

A Study of Cutaneous Adverse Drug Reactions in a Tertiary Care Centre in Central Andhrapradesh, South India

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Abstract

Background Cutaneous adverse drug reactions (CADR) are common, accounting 10-30% of reported adverse drug reactions. Severe and potentially life-threatening reactions may occur in approximately 1 in 1000 hospital patients. There is a spectrum of cutaneous adverse drug reactions varying from transient maculopapular rash to fatal toxic epidermal necrolysis (TEN). The most common morphological types of cutaneous ADRs range from maculopapular, urticaria/angioedema to fixed drug eruptions, and the common incriminating drug groups remain antimicrobials, anticonvulsants and non-steroid anti-inflammatory drugs (NSAIDs). **Aims:** To determine the prevalence of cutaneous adverse drug reactions among the patients attending KIMS, Amalapuram. **Methods:** **Type of study:** The study is a hospital based cross sectional study.

Duration: December 2018 - September 2020. **Place:** This study was conducted in Konaseema institute of medical sciences and research foundation & research foundation, Amalapuram, East Godavari, and Andhra Pradesh. **Method of collection:** Data will be collected after obtaining informed/written consent from the patient. Detailed history, clinical examination and relevant laboratory investigations will be done. The data will be entered into a case record form specially designed for the study and statistical analysis will be done. **Results:** In our Study 0.17% was the overall incidence of Cutaneous drug reactions during this period found in this study, females are outnumbered, The most common cutaneous adverse drug reactions were FDE 58 (46.77), followed by Maculopapular Drug Rash 18 (14.51%), Acneiform Eruption 10 (8.06%). **Conclusion:** The overall incidence in this study was 0.17%.

Keywords: Drugs, Cutaneous adverse drug reactions, FDE, Incidence.

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Introduction

An adverse drug reaction (ADR) is an undesirable clinical manifestation resulting from administration of a particular drug[1]. Cutaneous adverse drug reactions (CADR) are common, comprising 10-30% of reported adverse drug reactions. Most drug eruptions are mild, self-limited and generally, resolve after stopping the causative drug. Severe and potentially life-threatening reactions may occur in approximately 1 in 1000 hospital patients[2].

There is a spectrum of cutaneous adverse drug reactions varying from transient maculopapular rash to fatal toxic epidermal necrolysis (TEN)[3]. The most common morphological types of cutaneous ADRs range from maculopapular, urticaria/angioedema to fixed drug eruptions, and the common incriminating drug groups remain antimicrobials, anticonvulsants and non-steroid anti-inflammatory drugs (NSAIDs)[4,5].

Adverse drug reactions (ADRs) constitute one of the most important causes of morbidity, hospitalization, increased health expenditure and even death[6-9]. However, when drugs are marketed and used

extensively, new adverse events come to light. It is estimated that only 50% of the undesirable reactions can be detected during the pre-marketing clinical trials[10,11]. The dermatological manifestations of adverse drug reactions are more frequent. Studies have found that the incidence of cutaneous adverse drug reactions (CADRs) in developed countries as 1 to 3 %, while the incidence in developing countries is higher, between 2 to 5%[12]. Clinicians come across many instances of suspected CADR's in different forms. Hence, familiarity with these conditions to enable early diagnosis and prompt withdrawal of the causative drug to prevent mortality[12] Also, knowledge of drugs that can cause cutaneous adverse drug reaction can help physicians in choosing safer drugs and therefore can be helpful to society at-large.

The prevalence, clinical patterns of CADR and their causative drugs vary among different populations[7,8]. Hence we are conducting this study to determine the epidemiological and clinical patterns of cutaneous adverse drug reactions in our population as this knowledge is important to identify and treat the patients at the earliest and to prevent recurrences .

Aims and Objectives of the Study

1. To determine the prevalence of cutaneous adverse drug reactions among the patients attending KIMS&RF, Amalapuram.

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2. To study the clinical pattern of various cutaneous adverse drug reactions.
3. To compare this study with similar other studies done in India and abroad.
4. To ascertain the various causative drugs responsible.

