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FREQUENCY OF CLINICAL SPECTRUM OF ADVERSE CUTANEOUS DRUG REACTIONS AND THEIR CAUSATIVE AGENTS

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Abstract:
Drug reactions are undesired reactions that develop after the administration of the drug which is not the pharmacodynamic effect of the drug. It is seen that 10-30 % of all the reported cases of adverse drug reactions are cutaneous adverse drug reactions (CADR). We carried out this study to ascertain the frequency of the clinical spectrum of adverse cutaneous reactions and the provoking causative drugs.
Our study comprised of seventy patients who met the inclusion criteria. Biodata, demographic data and clinical details which included clinical features, duration of symptoms, history of drug ingestion and the type of drug ingested was also recorded. The CADR were diagnosed on the basis of clinical examination and histopathological grounds where required by expert dermatologists. History of drug use was recorded. Data was entered and analyzed using SPSS version 21.

Among the valid responses the mean age of the patients was 35.84 years with females preponderance71.43%. Most commonly found eruption was maculopapular rash 21.4%, followed by erythema multiforme (EM) 20.0%, and fixed drug eruption (FDE) 14.2%. Among the known drugs, antibiotics were the most common 41.82%, followed by NSAIDs 29.09% and anti-epileptics, 14.55%.

The clinical spectrum of CADR varies from mild skin maculopapular rashes to severe life-threatening cutaneous reactions with multi-organ involvement The pattern of ACDRs and the drugs causing them is remarkably different in ourpopulation. Knowledge of these drug eruptions, the causative drugs and the prognostic indicators is essential for the clinician.

Keywords: drug rash, erythema multiforme, cutaneous adverse drug reactions, fixed drug reaction, non steroidal anti inflammatory drugs.

INTRODUCTION:

Drug reactions are undesired reactions that develop after the administration of the drug which is not the pharmacodynamic effect of the drug. It is seen that 10-30 % of all the reported cases of adverse drug reactions are cutaneous adverse drug reactions (CADR)[1]. The incidence of CADR reported in developed countries is 1-3% and in developing countries is higher, 2-5%. Although majority of the cases are of cutaneous drug reactions but they are under reported and the exact pathogenesis is yet to be addressed. There is a wide variation in the clinical spectrum and presentation of CADR ranging from mild maculopapular rash to highly severe toxic epidermal necrolysis (TEN)[2]. These drug reactions have resulted in morbidity as well as mortality both in outdoor and indoor patients. It is noted that most of the adverse drug reactions are minor like fixed drug eruption, acneiform eruptions, lichenoid eruptions which are usually self-limiting, but sometimes severe and life threatening reactions like Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) can also arise, which range from 2.6% to 7% of all drug reactions[2, 3,4.] The diagnosis of CADR is usually made on clinical history and examination but a histopathology maybe warranted in some cases. In the current study, conducted in Pakistan in 2021, with 192 cases in total, the most common CADR was maculopapular rash, which accounted for the overall 69.9% of the cases[5]. The second most common form of CADR was acneiform eruption (25.91%).

In an Indian study with a total of 54 patients, the incidence of CADR was 0.09%. the most frequently encountered CADR was fixed drug eruption (FDE) noted in 35.2% cases. The most commonly encountered culprit drug was antibiotics (39%), followed by non-steroidal anti-inflammatory drugs (NSAIDS) (24%)[6]. According to the Naranjo's Probability scale it was observed that most cases of probable (68.5%) CADRs were of moderate severity (90.7%) [7].

It is imperative to create awareness regarding the culprit drugs to allow the physicians to choose safer medicines. Our study aims to determine the frequency of CADR in our population. We also plan to identify the clinical spectrum of CADR with their association with the commonly reported culprit drugs.

MATERIAL AND METHODS:

