INTRODUCTION

Adverse reactions to drugs are very common in everyday medical practice. The side effects of a drug cannot be avoided. The incidence and clinical pattern of drug eruption depends on the choice and frequency with which different drugs are used.\(^1\) Most commonly used drugs have reaction rates above 1\%.\(^2\) The severity of such reactions ranges from mild to fatal. Drug reactions may occur to any prescribed drug, over the counter medications and herbal concoctions. The main drugs implicated are antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs).\(^3\) Adverse drug reactions (ADRs) place a considerable economic burden on the society. It has been estimated that 5–9% of all hospital costs are related to ADRs. Therefore, prior to the administration of any drug, risk and benefit factors should be seriously evaluated. ADRs are a frequently overlooked complication of drug therapy.

Drugs that have been used for long periods may cause new types of eruption that have not been observed previously. Prospective studies are the only way to determine the risk-benefits of medicines and true incidence of ADRs.\(^4\) We undertook a study to evaluate the different clinical patterns of cutaneous drug reactions (CADRs) observed in our center and to determine the causative drugs responsible for the CADRs.

MATERIALS AND METHODS

The study was conducted in the Department of Dermatology at Central Hospital, South Central Railway, Lagaluda, Secunderabad (Hyderabad), after obtaining permission from the Institutional Ethics Committee. Patients attending the outpatient and inpatient departments of Dermatology were recorded. Naranjo's algorithm was used to determine the causality assessment. Clinical pattern of these adverse drug cutaneous reactions was studied. Causality assessment was done with the help of Naranjo's algorithm. Most of these drug eruptions were caused by AMAs. The occurrence of CADRs in the present study was in concurrence to various studies conducted in India.

Key Words: Cutaneous adverse drug reactions, clinical pattern, naranjo's algorithm

ABSTRACT

Background: Cutaneous eruptions are the most frequently reported adverse reactions to drugs. The pattern of cutaneous adverse drug reactions (CADRs) and the causative drugs keeps changing every year. Objective: The study was designed to ascertain the different clinical patterns of CADRs and to determine the causative agents. Materials and Methods: A prospective observational nonrandomized hospital-based study was carried out over a period of 6 months. The CADRs as observed in the outpatient and inpatient Departments of Dermatology were recorded. Naranjo’s algorithm was used to determine the causality assessment. Clinical pattern of these adverse drug cutaneous reactions was studied. Causality assessment was done with the help of Naranjo’s algorithm. Results: A total of fifty patients diagnosed to have CADRs were included in the study. The most common type of CADRs was urticaria (30%) followed by fixed drug eruption (FDE) (24%) and maculopapular eruption (12%). Antimicrobial agents (AMAs) (48%) were responsible for majority of the detected reactions, followed by nonsteroidal anti-inflammatory drugs (24%), antihypertensives (8%), and antiepileptics (4%). A total of 41 reactions (82%) showed probable causal association, 4 reactions had possible association (8%), and 5 cases of cutaneous drug reaction (10%) showed definite causal association with the drug. Conclusion: A wide clinical spectrum of CADRs ranging from FDE to mild maculopapular rash to serious Stevens–Johnson syndrome was observed. Most of these drug eruptions were caused by AMAs. The occurrence of CADRs in the present study was in concurrence to various studies conducted in India.
to June 2011. A prospective, observational, nonrandomized hospital-based study was carried out to record various adverse cutaneous drug reaction patterns. Patients with CADRs who have documented evidence of having taken the suspected drug, patients of either sex, and of all age groups were included. Cases associated with vaccines, cutaneous reactions due to over dosages of the drugs, patients on other systems of medicine, for example, Homeopathy, herbal, Ayurveda, etc., were excluded. A total of fifty patients suspected of having cutaneous drug reactions were evaluated. In every case, a detailed history was elicited regarding drug intake, 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, previous allergic history, etc. An informed consent was taken from each patient and a thorough clinical examination was conducted. The data were recorded on a predesigned pro forma.

If more than one drug was thought to be responsible, the most likely offending agent was noted and the impression was confirmed by subsidence of rash on withdrawal of the drug. All the information was carefully recorded in a predesigned pro forma. Naranjo’s algorithm was used for causality assessment of ADRs [Table 1]. It is a simple questionnaire that can be easily used at bedside to perform causality assessment of ADRs. The algorithm consists of 10 weighted questions that yield the following associations between total score and causal relationship.15

Obtained score helps in predicting causal association of a drug to that of observed CADR. Scores are as follows: 0 points = doubtful; 1–4 points = possible; 5–8 points = probable; and 9 or more points = definite.