Materials and Methods

- **Type of Study:** The study will be a hospital based cross sectional study.
- **Duration of Study:** December 2018 - september 2020
- **Place of Study:** This study will be conducted in Konaseema institute of medical sciences and research foundation & research foundation, Amalapuram, East Godavari, and Andhra Pradesh.
- **Source of Data:** Patients attending to dermatology out- patient department and in-patients of other departments in KIMS, Amalapuram, with cutaneous adverse drug reactions form the subject of the study.
- **Method of Collection of Data:** Data will be collected after obtaining informed/written consent from the patient. Detailed history, clinical examination and relevant laboratory investigations will be done. The data will be entered into a case record form specially designed for the study and statistical analysis will be done.
- **Inclusion Criteria:** Patients attending KIMS, Amalapuram, with cutaneous adverse drug reactions.

- **Exclusion Criteria:** Patient who is not giving informed consent.

Following Investigations Will be Done as and When Required

- Complete heamogram.
- Random Blood Glucose level.
- Complete urine examination.
- Liver Function Tests, Renal Function Tests.
- HIV Test.
- Pus for Culture and sensitivity.
- Skin Biopsy.
- Serum electrolytes.
- Chest X-ray PA view.
- Ultrasound abdomen.

Results

Out of 71,536 patients who attended SKIN OPD during the study period of 18 months a total of 124 patients diagnosed with cutaneous drug reactions, fulfilling the inclusion criteria were included in the study. 0.17% was the overall incidence of Cutaneous drug reactions during this period found in this study.

In our study Highest number of cases was seen in 21-30 years age group 41 (33.06%), followed by 31-40 years 38 (30.64%), 41-50 years 20 (16.12%), 51-60 years 9 (7.25%), 11-20 year 8(6.45%), >61 years 5 (5.03%), <1 and 1-10 years 1 (0.80%) respectively.

In our study A total of 124 patients had cutaneous adverse drug reactions, female patients (66 cases) out numbered males (58 cases)

Table 1: Distribution of Various Cutaneous Adverse Drug Reactions

S. No	Type of Cutaneous Adverse Drug Reactions	Frequency (%)
1	Acneiform Eruption	10 (8.06%)
2	Drug induced pigmentation	3 (2.41%)
3	DRESS	4 (3.22%)
4	EMF	2 (1.61%)
5	Exfoliative dermatitis	3 (2.41%)
6	FDE	58 (46.77%)
7	Hand- Foot Syndrome	1 (0.80%)
8	Lichenoid Eruption	3 (2.41%)
9	Maculopapular Drug Rash	18 (14.51%)
10	Phototoxic Reaction	2 (1.61%)
11	Purpura	2 (1.61%)
12	SJS	4 (3.22%)
13	SJS /TEN overlap	2 (1.61%)
14	TEN	2 (1.61%)
15	Urticaria	10 (8.06%)

The proportions of various cutaneous adverse drug reactions are shown in Table 1. The most common cutaneous adverse drug reactions were FDE 58 (46.77), followed by Maculopapular Drug Rash 18 (14.51%), Acneiform Eruption 10 (8.06%), (6.45%), Urticaria 10 (8.06%), DRESS and SJS 4 (3.22%), Drug induced pigmentation, Exfoliative Dermatitis, Lichenoid Eruption 3 (2.41%), EMF, Phototoxic reaction, Purpura, SJS /TEN overlap, TEN 2 (1.61%), Hand- Foot Syndrome 1 (0.80%). In the present study, FDE include bullous FDE, Urticaria include Urticaria + Angioedema.

In our study Out of 124 cases, 15 patients had severe cutaneous adverse drug reactions (SCAR) in the form of DRESS, Exfoliative dermatitis, SJS, SJS/TEN OVERLAP and TEN.

In our study Out of total 124 patients, mucosal involvement was in 44(35.48%), 28 [22.58%] cases had oral mucosa involvement,

4(3.22%) patients had genital involvement, 12[9.67%] had both oral and genital mucosal involvement.

In our study Recurrence was seen in 17 (13.7%), Maximum number of recurrences were seen with FDE followed by urticaria.

