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Original Research Article

Unraveling the tapestry of adverse cutaneous drug reactions: A clinico-epidemiological study

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ABSTRACT

Background: It is widely acknowledged that adverse drug responses on the skin can cause serious complications. Up to 2% of all adverse cutaneous medication eruptions are severe and life-threatening, however the majority of these reactions are benign. In order to quickly diagnose these grave cutaneous eruptions and start the necessary treatment, physicians should be aware of certain warning signs. To understand the causative drug, meticulous history and complete clinical examination is the key
Objective: Primary objective is to find the common group of drugs causing adverse cutaneous drug reactions. Secondary objectives are to study their morphology, gender and age distribution.
Materials and Methods: The cross-sectional study involved 130 patients. Informations including relevant history, clinical examination details, and drugs taken were noted in the pretested proforma. Quantitative and qualitative data were collected and graphically analysed. Data was studied under various aspects which included causative drugs, clinical presentation, age and gender ratio. SPSS Version 21.0 was used for most analysis and Microsoft Excel 2010 for graphical representation.
Results: Maculopapular rash, acneiform eruptions, urticarial rash, exfoliative dermatitis and fixed drug eruptions were the commonest forms of clinical presentations seen in our study. The cutaneous drug reactions were classified as per the study of Agarwal et al.
Conclusion: The limitations of treating adverse cutaneous drug reactions are the varied range of clinical symptoms, the complexity of the various drug-host interactions, and the relative scarcity of laboratory tests that are available for any conclusive and confirmatory drug-specific testing. That's why knowledge of clinical presentations and common drugs causing it is a must.

1. Introduction

Drugs are substances that can heal, control, or prevent diseases. Negative drug responses occur when a drug causes an unwanted or detrimental consequence (ADRs). Roughly 5% of all hospitalizations are due to them.[1] An adverse cutaneous response caused by a drug is any change in the structure or function of the skin, its appendages, or mucous membranes.[2,3] The incidence of Cutaneous adverse drug reactions among both outpatients and hospitalized patients in the Indian population was found to be 9.22 per 1,000.[4] Up to 2% of all adverse drug eruptions are severe and life-threatening. Hence their sound knowledge is of key importance to save lives with the earliest interventions possible.

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2. Materials and Methods

This is a cross sectional study of 130 patients with clinical diagnosis of cutaneous adverse drug reaction conducted over a period of 17 months from January 2021 to June 2022 at a tertiary care centers' dermatological outpatient department from south india. The study was commenced after acquiring clearance from the Institutional Ethics Committee. Informed oral and written consent were taken from patients and confidentiality of the information obtained was assured throughout the study. Information of all the patients including relevant history, clinical examination details, and drug therapy were noted in the pretested proforma. List of drugs taken before the appearance of reaction, whether monotherapy or polytherapy, presenting complaints, period, duration of symptoms, severity, the reason for drug intake, history, and drug-involved were recorded.

Complete general and dermatological examination of all the cases was done including morphology and distribution of skin lesion and serial clinical pictures. The cutaneous drug reactions were classified as per the study of Agarwal et al.[4] who classified as maculopapular rash, fixed drug eruptions, urticarial eruption, erythema multiforme, Steven Johnson syndrome, acute generalised exanthematous pustulosis, toxic epidermal necrolysis, DRESS, Exfoliative dermatitis and statistical analysis was made for all the quantitative and qualitative datas.

2.1. Statistical analysis

All the data was noted down in a pre-designed study proforma. Qualitative data was represented in the form of frequency and percentage. Quantitative data was represented using Mean ± SD. Results were graphically represented where deemed necessary. SPSS Version 21.0 was used for most analysis and Microsoft Excel 2010 for graphical representation.

