ORIGINAL ARTICLE

A Retrospective Study of Epidemiological and Clinical Patterns of ACDRs in Goa Medical College over a 6 Year Period

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Abstract:

Background: Adverse Cutaneous Drug Reactions (ACDRs) account for 3% of all hospitalizations. The spectrum of drug reactions can be varied from mild to life threatening forms. Since the diagnosis of ACDR is purely clinical, early and prompt identification and withdrawal of drug (s) is life saving for the patient. *Aim and Objectives***:** To study the epidemiological and common clinical patterns and drugs causing ACDRs in tertiary care hospital of Goa Medical College, Goa over a 6 year period. *Material and Methods:* This was a retrospective study conducted over a period of 6 years. The medical records were analyzed for demographic profiles, morphology of drug eruptions, common groups of drugs involved, presence of co-morbid factors, systemic and mucosal involvement, common haematological abnormalities encountered, time interval between drug intake and onset of rash and mortality. *Results:* Our study population had 256 patients and the age group of 21-40 years was commonly affected. Maculopapular rash followed by angioedema were the commonest morphology of drug rash patterns encountered in our study. The time interval between consumption of drugs and onset of ACDR varied with interval of 1-7 days being the commonest group in having 158 (61.7%) patients. Antibiotics followed by anticonvulsants and antiretrovirals were the commonest groups of drugs causing ACDR. We found that significant proportion of our patients had haematological, renal and hepatic system involvement. *Conclusion:* Early identification and withdrawal of the culprit drug remains the cornerstone in prevention of mortalities in ACDRs. A prior knowledge about the reaction patterns and common offending drugs in the population by the treating physician cannot be overemphasized.

Keywords: Adverse Cutaneous Drug Reactions, Drug Reaction Patterns, Mortality

Introduction:

Adverse Cutaneous Drug Reactions (ACDR) is the most frequent manifestations of Adverse Drug Reactions (ADRs) and account for 3% of all hospitalizations [1]. The spectrum of drug reactions can be varied from mild to life threatening forms like Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Such severe reactions require prolonged hospital stay and generate high costs associated with significant morbidity [2]. The diagnosis of ACDR is purely clinical and lab tests do not aid much in diagnosis. Hence, a thorough clinical history regarding drug intake coupled with high degree of suspicion is vital in making an early and prompt diagnosis. Early withdrawal of culprit drug(s) remains cornerstone in management of ACDRs. The incidence of ACDR is often difficult to ascertain as mild and transitory forms often goes unreported and some forms can mimic other diseases like viral exanthems or rarely collagen vascular disorders.

ACDRs can often affect all ages and is a global phenomenon. Female sex, increasing age, pregnancy, multiple drugs, immunosuppression, and presence of other co-morbidities like renal and hepatic failures are associated with increased risk [3]. As advances in medicine continue; newer drugs are introduced making the scenario more complicated and challenging.

The pattern of drug reactions often differs among various drugs and various population groups. Hence a prior knowledge is essential as it could help in choosing drugs wisely by treating physician thereby ensuring patient compliance and decreasing ACDRs.

Keeping this in mind and in order to study the epidemiological and common clinical patterns and drugs causing ACDRs, this retrospective study was undertaken in Goa Medical College over a 6 year period.

Material and Methods:

This retrospective study was conducted from dermatology ward of tertiary care hospital of Goa over a period of 6 years ranging from 2010 to 2015. The medical records of all patients admitted with ACDRs were reviewed and entered into a specially made proforma. The data was analyzed for demographic profiles, morphology of drug eruptions, common groups of drugs involved, presence of co-morbid factors, systemic and mucosal involvement, common haematological abnormalities encountered, time interval between drug intake and onset of rash and mortality. Patients who had consumed indigenous (ayurvedic and homeopathic) medicines were excluded as the herbal ingredients were not known. The study was approved by Institutional Ethics Committee.