In our study the above four classes of drugs were encountered .Out of 124 cases, 67 (54.3%) cases were due to antimicrobials including 9 cases due to ATT, 19 cases were due to NSAIDs, 11 cases were due to anticonvulsants and remaining 27 cases were due to other drugs.

More number of cutaneous reactions were seen with Fluoroquinolones 25 (20.16), followed by NSAIDs 19(15.32%), Anticonvulsants 11(8.87%), penicillins 9(7.25%), cephalosporins 8(6.45), and Tetracycline 3(2.41%).

Table 2: Drugs Commonly Involved in Cutaneous Adverse Drug Reactions

S. No	Drugs	Number of Cases	Percentage
1	Aceclofenac	1	0.80%
2	Aceclofenac + Paracetmol	1	0.80%
3	Allopurinol	1	0.80%
4	Ambroxol	1	0.80%

5	Amoxicillin	6	4.83%
6	Ampicillin	1	0.80%
7	Apixaban	1	0.80%
8	Aspirin	2	1.61%
9	ATT	8	6.45%
10	Carbamazepine	3	2.41%
11	Cefixime	3	2.41%
12	Cefoperazone+Sulbactam	1	0.80%
13	Cefpirome	1	0.80%
14	Ceftriaxone	2	1.61%
15	Cephalexin	1	0.80%
16	Cephalosporin	1	0.80%
17	Chloroquine	2	1.61%
18	Ciprofloxacin	9	7.25%
19	Clopidogrel	1	0.80%
20	Cotrimoxazole	4	3.22%
21	Cyclophosphamide	1	0.80%
22	Dapsone	1	0.80%
23	Diclofenac	4	3.22%
24	Griseofulvin	1	0.80%
25	Efavirenz	3	2.41%
26	Enteroquinol	1	0.80%
27	Ibuprofen	4	3.22%
28	Isoniazid	1	0.80%
29	Linezolid	1	0.80%
30	Methyl Prednisolone	9	7.25
31	Metronidazole	4	3.22%
32	Naproxen	1	0.80%
33	Norfloxacin	3	2.41%
34	Norfloxacin + Metronidazole	1	0.80%
35	NSAID	7	5.64%
36	Ofloxacin	12	9.67%
37	Paracetamol	6	4.83%
38	Paracetmol+Tramadol	1	0.80%
39	Penicillin	1	0.80%
40	Phenytoin	8	6.45%
41	Piperacillin+Tazobactam	1	0.80%
42	Sorafenib	1	0.80%
43	Tetracycline	2	1.61%

As shown in table 2 a total of 43 drugs were seen out of these Ofloxacin was the most common drug causing cutaneous adverse drug reactions with 12 cases, second common drugs were methyl Prednisolone and Ciprofloxacin with 9 cases, ATT and phenytoin in 8 cases each, NSAIDs with 7 cases, Amoxicillin and paracetamol in 6 cases each, diclofenac, cotrimoxazole, Ibuprofen, Metronidazole in 4 cases, Norfloxacin, Carbamazepine, Cefixime, efavirenz in 3 cases each, tetracycline, Chloroquine, Aspirin in 2 cases each, Sorafenib, Piperacillin + Tazobactam, Paracetmol + Tramadol, Norfloxacin + Metronidazole, Linezolid, Isoniazid, dapsone in 1 case each.

In our study Drug Reaction time, it is the time taken for the reaction to appear since the last exposure of the suspected drug. This was found to be 3 days in FDE, 7 days in TEN, 5.25 days in SJS, 33 days in exfoliative dermatitis.

In our study maximum number of cases were seen in patients taking drugs for diarrhea.

Clinical Photographs



Fig. 1: Generalized FDE



Fig. 2: SJS



Fig. 3: SJS/TEN Overlap

Discussion

Incidence of CADR

Out of total 71,536 total patients attending dermatology OPD during the study period of 18 months, 124 were diagnosed with cutaneous adverse drug reactions which constitute 0.17%. The incidence of ACDRs has been found to be 0.17% in a study by chatterjee et al[11] which is similar to our study. The incidence was little high in the studies done by Abanti saha et al¹² (0.27%) and choon et al[13] (0.86%).