We did a cross-sectional study which was conducted in the Department of Dermatology, Civil Hospital Karachi for the duration of one year from June 2021 to May 2022. The sample size was calculated via non-probability consecutive sampling technique and was 73 patients with the expected frequency of 5%, at a confidence interval of 95% and 5% margin of error. The patients included in this study were of both sexes aged greater than 18 years. Patients were diagnosed with minor skin reactions like maculopapular rash, acneiform eruptions, FDE, lichenoid reactions to severe types like erythema multiforme, Steven Johnson syndrome, and toxic epidermal necrolysis. The patients whom we excluded from the study were pregnant or breastfeeding women, patients with pyrexia of unknown origin, and patients on systemic steroids for some cutaneous or systemic conditions. An informed consent was also taken from the participants of the study. Biodata, demographic data and clinical details which included clinical features, duration of symptoms, history of drug ingestion and the type of drug ingested was also recorded. The CADR were diagnosed on the basis of clinical examination and histopathological grounds where required by expert dermatologists. History of drug use was recorded. Data was collected by the principal investigator and recorded on the predesigned proforma. Data was entered and analyzed using SPSS version 21. Frequencies and percentages were computed for qualitative variables like gender, cutaneous eruption (maculopapular rash, acneiform eruptions, FDE, lichenoid erythema multiforme/Steven Johnson syndrome/ toxic epidermal necrolysis), drugs (antiepileptic/, antibiotics/analgesics/NSAIDs/unknown) and mortality (yes/no). Quantitative variables were presented as mean±SD like age, duration of disease, and duration of drugs used. Effect modifiers like age, gender, duration of disease, and duration of drug use were controlled through stratification. Post-stratification Chi-square test was used to see the effect of modifiers on outcome. P value ≤ 0.05 was considered significant.

RESULTS:

We collected data from 79 participants; out of which 70 patients fulfilled the inclusion criteria. Among the valid responses, the mean age of participants was 35.84 years. Our study showed that majority of the patients were female 71.43% (n=50) and 28.7% (n=20) participants were males. Most of the participants were married at the time of collection of data (71.43%, n=50). On further query from the participants, it was found that the most common co morbidities were hypertension (7.14%, n=5) and neurological disease (epilepsy, multiple sclerosis, etc.) (7.14%, n=5) occurring in similar frequency, followed by diabetes note in 5.71 (n=4) participants. The biodata of the participants is summarized in Table 1.

SEX	**Male (%)**	**Female (%)**
	20 (28.57%)	50 (71.43%)
MARITAL STATUS	**Married**	**Unmarried**
	50 (71.43%)	20 (28.57%)
COMORBIDITY	**Diabetes Mellitus**	4 (5.71%)
	Hypertension	5 (7.14%)
	Chronic Hepatitis	1 (1.43%)
	Tuberculosis	0 (0.00%)
	Cardiac Condition(s)	1 (1.43%)
	Psychiatric Condition(s)	2 (2.86%)
	Neurological Condition(s)	5 (7.14%)
	Autoimmune Disease(s)	1 (1.43%)
	Other	3 (4.29%)

Table 1: Demographic data of the participants

Among the total responses, it was found that most patients belonged to the diagnosis of maculopapular rash (21.4%, n=15), followed by erythema multiforme (EM) (20.0%, n=14), and fixed drug eruption (FDE) (14.2%, n=10 (Figure 1). Three patients failed to reach a differential diagnosis and were labeled as non-specific (4.2%).