Results:

Our study population had 256 patients, out of which 123 (48%) were males and 133 (52%) were females. The M/F ratio was 0.9:1. The common age group of patients involved with ACDRs is summarized in Fig 1. The time interval between consumption of drugs and onset of ACDR varied, with the interval of 1-7 days being the commonest group in having 158 (61.7%) patients. This was closely followed by interval of more than 7 days in having 88 (34.4%) patients. Only 10 (3.9%) patients had acute onset of less than 24 hours. The various morphological patterns of drug rashes seen in our patient group is tabulated in detail in Table 1.

The common groups of drug causing ACDRs is listed in Table 2

Among the antibiotics, beta lactam group was commonest in having 55 patients (60%). Nevirapine was the commonest drug in ART group in having 19 patients (79%). Among anti-convulsants 24 patients (96%) had ACDR to the aromatic group. Among miscellaneous group, four patients reacted to dapsone, and antineoplastics, three patients to hormonal drugs, allopurinol and antimalarials, two patients to anti-TB, anti-psychotics and topical diclofenac each, and one patient each developed ACDR to heavy metal, hepatitis B vaccine and radio contrast media.

In our study, haematological, renal and hepatic systems were commonly involved with ACDRs. The details of hematological abnormalities are depicted in Fig 2.

Renal abnormalities were seen in 19 (7%) patients in the form of increased blood urea/creatinine (following sepsis and dehydration), renal failure, hematuria, urinary tract infection and glomerulonephritis. Severe hepatitis was encountered in 12 (5%) patients and was seen in patients having SJS-TEN, Erythema Multiforme Major (EMM) and Drug Hypersensitivity Syndrome (DHS). Mild to moderate hepatitis was seen in 44 (17%) and 40 (17%) patients respectively. Mucosal involvement is frequently encountered in ACDRs. Ocular involvement was most commonly seen in our series and involved 113 (44%) patients. Severe forms like SJS-TEN had severe manifestations in the form of corneal ulcers, pseudo membranes and conjunctivitis. Other manifestations encountered included periorbital edema, conjunctival congestion and superficial punctuate keratitis. Oral and genital involvement

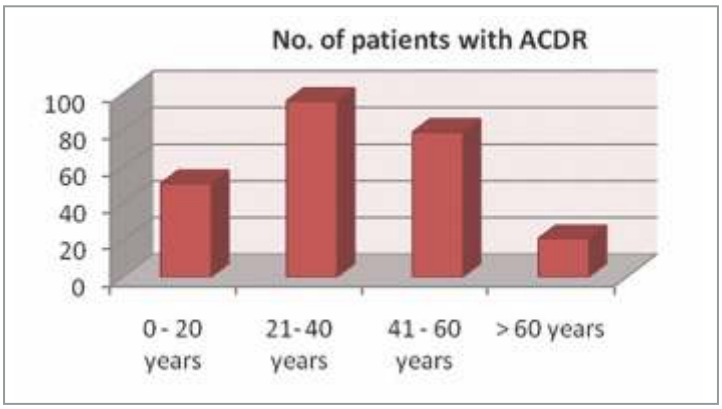

Fig 1: Common Age Groups of Patients Involved with ACDR

were seen in 88 (34%) and 101 (39%) patients respectively. Table 3 gives a detailed clinical profile of patients who succumbed to ACDRs.

Skin biopsy was performed in most of our patients who presented with ACDR except for angioedema and photosensitivity that did not have an evident skin rash. Clinico-pathological correlation was done in majority of our study population. Direct Immunofluorescence (DIF) was done only in certain group of patients presenting with rarer forms of bullous ACDR and few patients of vasculitic rash to confirm the diagnosis.

DHS was seen in 25 (10%) patients. Among these, 17 (68%) patients presented with a maculopapular rash while 8 (32%) patients had erythroderma. Two (8%) patients each having erythroderma and maculopapular rash had a fatal outcome with severe hepatitis and one (4%) patient among them had irreversible acute renal failure. Twenty three patients (92%) had mild to moderate hepatitis. Among the drugs causing DHS, anticonvulsant was the commonest group in having 12 (48%) patients, followed by antibiotics with 8 (32%) patients while 2 (8%) patients each were reported secondary to allopurinol and dapsone. Single (4%) patient had DHS secondary to antipsychotic (olanzapine).

