A study of cutaneous adverse drug reactions at a tertiary center in Jammu, India

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ABSTRACT

Aim: The aim was to study various morphological patterns of cutaneous adverse drug reactions (CADRs) and identify the culprit drug or drugs by establishing a causal link using Naranjo adverse drug reaction probability scale. **Materials and Methods:** The study was carried out between November 2010 and November 2011 at the Department of Dermatology, Government Medical College, Jammu. A total of 150 patients with CADR reporting to the dermatology department or referred from other departments were evaluated. Detailed history, clinical examination, hematological, and biochemical investigations were recorded. The venereal disease research laboratory test, HIV (ELISA), and histopathological examination were done wherever indicated. **Results:** A total of 150 patients were evaluated after applying the inclusion and exclusion criteria. The mean age of the patients with CADRs was 33.26 years. A majority of patients (30.6%) were in the age group of 21–30 years. The male to female ratio was 1.7:1.2. The most common CADRs were fixed drug eruption in 33.3% of patients followed by urticaria in 17.3%, and maculopapular rash in 13.3%. The most common classes of drugs implicated were antimicrobials in 40% of patients followed by nonsteroidal antiinflammatory drugs in 35.3%. The Naranjo adverse drug reaction probability scale indicated probable association of 77.3%, highly probable association of 12.6%, and 1% possible association with the implicated drugs. **Conclusion:** The pattern of CADRs and the drugs causing them is remarkably different in our population. Knowledge of these drug reactions, their causative drugs, and prognostic indicators is essential for the clinician.

Key words: Cutaneous adverse drug reactions, causal link, morphological patterns, Naranjo scale

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INTRODUCTION

Cutaneous adverse drug reactions (CADRs) have been seen to be one of the most common adverse drug reactions (ADRs) in various studies. A wide spectrum of cutaneous manifestations ranging from maculopapular rashes to toxic epidermal necrolysis (TEN) can be caused by different classes of drugs.[1] Studies have found the overall incidence of CADRs in developed countries as 1–3%, while the incidence in developing countries is thought to be higher between 2% and 5%.[2] Clinicians come across many instances of suspected CADRs in different forms. Therefore, not only the dermatologist, but the practicing physician should be familiar with these conditions to enable early diagnosis and prompt withdrawal of the causative drug to prevent mortality. We undertook a study at Government Medical College, Jammu, to characterize CADRs according to morphological pattern and to establish the corresponding, probably causative drug.

MATERIALS AND METHODS

In this study, 150 patients with CADR who reported to the dermatology department or were referred from other departments between November 2010 and November 2011 were evaluated. Written informed consent was taken of all patients. A detailed history regarding drug intake, cutaneous eruptions, associated systemic symptoms, the time gap between drug intake and skin eruption, dosage, duration, indication, and class of drug taken, and improvement in cutaneous eruption upon stopping the drug was recorded. A detailed general physical examination, cutaneous examination regarding morphology, pattern and distribution of eruption and mucosal examination was performed. Causality of the CADR was assessed according to the Naranjo adverse drug reaction probability scale, and CADRs were graded as highly probable, possible, and probable according to this scale.[3] At the end of the study, the data was analysed, and inferences were drawn using various statistical methods.

RESULTS

Of 150 patients studied, 82 were males, and 68 were females. The male to female ratio was 1.7:1.2 [Table 1]. The age range of patients was 9 months to 84 years, with a mean age of 33.26 years. Of all patients, maximum number of cases were in the age group of 21–30 years (30.6%) followed by 31–40 years (26%), with the least number in the age group >60 years (6.6%).

Fixed drug eruption (FDE) was the most common CADR, seen 50 patients (33.3%), followed by urticaria in 26 (17.3%), maculopapular rash in 20 (13.3%), acneiform eruptions in 17 (11.3%), erythema multiforme (EM) in 15 (10%). Five patients (3.3%) each had drug induced photosensitivity, steroid induced rosacea. TEN, angioedema, and drug-induced vasculitis was seen in 1 patient each (0.66%). Severe cutaneous adverse drug reactions (SCADRs) such as SJS, TEN, and erythroderma accounted for 6.6% of patients [Figure 1]. Stevens–Johnson syndrome (SJS) was seen in 5 patients, erythroderma in 4 and TEN in 1 patient.

The most common classes of drugs implicated were antimicrobials in 60 (40%) patients followed by nonsteroidal antiinflammatory drugs in 53 (35.3%), steroids (22), anticonvulsants (8) [Figure 2]. The most common individual drugs implicated in each CADR are shown in Table 2.

Few rare observations were made. In the case of FDE, 3 patients had developed FDE after taking fluconazole. One patient developed SJS after intake of cephexin-clauvulinic acid combination. One patient had risperidone-induced angioedema. EM induced by hormonal agents and terbinafine, and urticaria by rifampicin and phenobarbitone were also noted.