The data were subjected to descriptive analysis. Since it is an observational study, no statistical test was conducted.

RESULTS

Maximum study subjects were in the age group of 51–60 years, i.e., 40% followed by 20% in the age group of 31–40 years. Among the study subjects, male to female ratio was 0.9:1. The oldest patient in study was 80 years and the youngest was of 11 years. Age and sex distribution of patients in the study is shown in Table 2.

Proportion of patients who took single drug and multiple drugs was same, i.e., 50%. Onset of reaction in majority of the patients, i.e., 26 (52%) was between 24 h and 1 week, followed by <24 h and more than 1 week in 15 (30%) and 9 (18%), respectively, as shown in Table 3.

Gradual progression of symptoms after the onset of cutaneous drug reaction was seen in 84% while associated symptoms such as itching or burning were seen in 86% of the patients. Total duration of reaction was <1 week in 62% followed by more than 1 week in 38% of the patients. Itching was the predominant symptom in 78% of the study patients followed by burning in 40% of the patients. Multiple symptoms, i.e., fever, pain, itching, and burning were present in 38% of the study patients. History of similar episodes of cutaneous drug reaction to similar drug was present in 14% of the study patients.

Majority of CADRs comprised urticaria/angioedema cases (30%) followed by fixed drug eruption (FDE), i.e., 24%, acute generalized exanthematous pustulosis (AGEP) was the least in occurrence in our study (2%). Table 4 shows the distribution of various patterns of CADRs among the study patients.

Causality assessment was done with the help of Naranjo’s scale. Most of the study patients were in probable causality assessment of the Naranjo’s scale, i.e., 82%, followed by definite in 10% and possible in 8% of the patients. Results of causality assessment as done by Naranjo’s algorithm in different clinical types of CADR are shown in Table 5. Scale was most useful in establishing causality in cases of fixed drug reaction which demonstrated definite association in 33.33% cases of FDE. However, most of the CADRs (82%) were in probable causality assessment of the Naranjo’s scale.

Enalapril, lisinopril, furazolidone, β-lactam antibiotics, and NSAIDs caused urticarial eruptions. Ciprofloxacin was responsible for majority of FDRs. Cotrimoxazole, 

| Question                                                                 | Yes | No | Do not know |
|-------------------------------------------------------------------------|-----|----|-------------|
| Are there previous conclusive reports on this reaction?                  | +1  | 0  | 0           |
| Did the adverse event appear after suspected drug was administered?     | +2  | −1 | 0           |
| Did the adverse reaction improve when the drug was discontinued?         | +1  | 0  | 0           |
| Did the adverse reaction reappear when the drug was re-administered?    | +2  | −1 | 0           |
| Are there alternative causes (other than the drug) that could have caused the reaction? | −1  | +2 | 0           |
| Did the reaction reappear when a placebo was given?                     | −1  | +1 | 0           |
| Was the drug detected in blood (other fluids) in concentration known to be toxic? | +1  | 0  | 0           |
| Was the reaction more severe when the dose was increased or less severe when dose was decreased? | +1  | 0  | 0           |
| Did the patient have a similar reaction to the same/similar drugs in any previous exposure? | +1  | 0  | 0           |
| Was the adverse event confirmed by any objective evidence?               | +1  | 0  | 0           |
tetracycline, ampicillin, and paracetamol also caused FDR. Table 6 shows various drugs causing different types of cutaneous drug reaction.

Most of the CADRs were caused by antibiotics, i.e., 48%, followed by NSAIDs. A single drug can give rise to more than one morphological pattern of CADRs. Ibuprofen is the most common individual drug incriminated in the causation of CADRs which is 16%, followed by ciprofloxacin which caused 12%.

A total of 32% of the study patients had hemoglobin of <10 mg/dl. Leukocytosis was present in 8% of the study patients and eosinophilia was noted in 26% of the study patients suffering from cutaneous drug reaction. Oral provocation tests were done in consenting individuals with patients of fixed drug reaction, i.e., 14% and all were positive.

DISCUSSION

Any drug can cause ADR. Cutaneous reactions are the most common manifestations of ADRs. CADRs can be caused by a wide range of drugs. The spectrum of cutaneous manifestations ranges from simple maculopapular rash to life-threatening Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). A drug can produce different morphological types of reactions and different classes of drug can produce similar pattern of drug reaction. Some severe CADRs can result in serious morbidity and even death. Although cutaneous reactions are common, comprehensive information about their incidence, severity, and ultimate effects is often not available.