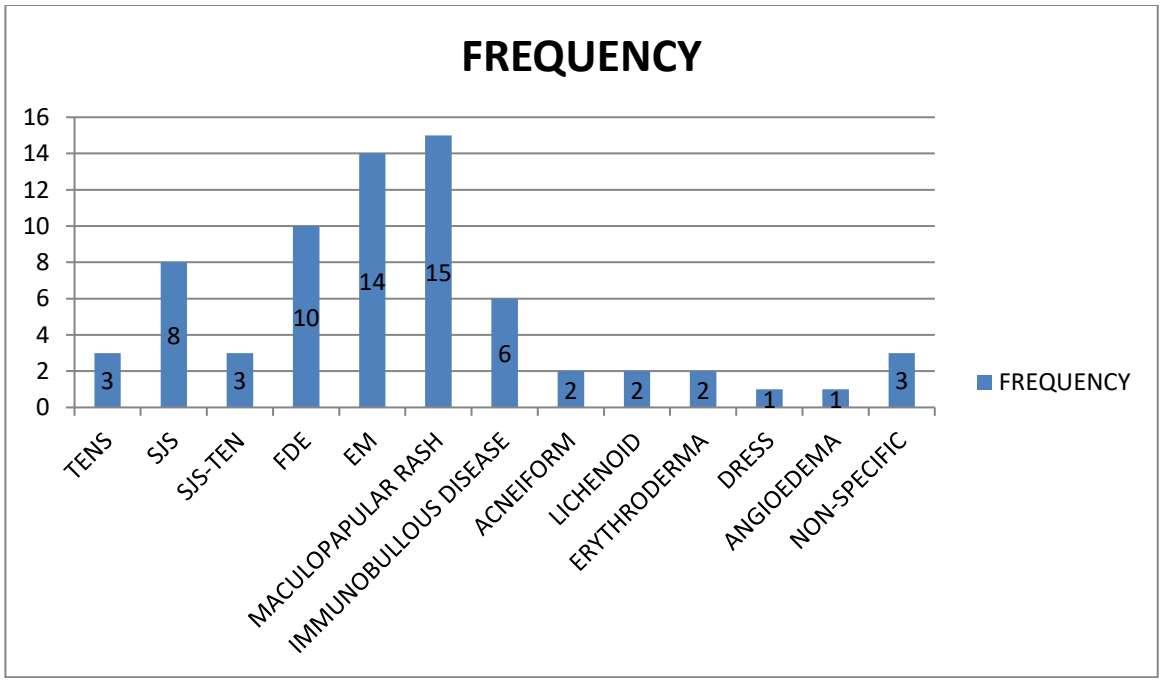

Figure 1: Frequency of Adverse Cutaneous Drug Reactions

It was noted that out of the responses collected, participants had a known drug which caused the symptoms. Among the known drugs, it was noted that antibiotics were the most common (41.82%,

n=23), followed by non-steroidal anti-inflammatory drugs (NSAIDs) (29.09%, n=16) and anti-epileptics (14.55%, n=8) (Figure 2).

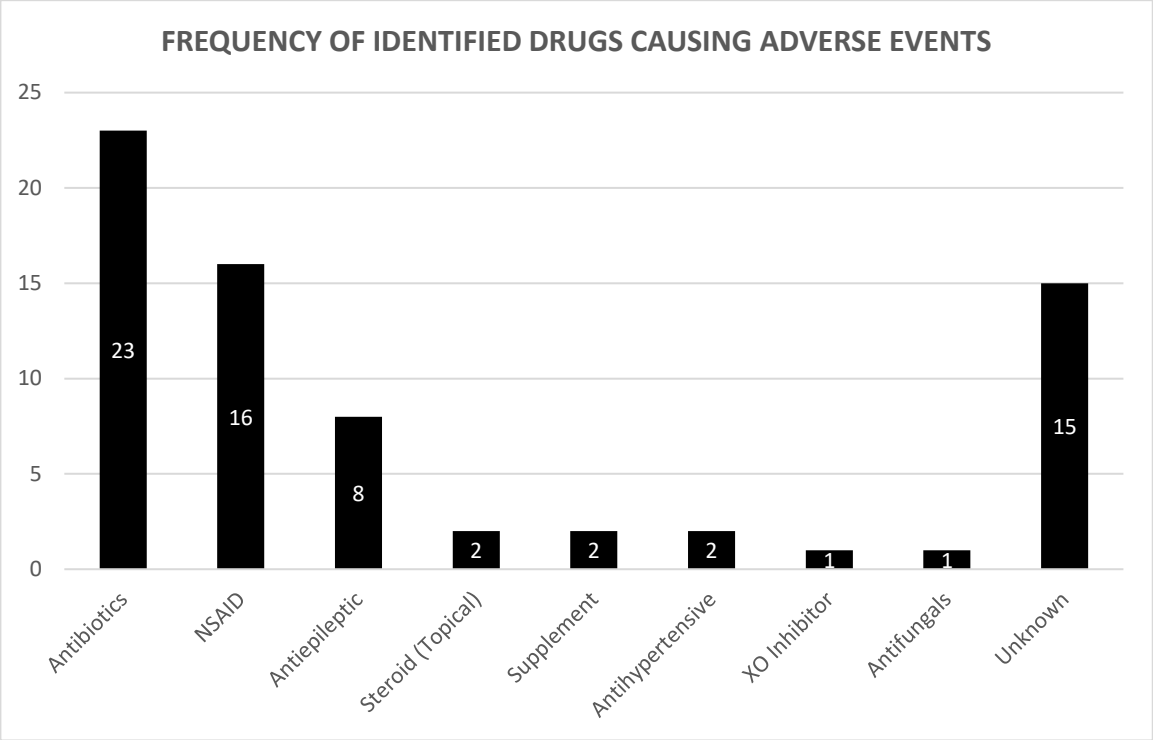

Figure 2: Frequency of identified Drugs causing adverse cutaneous Drug Reactions

It was also studied that 95.71% (n=64) of all the participants had no prior history of any drug reaction. Most respondents had a duration of disease limited to 1 to 10 days (82.86%, n=58) and only one respondent had duration extending beyond 30 days (1.43%, n=1) as summarized in Table 2. Highest number of respondents had used the drug for 1 to 10 days (47.14%, n=33) while for 24.23% respondents, the duration of drug use was unknown (n=17).

