneous ADRs in adult age groups, ranging from 21-40 years, were reported in the previous studies,[13,14]. There were 16 (53%) females and 14 (47%) males in our study. Female preponderance was already reported in various studies,[2,15,16]. The present study conducted for a period of 8 months, showed a total of 9 types of cutaneous ADRs in 30 cases. Cutaneous ADRs were most commonly observed with antimicrobial agents (53.33%) in our study. A previous study reported that antimicrobials were the main group of drugs (42.6%) to cause different types of skin reactions,[13] supporting our study.

In the present study majority of cutaneous ADRs occurred with antibiotics (43.2%). Several studies reported that antibiotics were major causative agents to develop cutaneous ADRs,[17,18] and few studies had shown that antibiotics were responsible for 45% and 38.8% cases of cutaneous ADRs respectively,[14,19], which were consistent with our results. In our study sulphonamides (19.8%), fluoroquinolones (16.7%), and penicillins (6.7%) were the main antibiotics to cause cutaneous ADRs. Similar to this, previous studies reported that sulphonamides, penicillins and quinolones were found to be the major cause of cutaneous ADRs,[13,14,19]. We observed SJS (2 cases), ED (1 case) and FDE (1 case) with cotrimoxazole and EM (1 case) with sulphadiazine. One patient on furazolidone developed FDE in our study which may be due to structural similarity to sulphonamide. Sulphonamides have been documented to produce erythema multiforme, exfoliative dermatitis and SJS [20,21,22,23], supporting our findings. Cefotaxime caused SJS (1 case) and cephalexin caused 1 case of EM in our study. Similarly there were reports of maculopapular rash, urticaria and SJS with penicillins and cephalosporins observed in several studies [13,17,18,24]. Among fluoroquinolones, ciprofloxacin produced SJS (1 case), ED (1 case), DHS (1 case) and ofloxacin EM (1 case) in our study. Photosensitivity, hyper sensitivity reactions, erythema multiforme and several skin reactions have been reported with fluoroquinolones by several authors [2,24,25,26]. A higher number of cutaneous ADRs were found with newer drugs like cephalosporins and

fluoroquinolones when compared to the reports of previous studies documented with older antibiotics [14]. Our findings were consistent with results of earlier studies, implicating similar ADRs with antibiotics.

Incidence of cutaneous ADRs with SM and INH were 6.6% and produced lichenoid eruption (1 case) and acneiform eruption (1 case) in our study. Incidence of cutaneous ADRs with anti-tubercular drugs in several studies were 11% and 7.4% respectively [24,27]. In consonance with our study, lichenoid eruption with SM and acneiform eruption with INH were reported earlier [2,28,29]. Incidence of DHS (1 case) was observed in 3.3% with dapsone in our study. Previous studies showed similar type of reaction with dapsone 1.6%,[30] and 2.5% [2], which were lesser compared to our study.

Second major group of drugs involved in cutaneous ADRs were anticonvulsants and the incidence was 16.6% in our study. In several studies the incidence was reported as 23.8% and 25% respectively [19,24] which was higher than our study. We observed SJS (3 cases), DHS (1 case), and FDE (1 case) with pehnytoin sodium in our study. Similarly, several studies had shown that SJS, FDE and DHS were the main cutaneous ADRs seen with phenytoin sodium,[3,31,32]. We got ADRs only with phenytoin sodium, where as other studies reported ADRs with phenytoin as well as with carbamazepine [13,19,24].

In several studies, incidence of cutaneous ADRs with NSAIDS were 21%, 18% and 19% respectively [2,13,19]. The commonly implicated reactions were purpura, maculopapular eruption and FDE [2,3,13,19,32] and common drugs were ibuprofen [2] and acetaminophen [24]. In our study, incidence of cutaneous ADRs, with NSAIDS were 13.33%, which occurred with nimesulide (1 case) and diclofenac sodium (1 case), which was less when compared to the previous studies. We did not notice any cutaneous ADRs with ibuprofen or acetaminophen.

In the present study, herbal drugs caused 13.33% of cutaneous ADRs which included SJS (1 case), exfoliative dermatitis (1 case), erythema multiforme (1 case) and drug induced pemphigus (1 case). Cutaneous ADRs with herbal drugs were 4% in one study [24]. The incidence of ADR's to herbal drugs and indigenous medicines constitute a substantial high percentage in our study compared to existing literature. It further necessitates more studies for analysis of these drugs. Lack of literacy and medical record keeping leads to repeated administration of drugs which increase the incidence and severity of ADR's which necessitates patient education and avoidance of self administration and re-administration of drugs. Adverse drug reactions with herbal drugs are now receiving attention, formerly accorded only ADRs to drugs. Some herbal medicines in particular, ayurvedic remedies contain arsenic or mercury that can produce typical skin reactions. Other popular remedies that can cause dermatological side effects include St. John's wort, kava, aloe vera, eucalyptus, camphor, henna and yohimbine [33,34,35].

Ice cream ingestion caused FDE (1 case) in 3.3% of cases in our study and it can be due to presence of tartrazine in ice cream. It had been explained that ice cream consists of colouring and flavouring agents and these substances are prone to develop ADRs in certain individuals [36]. Additives and preservatives are common causes of uritcaria. The exact percentage of reactions to additives is not known, but is considered to be important in fewer than 10% of patients with chronic urticaria. Most frequently implicated food additives are tartrazine and other azo-dyes which can cause ADRs include amaranth and sunset yellow [2,37].

Several studies had reported that most common skin reaction was maculo papular rash with incidence of 42.7%, 31.57%, 39.5% and 21% respectively [14,16,19,24]. The commonest skin

reaction occurred in our study was SJS (26.6%). This was because our hospital is a tertiary care centre, where mostly severe cases come to the hospital. Incidence of SJS In several studies, was 22.22%, 19.5% and 28.1%, respectively [2,14,19]. Our results are consistent with the above studies. The most common drugs implicated to cause SJS, in our study were phenytoin sodium (10%) followed by co-trimoxazole (6.6%), cefotaxime (3.3%), ciprofloxacin (3.3%) and herbal drugs (3.3%). It had been reported that anti-convulsants were the most frequent drugs to cause SJS [13]. Similar to our study, in one study phenytoin sodium developed SJS in 9.6% of cases [19], where as in another study, SJS occurred most commonly with carbamazepine (24%) [18]. Life threatening cutaneous ADRs were reported to be more (43.8%) with anticonvulsants, in one study [13], where as we observed more of life threatening cutaneous ADRs, with antibiotics (13.3%), followed by anti-convulsants phenytoin sodium (10%) and herbal drugs (3.3%). Co-trimoxazole alone caused 6.6% of life threatening ADRs (SJS) in our study. SJS is associated with high morbidity, most common with sulpha drugs and is fatal in about 5.5% of cases [38]. Similarly, in our study, one patient on co-trimoxazole therapy expired due to development of SJS (3.3%).

Dechallenge of the offending drug was done in all cases after identification of ADRs and the patients were treated appropriately. Severe cases were managed and closely monitored until discharge. Rechallenge was not done in any case. In conclusion, the drugs causing ADRs were similar in many ways to those observed in other countries.

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