In this study, the frequency of CADRs was maximum in patients with age group of 51–60 years (40%), followed by 31–40 years (20%). This is in conformity with two studies which also observed that elderly being the most commonly affected. ADRs increases with age, this may be due to increased use of medications by elderly, increased potential for drug–drug interactions, and altered drug handling by the body (i.e., altered pharmacokinetics). However, a study done in South India and a study from North India reported that the most common age group

| Table 2: Age and sex distribution of study subjects |
|---------------------------------------------------|
| Age group (years)                  | Male (%) | Female (%) | Total (%) |
| 11-20                              | 0 (0)    | 2 (7.7)    | 2 (4)     |
| 21-30                              | 1 (4.2)  | 2 (7.7)    | 3 (6)     |
| 31-40                              | 4 (16.7) | 6 (23.1)   | 10 (20)   |
| 41-50                              | 5 (20.8) | 3 (11.5)   | 8 (16)    |
| 51-60                              | 10 (41.7)| 10 (38.5)  | 20 (40)   |
| 61-70                              | 4 (16.7) | 1 (3.8)    | 5 (10)    |
| 71-80                              | 0 (0)    | 2 (7.7)    | 2 (4)     |
| Total                              | 24 (100)| 26 (100)   | 50 (100)  |

| Table 3: Onset of reaction among study patients |
|------------------------------------------------|
| Onset of reaction                | Male (%) | Female (%) | Total (%) |
| <24 h                            | 7 (29.2) | 8 (30.8)   | 15 (30)   |
| 24 h to 1 week                   | 14 (58.3)| 12 (46.2)  | 26 (52)   |
| >1 week                          | 3 (12.5) | 6 (23.1)   | 9 (18)    |
| Total                            | 24 (100)| 26 (100)   | 50 (100)  |

| Table 4: Distribution of various patterns of cutaneous adverse drug reactions among study subjects |
|--------------------------------------------------------------------------------------------------|
| Diagnosis                                         | Male (%) | Female (%) | Total (%) |
| Acneiform eruption                                | 2 (8.3)  | 3 (11.5)   | 5 (10)    |
| Acute generalized exanthematous pustulosis        | 0 (0)    | 1 (3.8)    | 1 (2)     |
| Erythema multiforme                               | 0 (0)    | 2 (7.7)    | 2 (4)     |
| FDE                                               | 9 (37.5) | 3 (11.5)   | 12 (24)   |
| Hyperpigmentation                                 | 2 (8.3)  | 1 (3.8)    | 3 (6)     |
| Lichenoid eruption                                | 0 (0)    | 2 (7.7)    | 2 (4)     |
| Maculopapular eruption                            | 2 (8.3)  | 4 (15.4)   | 6 (12)    |
| SJS                                               | 2 (8.3)  | 2 (7.7)    | 4 (8)     |
| Urticaria + angioedema                            | 4 (16.7) | 1 (3.8)    | 5 (10)    |
| Urticaria                                         | 3 (12.5) | 7 (26.9)   | 10 (20)   |
| Total                                             | 24 (100)| 26 (100)   | 50 (100)  |

FDE: Fixed drug eruption, SJS: Stevens–Johnson syndrome

| Table 5: Cutaneous adverse drug reactions and Naranjo’s algorithm |
|---------------------------------------------------------------|
| Cutaneous ADR’s                                      | Definite (%) | Possible (%) | Probable (%) | Total (%) |
| Acneiform eruption                                    0 (0)         | 0 (0)        | 5 (12.2)     | 5 (10)     |
| Acute generalized exanthematous pustulosis          0 (0)         | 0 (0)        | 1 (2.4)      | 1 (2)      |
| Erythema multiforme                                  0 (0)         | 1 (25)       | 1 (2.4)      | 2 (4)      |
| FDE                                                 4 (80)        | 0 (0)        | 8 (19.5)     | 12 (24)    |
| Hyperpigmentation                                    0 (0)         | 0 (0)        | 3 (7.3)      | 3 (6)      |
| Lichenoid eruption                                   0 (0)         | 0 (0)        | 2 (4.9)      | 2 (4)      |
| Maculopapular eruption                               0 (0)         | 0 (0)        | 6 (14.6)     | 6 (12)     |
| SJS                                                 0 (0)         | 0 (0)        | 4 (9.8)      | 4 (8)      |
| Urticaria + angioedema                               0 (0)         | 1 (25)       | 4 (9.8)      | 5 (10)     |
| Urticaria                                           1 (20)        | 2 (50)       | 7 (17.1)     | 10 (20)    |
| Total                                               5 (100)       | 4 (100)      | 41 (100)     | 50 (100)   |