3. Results

This cross- sectional study was conducted on 130 patients of adverse cutaneous drug reactions visiting the skin out - patient department and it yielded the following results:

In our study, the most common age group to be affected was from 21-30 years [Figure 1]. The most common presentation [Table 1] was maculopapular rash (20%) which was followed by acneiform eruptions (14.6%) , urticarial eruptions (12.3%), exfoliative dermatitis (10.7%), fixed drug eruptions (10.0%), angioedema (12%), erythema multiforme (6%), lichenoid rash (6%), DRESS (4%), Steven Johnson syndrome (3%), generalized pruritus (3%), bullous disorder (3%), oral ulcers (2%), AGEP (2%),Toxic epidermal necrolysis (1%).

Maculopapular rash was seen in almost all age groups making it the largest in number. The most common lesions [Figure 1] seen in age group of 11-20 years was urticaria, in 21-40years was maculopapular rash, 41-50years was exfoliative dermatitis.

The common age group for fixed drug eruptions were found to be 21-30 years. Cases of DRESS and Steven Johnson syndrome were seen in age group of 21-30 years.

The most common group of causative drugs [Table 2] were 30% with antibiotics, 29% with NSAIDs, and 21% with anticonvulsant drugs. Ciprofloxacin was the commonest antibiotic causing equally 8.4% of cases in males and females in our study followed by 4.6% with amoxicillin and 4.6% with ceftriaxone. NSAIDs implicated in our study were 16.9% cases with diclofenac, 5% of cases with paracetamol, 6.9% with ibuprofen. Commonest anticonvulsant in our study was found to be phenytoin with 14.6% of cases followed by 3.8% cases caused by carbamazepine. In our study, we saw that diclofenac caused the majority of adverse reactions causing most commonly urticarial eruptions.

4. Discussion

An adverse cutaneous response is an undesirable change in the skin, its appendages, or mucous membranes that occurs after pharmaceutical exposure.[3] About 2%-3% of all hospitalized patients have an adverse cutaneous response to their medication in which only around 2 percent of skin responses are life-threatening. Recent data on the epidemiology of ACDRs are few, however some studies show the incidence of ACDR in impoverished countries like India in 2-5% of in-patients[4,5] due to easily available over the counter medications, while others showed in 1-3% in industrialized countries.[6] The common age group for fixed drug eruptions were found to be 21-30 years which was different from a study done by Anandhi et al.[7] where they found the majority of cases of FDE to fall under 40-50 years.

The number of females in our study were 71(54.6%) and 59 (45.3%) number of males. However, during the study done by Ruchika Nandha et al of the total 91 cases reported 47 (51.7%) were females and 44 (48.3%) were males which was consistent with our ratio

Mucosal involvement was seen in 15.4% of females and 13.5% of males. Koregol S et al[8] in their study reported cutaneous involvement without involving mucosa in half of the cases, likewise 48 percent had both cutaneous and mucosal involvement.

In our study, there were 53% females and 45.37% males. In our study, the most common age group involved was between 31 to 40 years which had 26.9% of our cases.

Thappa et al[8] in their study showed fixed drug eruptions to be present in 32 percent of their cases. Maculopapular rash was seen in 13 percent in their study which is less than in our study. Urticarial lesions were reported in 8 percent in their study. DRESS was reported in 4% in our study whereas Shear et al in their study reported little higher in