DAYS	DURATION OF DRUG USE	DURATION OF DISEASE
1 to 10 Days	33	58
11 to 20 Days	7	6
21 to 30 Days	6	5
>30 Days	7	1
Unknown	17	0

Table 2: Duration of Drug Use and Disease

Analysis according to drug class:

In the *antibiotic group* (n=23), average age of the respondents was 34.78 years, 43.48% were male (n=10), and 56.52% were female (n=13). It was noted that most patients in the antibiotic group fell in the category of maculopapular rash (30.4%, n=7), followed by fixed drug eruptions (26.0%, n=6) and then erythema multiforme (17.3%, n=4). The duration of disease in the antibiotic group was overwhelmingly limited to 1 to 10 days (95.65%, n=22). Duration of drug use, however, was distributed as: 1 to 10 days (52.17%, n=12), 10 to 20 days (4.35%, n=1), 20 to 30 days (8.70%, n=2). In the same group, 34.78% of the respondents (n=8) had an unknown duration of drug use (figure 3).

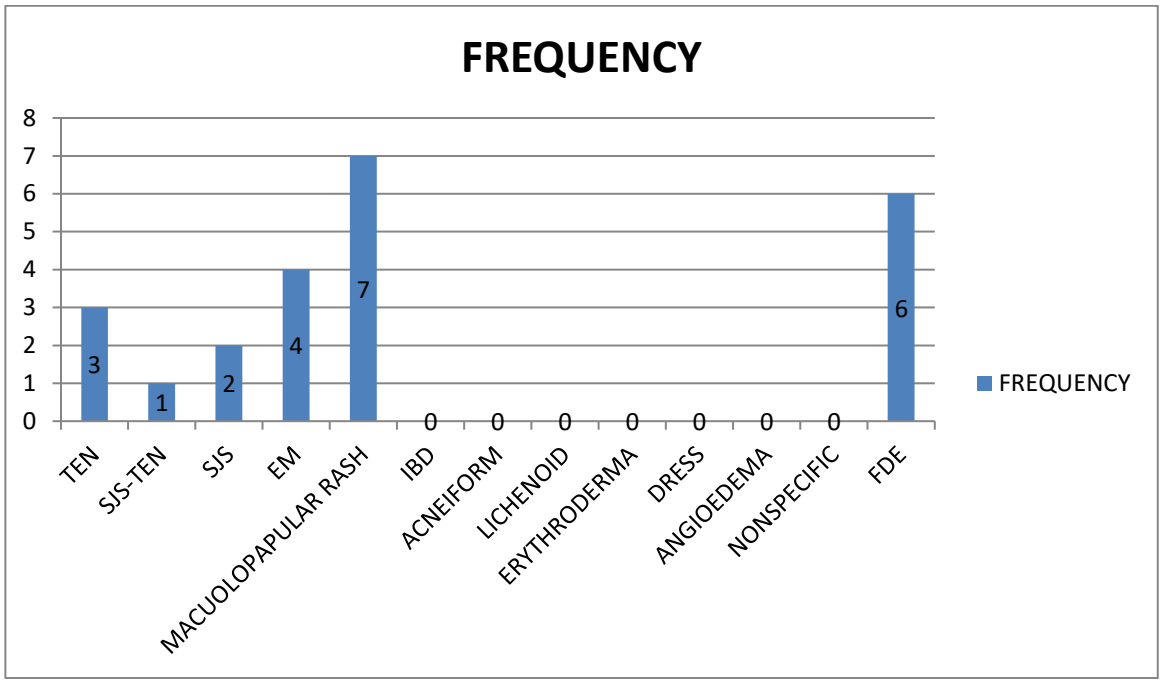

Figure 3: Analysis between Antibiotic group and CADR

In the *NSAIDs group* (n=16), mean respondent age was 42.56 years, and 12.50% were males (n=2), and 87.5% were female (n=14). Maculopapular rash (37.5%, n=6) was the most common manifestation of the NSAID group, followed by fixed drug eruptions (31.2%, n=5) and then SJS (18.75%, n=3). Disease duration, similar to antibiotics, was mostly limited to 1 to 10 days (93.75%, n=15), while duration of drug use was also mostly 1 to 10 days (68.75%, n=11) (figure 4).