FDE: Fixed drug eruption, ADR’s: Adverse drug reactions, SJS: Stevens–Johnson syndrome
affected by cutaneous drug reaction was 20–39 years. This difference may be related to the regional variation in health care-seeking behavior of the population and type of patients attending the hospital. In our study, females experienced slightly more number of CADRs as compared to males (male: female ratio of 0.9:1). Similar findings were seen in studies done in India[6,10] and abroad.[12]

In the present study, polypharmacy was observed in 50% of the cases. In such cases, the most likely agent responsible for reaction was considered to be the cause of given cutaneous drug reaction based on a clinical experience of a dermatologist and a review of literature. This was further confirmed by subsidence of the rash on withdrawal of drug (dechallenge). Polypharmacy can lead to drug interactions and thereby increase the rate of ADRs. However, we observed the finding that the exact cause of drug reaction in a patient on multiple drugs is extremely difficult in the clinical practice, especially in a resource-limited setting like ours.

In the present study, the onset of reaction in majority of the study patients (52%) was between 24 h and 1 week, followed by <24 h in 30% of the patients. This is in concordance with the study done in North India, who described in their study a reaction time of 1–7 days.[11] The approximate time period for the development of different types of CADRs as described in the literature is as follows: Maculopapular rash <7 days, urticaria 7–21 days, SJS, TEN, electromagnetic field 1–3 weeks, drug hypersensitivity syndrome (DHS) 2–6 weeks, Photodermatitis up to 1 year, exfoliative dermatitis 1–6 weeks, and FDE 30 min to 16 h.[13] Our observations with regard to latency of drug reaction are concuring with similar observations by previous investigators. Gradual progression of symptoms was seen in majority (84%) of the patients. Total duration of drug reaction was <1 week in majority (62%) of the

| Table 6: Commonly incriminated drugs causing cutaneous adverse drug reactions |
|---------------------------------|----------------|---------------------------------|
| **Group (%)**                  | **Drugs (%)** | **Cutaneous ADR's**             | **Number of patients** |
|-------------------------------|--------------|---------------------------------|-----------------------|
| Antibiotics (48)              | Amoxicillin (8.4) | Maculopapular eruption        | 1                     |
|                               | Urticaria + angioedema | 1 |                       |
| Ampicillin (16.5)             | Maculopapular eruption | 3 |                       |
|                               | FDE           | 1 |                       |
| Augmentin (amoxicillin + clavulanic acid) (4.2) | Acute generalized exanthematous pustulosis | 1 |                       |
| Cefotaxime (4.2)              | Urticaria     | 1 |                       |
| Ciprofloxacin (25)            | FDE           | 6 |                       |
| Isoniazid (4.2)               | Acneiform eruption | 1 |                       |
| Clofazimine (8.4)             | Hyperpigmentation | 2 |                       |
| Minocycline (4.2)             | Hyperpigmentation | 1 |                       |
| Cotrimoxazole (20.7)          | FDE           | 3 |                       |
|                               | Maculopapular eruption | 1 |                       |
|                               | SJS           | 1 |                       |
|                               | FDE           | 1 |                       |
| Tetracycline (4.2)            | Erythema multiforme | 2 |                       |
|                               | Lichenoid eruption | 1 |                       |
| NSAIIDs (24)                  |                | 1 |                       |
|                               |                | 1 |                       |
|                               |                | 1 |                       |
|                               |                | 1 |                       |
| Diclofenac sodium (16.7)      | Urticaria     | 3 |                       |
|                               | Lichenoid eruption | 1 |                       |
| Paracetamol (8.3)             | FDE           | 1 |                       |
| Aspirin (8.3)                 | Urticaria     | 1 |                       |
| Anti-epileptic (4)            | Carbamazepine (50) | SJS |                       |
|                               | Phenytoin (50) | SJS |                       |
| Anti-hypertensive (8)         | Enalapril (50) | Urticaria + angioedema | 2 |                       |
|                               | Losartan (25) | Urticaria + angioedema | 1 |                       |
|                               | Lisinopril (25) | Urticaria | 1 |                       |
| Others (16)                   | Oral contraceptive pills (12.5) | Acneiform eruption | 1 |                       |
|                               | Furazolidone (37.5) | Urticaria | 3 |                       |
|                               | Prednisolone (37.5) | Acneiform eruption | 3 |                       |
|                               | Allopurinol (12.5) | SJS | 1 |                       |

ADR: Adverse drug reaction, FDE: Fixed drug eruption, NSAIIDs: Nonsteroidal anti-inflammatory drugs, SJS: Stevens-Johnson syndrome

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cases. Associated symptoms in the form of itching, burning, fever, and combination of these symptoms were seen in 86% of the study patients.