Table 1: Depicts the Various Morphological Patterns of Drug Rashes Encountered in Our Patients

Morphology	Number of patients	Percentage
Maculopapular rash	47	18
Angioedema	40	16
Erythema Multiforme	33	13
Urticaria	33	13
Vasculitis	23	9
Erythroderma	17	7
Stevens Johnson Syndrome	17	7
Fixed Drug Reaction	15	6
Lichenoid eruption	14	5
Psoriasisiform eruption	6	2
Photosensitivity	6	2
Toxic Epidermal Necrolysis	3	1
Other Bullous ACDR	2	0.78
Total	**256**	**100**

Table 2: Common Group of Drugs Causing ACDR in Our Study

Group of Drugs	Number of Patients	Percentage
Antibiotics	92	35.94
NSAIDS	77	30.08
Anticonvulsants	25	9.77
ART	24	9.38
Antidiabetics	11	4.3
Antihypertensive	10	3.91
Miscellaneous Drugs	26	10.16

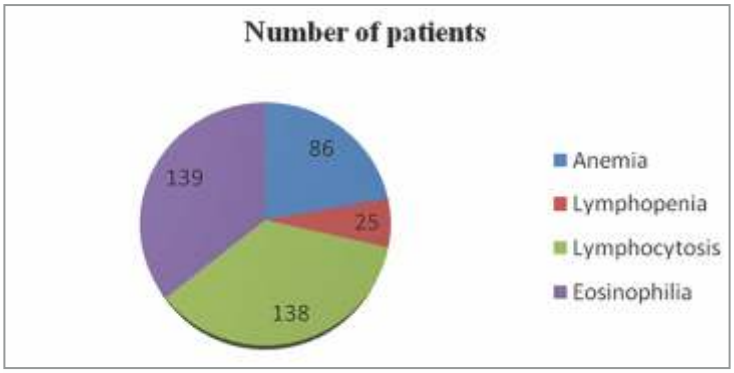

Fig. 2: Hematological Involvement in Patients with ACDR

Table 3: Fatal Outcomes and Co-Morbidities of ACDR

Age/Sex	Drugs	Morphology	Cause of Death	Co-morbidities
75/F	Phenytoin	Maculopapular	Cardiac (MI)	CVA, DM, sepsis with Hepatitis and Acute renal failure
69/M	NSAIDS	Erythroderma	Cardiac (MI)	DM
56/F	AKT	Toxic Epidermal Necrolysis	Sepsis	Koch's meningitis, DM with hepatitis
74/M	Allopurinol	Toxic Epidermal Necrolysis	Sepsis	DM, Hypertension, nephropathy, IHD with Hepatitis and Acute renal failure
32/F	Carbamazepine	Toxic Epidermal Necrolysis	Sepsis	with Hepatitis
67/F	Cephalosporin	Stevens Johnson Syndrome	Sepsis with DIC	DM, Hypertension with Hepatitis and Acute renal failure
35/F	Anticonvulsants	Stevens Johnson Syndrome	Sepsis with shock	seizure disorder with Hepatitis
45/F	Anticonvulsants	Stevens Johnson Syndrome	Sepsis	seizure disorder with fulminant hepatitis
70/M	Dapsone	Erythroderma	Sepsis	Hansens with hepatitis

Discussion:

ACDRs vary in patterns of morphology, severity and distribution. Prompt identification of the culprit drug often ensures a complete cure. It is of utmost importance for the practising dermatologist or physician to be armed with a thorough knowledge regarding the clinical spectra of ACDR and also to identify those patient groups who have additional risk factors which makes them more prone for ACDRs. Hence, prescribing medicines to previously sensitized individuals or advising related medications with cross reactivity which are common medico legal pitfalls can be easily avoided.