The interval between drug intake by all routes and CADR ranged from a few minutes to 30 days. Among the investigations, eosinophilia was seen in 20 patients (13.3%), altered liver function tests in 8 (5.3%), and altered renal function tests in 5 (3.3%). A biopsy was done to support drug etiology in 8 patients. HIV was done wherever required and was reactive in none. According to the causality assessment using Naranjo adverse drug reaction probability scale, out of 150 patients, 116 (77.3%) had probable association, 19 (12.6%) had highly probable, and 15 (1%) had a possible association with the drug.

DISCUSSION

In the present study, a total of 150 patients were studied, and various morphological patterns of CADR were observed. In our study, maximum number of patients belonged to the age group of 20–39 years with a mean age being 33.26 years. The youngest patient was 9 months old and the oldest 84 years old. These findings were in accordance with two other studies by Pudukadan and Thappa and Sharma *et al*.[4,5] Another study by Kongkaew *et al*. found more CADRs in the elderly probably due to increased use of medications and altered drug metabolism in them.[6] The males in our study outnumbered the females. The male to female ratio was 1.7:1.2 in our study which was in conformity with another study from Gujarat.[7] Sushma *et al*. also found a male preponderance in their study.[8]

The most common CADR was FDE, which accounted 33.3% of all CADRs in our study. The second most common CADR was urticaria (17.3%) followed by maculopapular rash (13.3%), which was comparable to the study by Patel and Marfatia.[9]

Table 1: Distribution of patients in each CADR

CADR	Males	Females	Total
FDE	31	19	50
Urticaria	14	12	26
Maculopapular rash	8	12	20
Acneiform eruptions	11	6	17
EM	8	7	15
Photosensitivity	3	2	5
Steroid-induced rosacea	0	5	5
Vasculitis	0	1	1
Angioedema	0	1	1
SJS	4	1	5
TEN	1	0	1
Erythroderma	2	2	4
Total	82	68	150

CADR: Coetaneous adverse drug reaction, FDE: Fixed drug eruptions, EM: Erythema multiforme, SJS: Steven–Johnson syndrome, TEN: Toxic epidermal necrolysis

Table 2: Distribution of most common drugs in each CADR

CADRs (number of patients)	Common drugs implicated	Number of patients using them
FDE (50)	Tinidazole, paracetamol	15, 11
Urticaria (26)	Paracetamol, diclofenac	10, 5
Maculopapular rash (20)	Amoxycillin, paracetamol	4, 3
Acneiform eruptions (17)	Steroids	17
EM (15)	Paracetamol, amoxycillin	3, 3
Photosensitivity (5)	Brufen	2
SJS (5)	Phenobarbitone	3
Erythroderma (4)	ATT	3
TEN (1)	Phenobarbitone	1
Vasculitis (1)	Amoxycillin-dicloxacillin	1
Angioedema (1)	Respiredone	1
Rosacea (5)	Betamethasone, clobetasol	2, 2

CADR: Coetaneous adverse drug reaction, FDE: Fixed drug eruptions, EM: Erythema multiforme, SJS: Steven-Johnson syndrome, TEN: Toxic epidermal necrolysis, ATT: Antitubercular treatment

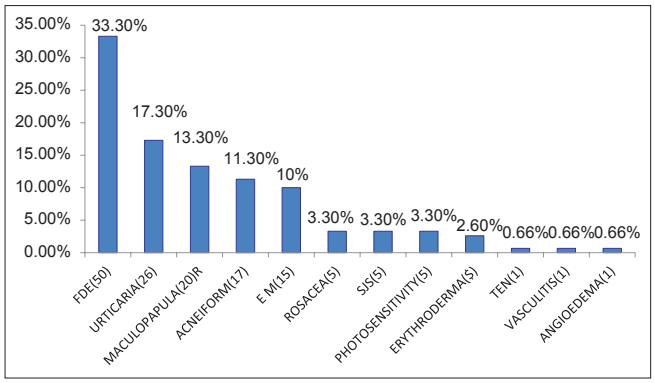

Figure 1: Distribution of morphological patterns of cutaneous adverse drug reactions among 150 patients