Of the 50 cases, 40% (20) patients gave a history of previous systemic illness. Multiple medical comorbidities increase the chance of developing adverse drug eruptions. This is because of increased intake of various drugs for these associated comorbidities and possible drug reactions among various drugs. ADRs are influenced by several factors such as prolonged hospital stay, the classes of drug used, and polypharmacy. Our study also confirms these findings. History of similar cutaneous reaction in the past was present in 14% of the patients and all of them were prescribed with the same drug/class of drug without attaching significance to past history by physicians. For causality assessment, Naranjo’s algorithm was used. This consists of a simple questionnaire which can be easily used in our clinical practice. Other causality assessment scales used in previous studies being WHO protocol and Kramer algorithm. According to Naranjo’s algorithm, 41 cases (82%) had probable, 5 cases (10%) had definite, and 4 cases (8%) had possible causal relationship with the drug in the present study. Objective tests for diagnosis of ADR have been given importance in Naranjo’s scale. However, there are no specific tests for the diagnosis of CADR. Bioanalytical methods measure blood level of drugs by utilizing various methods such as high-performance liquid chromatography, liquid chromatography–mass spectrometry, liquid–liquid extraction, solid phase extraction, and protein precipitation. These tests are not universally available in India. Similarly, its utility in actual practice is not known due to lack of experience of the above-mentioned tests. Mere presence or elevated drug levels may not be an indicator of their role in the causation of CADR. Histopathology is more helpful in our setup for making a diagnosis of CADR such as fixed drug reaction, SJS/TEN, lichenoid drug reaction, psoriasiform drug reaction, AGEP, and DHS.

Absolute eosinophil count was elevated in 26% of the patients in our study, with values more than 300 cells/mm³. These raised values were seen mostly in patients of urticaria and SJS. Elevated peripheral eosinophil count is an uncommon finding in cutaneous drug eruptions and its presence or absence is of little importance in excluding or confirming the diagnosis. However, a study done in South India demonstrated consistently higher absolute eosinophil counts in serious CADRs and concluded that absolute eosinophil counts may be useful in assessing the prognosis early in the disease course.

CADRs can assume various morphological patterns. In the present study, urticaria was the most common reaction followed by FDE and maculopapular eruption. Two studies from India reported FDE to be the most common type of CADR. The largest number of CADRs were associated with the use of antimicrobial agents (AMAs) (48%), followed by NSAIDs (24), and antihypertensives (8%). A large study done in Italy also reported that AMAs were the most common cause of CADRs. Previous studies in India also have shown that AMAs are the major causative agents for CADRs. Among the AMAs, CADRs were commonly associated with penicillin group of antibiotics followed by cephalosporins. This is in concordance with a report from the Boston collaborative drug surveillance program. However, in studies done in other parts of India, cotrimoxazole continues to be the commonly incriminated AMA. This could be attributed to the wide spread use of β-lactam antibiotics in our setup or different trends in the use of AMAs in various regions. Anyhow, the use of cotrimoxazole has declined in the recent past, hence the offender has given place for other AMAs.

The most common group of drugs associated with FDE were AMAs, ciprofloxacin was the common agent (50%) among AMAs to cause FDE followed by cotrimoxazole in 25% of the cases. This is in conformity with the reports of ciprofloxacin being emerging as the most common cause of FDE. However, other studies done in India report sulfonamides being the most common cause of FDE. This difference may be due to the different prescribing habits in our hospital. NSAIDs were associated with the majority of drug-induced urticaria, i.e., 50%. This is similar with the findings of a study done in India and the UK. Serious CADRs (SJS) were recorded in 8% of the patients. The reaction time varied from 2 days to 1 week. Most of the reactions (75%) were associated with anticonvulsants such as phenytoin and carbamazepine (aromatic antiepileptics). Similar findings have been reported by a study done in North India. Complications were seen in patients with SJS and included ocular involvement and oral candidiasis. Thus, our study had a wide clinical spectrum of CADRs ranging from mild FDE, maculopapular rash to serious SJS.

Severe reactions are unlikely to be detected in premarking clinical trials because of low frequency of such severe reactions (<1 reaction/5000 exposed patients). 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. In India, the data about adverse drug event can be reported, and information about specific drug reaction can be asked at websites such as http://www.mspcindia.org/dic and http://www.cdsco.nic.in. 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**

Our study has provided baseline information about the proportion of CADRs in our practice and their morphological distribution among different age group, genders, and causative drugs. It emphasizes the need for more extensive ADR monitoring in the hospital and will be useful in generating more data about ADR. We recommend that prescription patterns of drugs in a particular hospital setup should be monitored on a regular basis, preferably by a clinical pharmacologist.

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**Conflicts of interest**

There are no conflicts of interest.

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