Age distribution of various cutaneous adverse drug reactions

The age of the patients ranged from 6 months to 75 years. The majority of patients (41 patients or 33.06%) fall in the age group from 21-30 years followed by age group 31-40 years (38 patients or 30.64%). Likewise, 21-30 year age group patients formed the majority in the studies done by Ruchika Nandha et al[14] and Satyendra Kumar et al[15]. In a study by Tejashwani et al[16] majority of patients fall in the group 31-40 years (24.44%). In a study by Sultana et al[17] majority of patients were above 60 years of age (34.6%).

Gender distribution in cutaneous adverse drug reactions

In our study, females 66 (53.22%) were affected more than males 58 (46.77%) with male : female ratio of 1:1.01. Similarly, in the study done by Ruchika Nandha et al[14] and Saritha et al[18], 47 (51.7%)

were females and 44 (48.3%) were males with male to female ratio of 0.93:1, which is slightly lesser than the present study. Predominance of males was reported in few studies. In a study by Niharika jha et al[19] males were affected more than females with males:female ratio of 1.32:1 which is in contrast to our study. Equal ratio has also been reported in other studies. Khot Anant et al[20] showed a total of 70 patients had CADR, out of which 23 were males & 47 were females (male to female ratio was 1:2) which was slightly higher than the present study.

Clinical types of cutaneous adverse drug reactions

The most common cutaneous drug reaction in this study was FDE (46.77%) which was similar to the study done by Rohini Sharma et al⁷ (33.3%), Nivetha T et al[29], Satyendra Kumar et al[15] (45.71%) and Thappa et al[22] (31.1%).(Fig.1) In a study done by Niharika Jha et al[19] (46.64%) and Choon et al[13] (42.3%), maculopapular drug rash was the commonest cutaneous drug reaction, whereas in our study Maculopapular rash was seen in 18 [14.51%] patients and was the second commonest drug reaction following FDE. In a study by Khot Anant et al[14], urticaria (37.14%) was the commonest cutaneous adverse drug reaction whereas it was the third common CADR in this study (8.06%). DRESS cases were 4 [3.22%] in number but in a study by Shear et al[23] 9% of cases were due to DRESS which is higher than our study. SJS constituted 4[3.22%] cases, but was only 3% in a study by Raksha MP et al[24]. TEN

cases were 2 [1.61%] in number but only 1% in a study by Raksha MP et al[24] which is lesser than our study. EMF cases were 2[1.61%] in our study but 6.7% in the study by Thappa et al[22] which is more when compared to our study. Acneiform eruptions were 10 [8.06%] in number whereas Thappa et al[22] recorded 3.3% which is lesser than our study.

Out of 124 cases in this study, 15 cases(12.09%) were severe cutaneous adverse drug reactions which included DRESS (26.6%), Exfoliative dermatitis (20%), SJS (26.6%), SJS/TEN overlap (13.3%) and TEN (13.3%) (Fig. 2 & 3). In a study by Niharika Jha et al[19], SCARs accounted for 4.65% which was lesser than the present study. Whereas in a study by Sasidharan Pillai et al[18], SCARs accounted 13.20% which was slightly higher than our study.

Site of Mucosal involvement in various types of cutaneous adverse drug reactions

Out of total 124 patients, mucosal involvement was in 44(35.48%) cases in this study which is higher than the study by Faisal et al[25] where about 32.7% of the patients (68/208) had mucosal involvement, the manifestations of which varied according to the type of rash. In this study 28 [22.58%] cases had oral mucosa involvement, 4(3.22%) patients had genital involvement, 12[9.67%] had both oral and genital mucosal involvement. In a study by Niharika Jha et al[19], mucosal involvement was seen in 27.52% which was lesser than this study.

Recurrent episodes in various types of cutaneous adverse drug reactions

Out of 124 patients 19 [15.32%] patients had recurrent episodes which are lesser than in a study by Thappa et al[22] where of the 90 consecutive patients, 25(27.7%) had consumed the same drug earlier, 13 (14.44%) had a similar cutaneous reaction earlier and 12 (13.33%) had no reactions. In a study by Tejashwani et al[26] mucosal involvement was seen in 18.88% which is higher than this study.