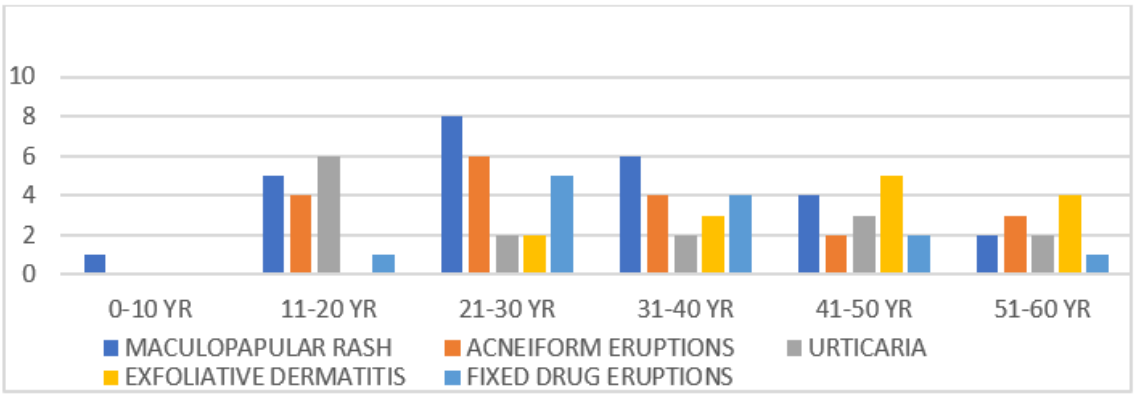

Figure 1: Distribution of age group and common presentations

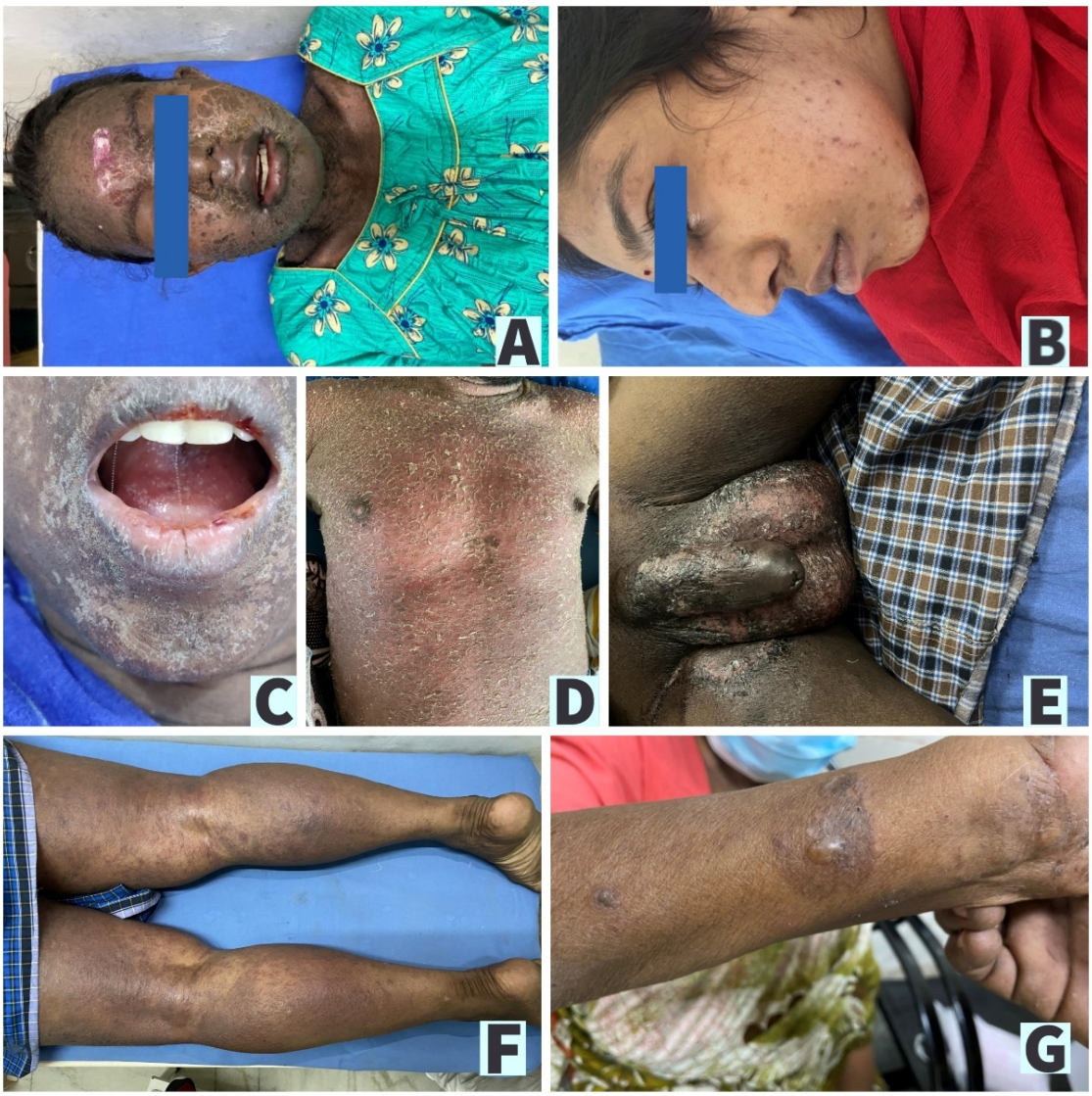

Figure 2: (Clockwise A to G); A: Drug related eosinophilia and systemic symptoms; **B:** Acneiform eruptions; **C:** Oral ulcers; **D:** Drug induced erythroderma; **E:** Steven johnson syndrome; **F:** Maculopapular rash; **G:** Bullous fixed drug eruption

Table 1: Distribution of participants according to presentation

Type of reaction	Number of cases	%	Males	%	Females	%
Maculopapular	26	20.0%	16	27.1%	10	14.0%
Acneiform eruptions	19	14.6%	10	16.9%	9	12.6%
Urticarial eruption	16	12.3%	6	10.1%	10	14.0%
Exfoliative dermatitis	14	10.7%	6	10.1%	8	11.2%
Fixed Drug Reaction	13	10.0%	6	10.1%	7	9.8%
Angioedema	12	9.2%	8	13.5%	4	5.6%
Erythema Multiforme	6	4.6%	2	3.3%	4	5.6%
Lichenoid rash	6	4.6%	2	3.3%	4	5.6%
DRESS	4	3.0%	0	0%	4	5.6%
Steven Johnson Syndrome	3	2.3%	1	1.6%	2	2.8%
Generalized Pruritus	3	2.3%	2	3.3%	1	1.4%
Bullous disorder	3	2.3%	0	0%	3	4.2%
Oral ulcers	2	1.5%	0	05	2	2.8%
Acute Generalized Exanthematous Pustulosis	2	1.5%	2	3.3%	0	0%
Toxic Epidermal Necrolysis	1	0.7%	0	0%	1	1.4%
Total	130		59 (45.3)		71 (54.6)	

Table 2: Distribution of the study participants based on the list of drugs involved

Causative drugs	Total	%	Male	%	Female	%