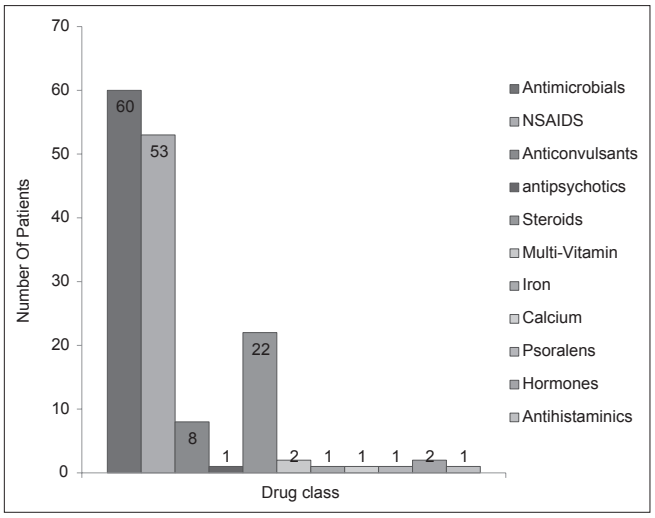

Figure 2: Distribution of causative drugs among 150 patients

Acneiform eruptions formed a major part of CADRs in our study accounting for 11.3% of patients. Another study by Tank *et al*. reported acneiform eruptions in 1.5–7.5% of patients.[10] Steroid induced rosacea, and photosensitivity was seen in 5 patients each which were in consonance with a study from south India.[11] SCADRs accounted for 6.6% of total CADRs in our study, in line with the incidences found by Noel *et al*. and Sehgal *et al*. in their studies.[11,12] However, another study from Chandigarh reported a higher incidence of SCADRs at14.4%.[5]

The most common class of drugs implicated were antimicrobials (40%) followed by NSAIDS (35.3%) in our study. Nandha *et al*. and Naldi *et al*. also found antimicrobials as the most common offending drug class followed by NSAIDS.[2,13] Corticosteroids were found to be the third most common drug class implicated in CADRs accounting for 14.6% of the patients followed by antiepileptics in 5.3%. Our findings here are in agreement with an earlier study from Gujarat.[10] Among the antimicrobials, we found tinidazole to be the most common offending drug; however, Pudukadan and Thappa and Sharma *et al*. found sulfonamides to be the most common drug.[4,5] Among the NSAIDS, paracetamol was the most common drug which was in agreement with an earlier study by Noel *et al*.[11]

Among FDE patients, tinidazole was the most common drug implicated in our study but earlier studies by Sharma *et al*. and Patel and Marfatia found cotrimoxazole to be common. We also found 3 cases of FDE due to fluconazole which was reported earlier by Mahendra *et al*. and Shukla and Prabhudesai.[14,15] Among the urticaria patients, paracetamol was the most common implicated drug, similar to that reported earlier by Sharma *et al*. and Chatterjee *et al*.[5,16] However Jhaj *et al*. in their study found penicillins to be most common drug among urticaria patients.[17] Maculopapular rash was the most commonly reported due to amoxicillin in our study which was in conformity the findings of Ghosh *et al*.[18] Among the SCADRs, anticonvulsants formed a major share similar to earlier studies by Noel *et al*. and Sehgal *et al*.[11,12] In our study, there was one patient of SJS due to cephalosporin-clauvulinic acid combination, similar to the findings by Salvo *et al*. in their study.[19] The addition of clauvulinic acid increases the chance of SCADRs. Photosensitivity was seen in 5 patients and ibuprofen was the most commonly implicated drug. Bergener *et al*. also reported ibuprofen as the most common drug causing photosensitivity.[20] One case of risperidone-induced angioedema was noted in our study. There have been very few case reports on risperidone-induced angioedema from India.[21]

Eosinophilia was seen in 13.3% patients in our study. Romagosa *et al*. reported eosinophilia in 12% of patients.[22] They stated that a peripheral eosinophil count carries little diagnostic value in the setting of CADRs, but eosinophil counts more than 1000 cells/mm^3 indicate a serious drug-induced cutaneous eruption. Thus, this can be a useful indicator among patients suffering from severe CADRs such as SJS, TEN, and erythroderma. Altered liver and renal function tests predispose to severe CADRs because of abnormal drug metabolism and clearance from the body. In our study, this was seen in 8.6% of patients but Pudukadan and Thappa found altered liver function tests and renal function tests in 23.3% of patients.[4] Histopathological examination was performed in 8 patients in our study and was consistent with the clinical diagnosis in all patients.

In our study, the implicated drug was found to be the probable cause in 77.2% patients whereas in 12.6% patients it was a highly probable cause. Suthar and Desai also found similar patterns of causality assessment, with 74.2% patients having a probable association and 11.4% having a highly probable association with the implicated drug.[7] This could be attributed to the higher number of re-exposure CADRs in our study and improvement following stopping the offending drug, thus strengthening the drug etiology.

CONCLUSION

In summary, early recognition of various morphological patterns is important not only for the dermatologists but also for the clinicians of other specialties so that the culprit drug is recognized and stopped immediately. CADRs are a common reason for litigation. Not warning a patient about potential adverse effects, prescribing medicine to a previously sensitized patient or prescribing a cross-reactive medication are the common and avoidable medicolegal pitfalls.

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