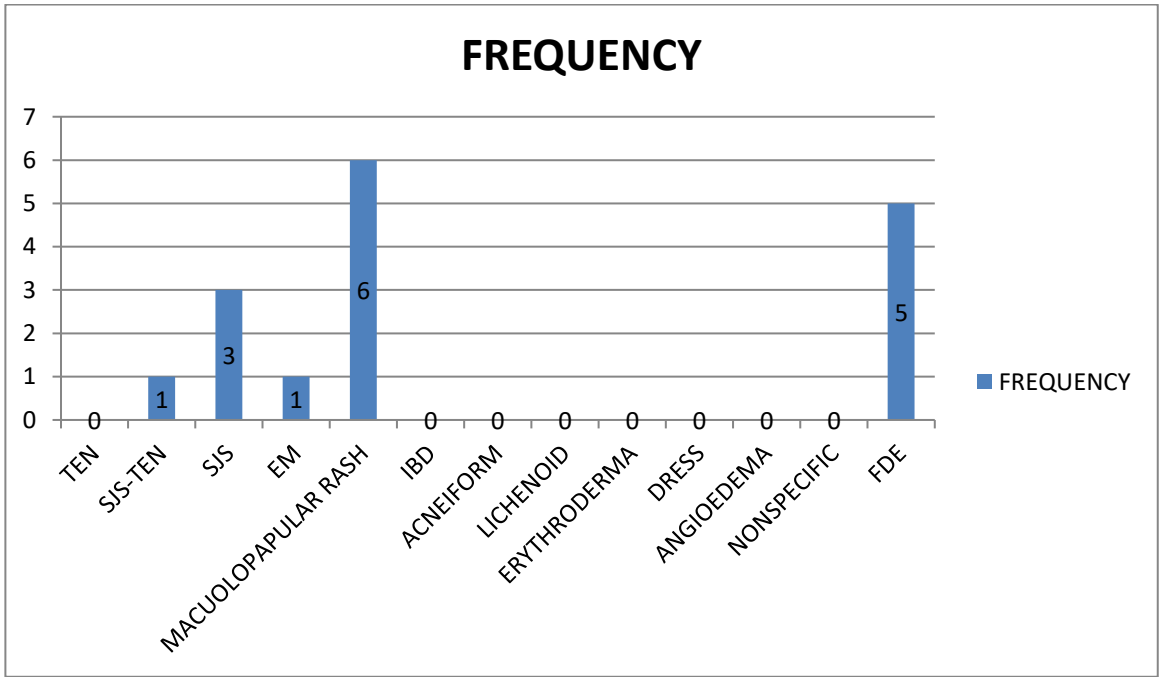

Figure 4: Analysis between NSAID group and CADR

In the *anti-epileptics group* (n=8), mean age of all respondents was 26 years, 25.00% were male (n=2), and 75.00% were female (n=6). EM was most common affliction amongst this group, accounting for 50.0% of all cases (n=4) followed by SJS (25.0%, n=2). One patient's presentation was described as unknown or non-specific (12.5%), while one was preliminarily diagnosed with

DRESS (12.5%). Duration of disease, similar to other classes, was largely 1 to 10 days (87.5%, n=7) (figure 5).