Diclofenac	22	16.9	8	13.5	14	19.7
Paracetamol	7	5.3	2	3.3	5	7.0
Ibuprofen	9	6.9	7	11.8	3	4.2
Phenytoin	19	14.6	14	23.7	5	7.0
Carbamazepine	5	3.8	2	3.3	3	4.2
Febuxostat	2	1.5	0	0	2	2.8
Nitrofurantoin	2	1.5	0	0	2	2.8
Ciprofloxacin	11	8.4	5	8.4	6	8.4
Methylprednisolone	10	7.6	2	3.3	8	11.2
Isoniazid	2	1.5	2	3.3	0	0
Amoxicillin	6	4.6	2	3.3	4	5.6
Acyclovir	2	1.5	1	1.6	1	1.4
Griseofulvin	1	0.7	1	1.6	0	0
Metronidazole	1	0.7	0	0	1	1.4
Enalapril	5	3.8	2	3.3	3	4.2
Dapsone	3	2.3	1	1.6	2	2.8
Chloroquine	1	0.7	1	1.6	0	0
Mefenamic acid	4	3.0	0	0	4	5.6
Norfloxacin	3	2.3	1	1.6	2	2.8
Doxycycline	3	2.3	2	3.3	1	1.4
Ceftriaxone	6	4.6	2	3.3	4	5.6
Methotrexate	2	1.5	1	1.6	1	1.4
Benzathine penicillin	2	1.5	2	3.3	0	0

their study. SJS was found in 3 in our study. Similar results were reported by Raksha et al. Toxic epidermolysis case was the rarest in our study (1%) which is also as same as Raksha et al (1%). Urticaria (17.3%) and fixed drug eruption (33%) were described as the most prevalent adverse reactions to drugs by Sharma et al.[8] Maculopapular rash was reported only in 13 percent in their study which is very less as compared to our study. Patel and Marfatia reported findings similar to Sharma et al study. Tank et al. discovered that 7.5% of patients had acneiform eruptions.[6]