The age group in our study was from 1.6 to 74 years. We found that the age group of 20 to 40 years was commonly affected. This is in accordance with Indian studies done before [1, 4, 5]. There has been a lot of variation in age groups reported with some studies showing 40 to 60 years as commonly affected [6]. The increased consumption of medications with advancing age leads to heightened potential for drug interactions. The age disparity in various studies may be due to regional variations in health care seeking behaviour of populations [4].

A slight female preponderance was noted in our study. This is in concordance with studies done before [7, 8]. However, some studies have also shown a male predominance [3, 9]. Difference in pharmacokinetics, body weight, composition, hormonal effects on drug metabolism have been suggested as potential explanation for effects of gender on ACDR [10]. Drugs causing ACDRs can be diverse and vary with different populations. In our study, antibiotics were the commonest drug group followed by NSAIDS, anticonvulsants and ART. We found a high incidence of rash secondary to initiation of ART which is not reported in studies before. A possible logical explanation could be that since our hospital is a tertiary centre, it has an attached ART centre which dispenses free ART drugs. Hence any skin rashes were referred to our department. Maculopapular or morbilliform rash (18%) followed by urticaria and angioedema, bullous ACDRs were the commonest morphologies encountered in our study. This is in accordance to findings reported before [5, 9]. SJS, TEN and bullous EM were the commonest types of bullous ACDRs in our study. Time intervals between onsets of drug intake to the manifestation of drug rash can vary. It can range from less than 24 hours to more than 7 days. In our series of patients, less than 24 hour interval gap was seen in acute urticaria, angioedema, Fixed Drug Eruption (FDE) and morbilliform rashes. Most of our patients, 158 (61.7%) had onset within a week and included maculopapular rashes, SJS- TEN, EM, FDE, lichenoid and psoriasiform rashes. More than 1 week interval was seen in patients who presented with erythroderma, lichenoid rash, TEN and vasculitis. Systemic involvement (haematological, hepatic, and renal) was noted in patients with SJS-TEN, erythroderma and angioedema. The incidence of involvement was much higher in patients with pre-existing risk factors like diabetes, chronic kidney disease, seizures etc than with drug rash alone.

Abnormalities in liver function tests have been identified independent indicator of severity of drug induced cutaneous eruptions [11, 12]. Ninety six (38%) patients in our study population had hepatitis, severe and fulminant types were notably

found in SJS-TEN and DHS. Among haematological parameters, eosinophilia is a consistent and exclusive finding of severe drug reactions [1, 13] and was also seen in our study. It has been reported that patients with peripheral eosinophilia showed more severe clinical manifestations, required systemic therapies and had much longer recovery time. Guidelines of American Academy of Dermatology state that eosinophil count more than 1000 cells/mm^3 indicate severe drug induced eruptions [11].

Approximately 90% patients with DHS have cutaneous manifestations which can range from exanthematous rash to TEN. The extent of cutaneous involvement however does not reflect the severity of internal organ damage [14]. In our group of patients with DHS, maculopapular rash was the commonest cutaneous manifestation and hepatitis with eosinophilia was the predominant extra cutaneous manifestation which is in accordance with other studies [15, 16]. Mucosal involvements (ocular, oral and genital) were seen in bullous ADRs (SJS-TEN, EM, FDEs) and urticaria. Sepsis was noted as the commonest cause of death in our patients; probably attributed to loss of skin barrier and underlying systemic diseases causing immunosuppression.

Conclusion:

Antibiotics, anticonvulsants and NSAIDS were the commonest group of drugs implicated in our study. Maculopapular or morbilliform rash was the commonest morphology encountered in our study. We found eosinophilia to be consistent feature in drug eruptions. Early identification and withdrawal of the culprit drug remains the cornerstone in prevention of mortalities in ACDRs. A prior knowledge about the reaction patterns and common offending drugs in the population by the treating physician cannot be overemphasized.

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