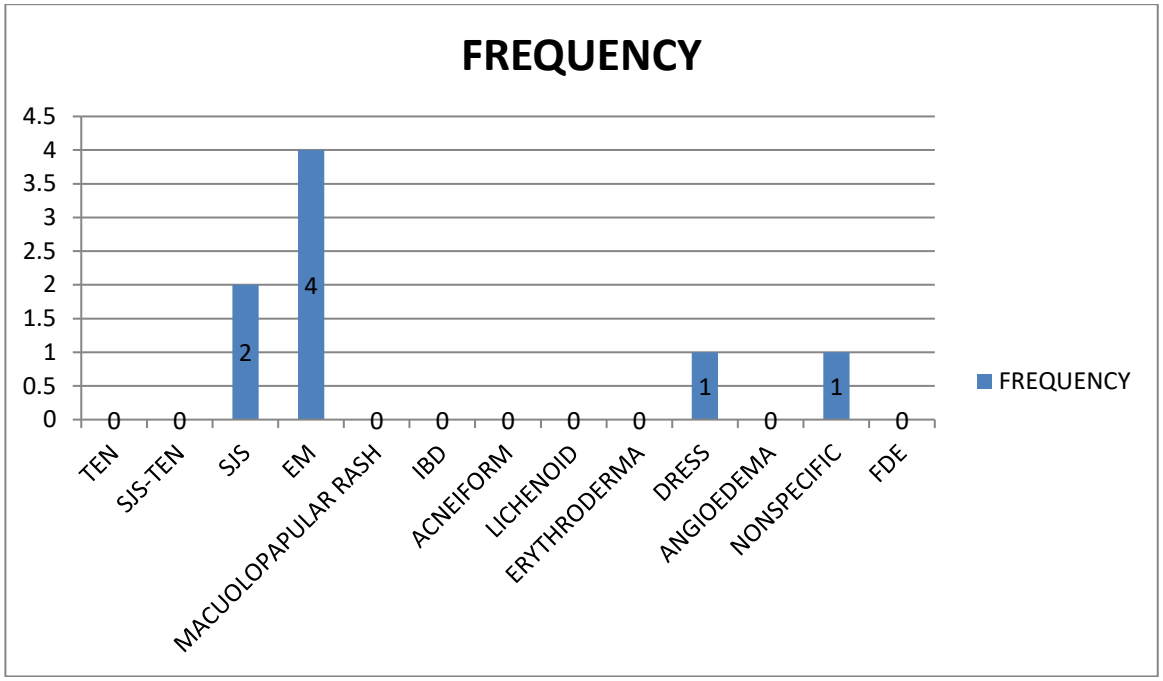

Figure 5: Analysis between Anti-epileptics and CADR

Analysis according to preliminary diagnosis:

Amongst all respondents, maculopapular rash (21.4%, n=15) was the most common presentation. It was observed that 20.0% (n=3) patients were males and 80.0% (n=12) were females. It was seen that in the maculopapular rash group, most lesions were caused by antibiotics (46.6%, n=7), followed by NSAIDs (33.3%, n=5) and among rest of the three patients, one patient developed due to anti-epileptics (6.66%), one due to anti-hypertensive (6.66%) and in one group no drug was identified (6.66%), findings of which are summarized in Table 3.

SEX	**MALE**	3 (20.0%)
	FEMALE	12 (80.0%)
DRUG	**ANTIBIOTICS**	7 (46.6%)
	NSAIDS	5 (33.3%)
	ANTI-EPILEPTICS	1 (6.66%)

Table 3: Correlation between Maculopapular rash and Drug Class

Accounting for 20.00% of all responses, EM was the second-most common preliminary diagnosis in our study (n=14). It was noted that 14.29% participants were male (n=2), while 85.71% were female (n=12). Antibiotics and antiepileptic contributed 28.57% each (n=4) in this group. NSAIDs and supplemental drugs each caused 1 case of EM in our study (7.14%, n=1), while 28.57% (n=4) responses were noted to have unknown drugs. Most cases (85.71%, n=12) had characteristic targetoid lesions on presentation while 35.71% had confluent erythema (n=5), findings of which are summarized in Table 4.

SEX	**MALE**	2 (14.29%)
	FEMALE	12 (85.71%)
DRUG	**ANTIBIOTICS**	4 (28.57%)
	NSAIDS	1 (7.14%)
	ANTI-EPILEPTICS	4 (28.57%)

Table 4: Correlation between Erythema Multiforme and Drug Class

Accounting for 14.2% (n=10) of all responses, FDE was the third-most common preliminary diagnosis in our study. In this group 50.00% were males (n=5), while 50.00% were female (n=5). Antibiotics caused 60.00% of all reactions (n=6) and NSAIDs caused the remaining 40.00% (n=4). Most common presenting signs were plaques (70.00%. n=7), and blistering (40.00%. n=4), findings or which are summarized in Table 5.