Various Drug classes involved in cutaneous adverse drug reactions

In this study the various drug classes that caused adverse drug reaction were:

The commonest offending drug class in this study was antimicrobials (54.3%) which is similar to the studies done by Nivetha T et al[21] (56%), Niharika Jha et al[19] (64.7%), Chatterjee et al[11] (34.1%), Thappa et al[22] (58.8%) and Choon et al[13] (77.1%). In a study by Tejashwani et al[26], NSAIDs (16.66%) were the most common offending drug class whereas in this study, NSAIDs (15.32%) were second most common drug class causing cutaneous drug reaction. In a study by Sultana et al[16], anticonvulsants (26.9%) were the commonest offending drug class whereas in this study, anticonvulsants (8.87%) were the third most common drug class causing cutaneous drug reaction.

Drugs commonly involved in cutaneous adverse drug reactions:

In the present study, the commonest drug causing cutaneous adverse drug reactions was Ofloxacin, recorded in 12 cases (9.67%) followed by ciprofloxacin and methyl prednisolone in 9 cases each (7.25%). In a study by Van der Lindin et al[17] the most frequent reactions were observed in patients receiving Ofloxacin, which is similar to our study but Thappa et al[22] observed 7.8% cases for Ofloxacin which is lesser than our study.

Limitation of this study was the sample size, maybe due to under-reporting & at times the patients will consult a general practitioner for an adverse drug reaction, there is no way how we can track them.

Summary

- Out of 71,536 patients who attended SKIN OPD during the study period of 18 months a total of 124 patients diagnosed with CDR, fulfilling the inclusion criteria were included in the

study. 0.17% was the overall incidence of CDR found in this study during this period.

- Highest number of cases were seen in 21-30 years age group 41 (33.06%).
- Female patients are more than males with males 58 (46.77%) and females 66 (53.22%).
- The most common cutaneous adverse drug reactions were FDE 58 (46.77%), followed by Maculopapular Drug Rash 18 (14.51%), Acneiform Eruption 10 (8.06%), Bullous FDE 8 (6.45%), Urticaria 10 (8.06%), DRESS and SJS 4 (3.22%), Drug induced pigmentation, Exfoliative Dermatitis, Lichenoid Eruption 3 (2.41%), EMF, Phototoxic reaction, Purpura, SJS /TEN OVERLAP, TEN 2 (1.61%), Hand- Foot Syndrome 1 (0.80%).
- Among the individual CADR, FDE was most commonly caused by Fluoroquinolones.
- Out 124 cases, 15 cases were severe cutaneous drug reactions which included 4 cases of DRESS, 3 cases of Exfoliative dermatitis, 4 cases of SJS and 2 cases of SJS/TEN overlap and TEN each.
- a total of 49 drugs were found responsible for cutaneous drug reactions, of these Ofloxacin was the most common drug causing cutaneous adverse drug reactions with 12 cases, second common drugs were methyl Prednisolone and Ciprofloxacin with 9 cases, ATT and phenytoin in 8 cases each, NSAIDs with 7 cases, Amoxicillin and paracetamol in 6 cases each, diclofenac, cotrimoxazole, Ibuprofen, Metronidazole in 4 cases each, Norfloxacin, Carbamazepine, Cefixime, efavirenz in 3 cases each, tetracycline, Chloroquine, Aspirin in 2 cases each, Sorafenib, Piperacillin + Tazobactam, Paracetamol + Tramadol, Norfloxacin + Metronidazole, Linezolid, Isoniazid, dapsone in 1 case each.
- Oral Mucosal involvement was most commonly seen with NSAIDs followed by Metronidazole, Phenytoin, Norfloxacin, and Ofloxacin in succession.

Conclusion

The overall incidence in this study was 0.17%. This may represent just the tip of an iceberg as many cases do not present to the opd due to lack of awareness, negligence or they will consult a general practitioner for a Cutaneous adverse drug reaction .

Knowledge of various clinical patterns of cutaneous adverse drug reactions and causative drugs is important to the clinicians, which aids in early detection of the adverse event and helps in reducing the morbidity and mortality associated with it.

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