Maculopapular drug eruption was the most common ACDR in a research by Rajendran et al, occurring in 31.5% of patients. FDE occurred in 13.4% of patients and erythema multiforme in 6.5% of patients. Antimicrobials were responsible for 40% and 57% of instances of maculopapular drug eruption and erythema multiforme, respectively; anticonvulsants were responsible for 22% and 15%. Again, antimicrobials were the leading cause of

FDEs (48%), followed by analgesics (31%). The majority of lesions were located on the face, upper limbs, and lower limbs. 31% of total patients displayed mucosal involvement.[9]

Ciprofloxacin was the commonest drug causing maculopapular reactions in our study. Other causes for maculopapular rash included phenytoin, amoxicillin, ciprofloxacin, cefixime, acyclovir, griseofulvin. Cotrimoxazole was found to cause both Maculopapular rash and FDE.

In a study by Thappa et al,[8] Cotrimoxazole was the leading agent in FDEs (29.5%) which differed from our study. Acneiform eruptions were seen to be caused by methylprednisolone in 13.8% of cases and few cases of isoniazid and diclofenac.

Phenytoin caused maculopapular rash, erythroderma and single cases of DRESS and TEN.

In a study by Noel et al,[10] phenytoin caused maximum of maculopapular rashes which was in contrary to our study where ciprofloxacin caused maximum of them. Amoxicillin was found to cause FDE in 2 cases. It also caused maculopapular rash and urticaria. In a study by Ghosh et al,[11] amoxicillin was the leading agent for maculopapular rash which differed from our study. Paracetamol caused fixed drug eruptions, urticarial rash and angioedema.

Chatterjee et al.[12] conducted a data analysis, revealing that urticaria and fixed drug rashes constituted the predominant morphological reaction-types. The primary culprits identified were carbamazepine and phenytoin. The study categorized the prevalent offending drug groups as antimicrobials (34.10%), anticonvulsants (32.88%), and anti-inflammatory drugs (21.51%). Less frequent offenders included antipsychotics, antidepressants, antihypertensives, oral contraceptives, antidiabetics, insulin, vaccines, radio contrasts, pancreatic enzyme supplements, homeopathic, and ayurvedic preparations. The top offending drugs were carbamazepine (16.23%), phenytoin (15.15%), and cotrimoxazole (13.53%), with antimicrobials being the most frequently implicated drug group. Various studies indicate that the prevalent morphologic patterns consist of exanthematous, urticarial and/or angioedema, fixed drug eruption, and erythema multiforme.[12] Additionally, some studies have highlighted exanthematous eruption as the most common type of drug eruption.[13,14] With regards to disease distribution for which the causative drugs were taken, myalgia was the commonest in females and seizure disorder in males. Around 20 percent females ingested drugs for headache. However, Koregol S et al[15] reported maximum drug reactions reported were seen for drugs taken for upper respiratory tract infections followed by seizure disorder.

5. Conclusion

The early diagnosis of the ACDR, the identification of the offending drug, and the prompt omission of it hold the key to care and the prevention of severe drug reactions. This requires all practising physicians, not just dermatologists to be knowledgeable about these disorders in order to identify them quickly and be equipped to treat them appropriately. We all agree that it is practically most challenging to find the causative drug when the patient is on multiple drugs. The diagnosis of ACDR is thus solely based on clinical judgement in practice which necessitates periodic elaborate publications in this regard.

6. Source of Funding

None.

7. Conflict of Interest

None.

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