SEX	**MALE**	5 (50.0%)
	FEMALE	5 (50.0%)
DRUG	**ANTIBIOTICS**	6 (60.0%)
	NSAIDS	4 (40.0%)
	ANTI-EPILEPTICS	0 (00.0%)

Table 5: Correlation between Fixed Drug Eruption and Drug Class

DISCUSSION:

Adverse cutaneous drug reactions are a common occurrence in clinical practice, presenting as a diverse array of dermatological manifestations[8].CADR can range from mild maculopapular rashes to severe, debilitating and harmful reactions like SJS and TEN. Understanding the frequency of clinical patterns and identifying the causative drugs is crucial for effective patient management and drug safety monitoring[9]. The frequency of ACDRs varies across different age groups and medical conditions[10]. Vigilance among healthcare professionals is critical for accurate and timely diagnosis as well as preventing the escalation of reaction. The importance of patient education cannot be overstated, empowering patients with knowledge about potential reactions and encouraging open communication supports shared decision-making, fostering a collaborative healthcare approach[11]. There is a paucity of research work regarding CADR in developing countries, especially in Pakistan. The prevalence in developing countries is found to be higher than in developed countries which can be attributed to decreased reporting and access to healthcare by the patients[12].

In our study out of 70 patients, 50 are female and 20 are male patients showing female preponderance, which conforms to a study by Pudukadan. D. et al[13].

The commonly reported CADRs were maculopapular which was reported in 15 patients out of 70 patients, followed by erythema multiforme in 14 participants and fixed drug eruptions in 10 patients. The results are in concordance with the study conducted by Hina et al in 2021[5]. In her study, it was also concluded that out of the 193 participants, 135 (69.9%) participants developed maculopapular rash as a drug reaction[5].In a study by Garg and John in 2015, maculopapular rash was reported as the most frequent type of CADR (48.8%) followed by acneiform eruption (25.91%)[14]. In another study by Ding and Lee it was observed that 28.1% of cases were SJS, 5.7% were TEN, 5.3% were urticaria/angioedema, and (5.3%) were FDE[15].The authors reported the time interval since the administration of the drug to the development of clinical features. It was concluded that CADR like maculopapular rash, acneiform, SJS, and urticaria developed in the patients within 24 hours. A study by Agrawal and Ghate showed slightly variable results of the lag phase of maculopapular rash, acneiform, and EM which developed in 5.66 hrs[15].

In our study, the most common culprit drug was antibiotic which was reported in 41 percent (n=23) of cases, followed by NSAIDS (29.09%, n=16) and anti-epileptics (14.55%, n=8). In the study by Hernandez-Salazar A, et. al., the most common culprit drugs identified was amoxicillin clavulanate, amphotericin B and metamizole[8]. This is in concordance with our study where antibiotics were found to be the most common culprit agent. It is important to inquire about medications of all types from the patients including allopathic, homeopathic, ayurvedic, or traditional products in any form[10]. These include over the counter medications such as pain killers, multi-vitamins, oral contraceptives or laxatives[10]. The patients should also be inquired about any previous history of drug reactions and exposures[10]. Genetic susceptibility has also been found in some cases of CADRs along with reactivation of viruses and tissue specific memory T cells[9]. The study by F Fiszenson-Albala, et. al. also concluded that antibiotics were the most common precipitating drug identified[12]. In the antibiotic group, penicillins were identified as the most common agent[12]. However in the study by Pudukadan

D, et. al., the most common identified drugs were co-trimoxazole and dapsone for causing CADRs[13]. It is seen in our study as well as others that anti-epileptics are mostly implicated in the precipitation on SJS/TEN[15].

Our study summarizes the frequency of adverse cutaneous drug reactions in our population along with their types and causative agents. It is known that once the offending drug is identified, the management becomes easier. First step comprises of discontinuation of the offending agent and avoid agents with similar cross-reactivity. Most patients are managed with supportive care; however, severe CADRs require intensive care management with a multi-disciplinary approach.

CONCLUSION:

The clinical spectrum of CADR varies from mild skin maculopapular rashes to severe life-threatening cutaneous reactions with multi-organ involvement. It is important to identify these clinical manifestations as they may mimic other types of inflammatory dermatosis and make the diagnosis difficult. A through clinical history should be sought to identify the implicating agents. The patients need to be counseled regarding the causative factors and avoidance in the future. Any other form of identification such as cards or emergency identification with the list of patient's drug allergies should be carried by the patients at all times. Adverse drug reactions are difficult to identify and distressing for both the patients and their physician. In most cases, failure to counsel the patients regarding the common adverse reactions of the prescribed medications and their potential for cross-reactivity with other drugs is an important and crucial medico legal pitfall.

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