SAS Journal of Medicine ISSN 2454-5112
SAS J. Med., Volume-3; Issue-7 (Jul, 2017); p-154-157
Available online at http://sassociety.com/sasjm/

Original Research Article

A Clinico-Epidemiological Study of Various Patterns of Cutaneous Adverse Drug Reactions

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Abstract: Since time immemorial, medications of various kinds have been used by physicians with the noble intention of curing the sufferer of his ailments. Yet, paradoxically, this well-meaning intention may become the nemesis of many a sufferer. With the increase in number of drugs & HIV prevalence, adverse drug reactions have became common and cutaneous drug reactions constitute a major proportion. A clinico-epidemiologica study was undertaken in the department of Dermatology, Venerology & Leprosy, Siddhartha medical college, Vijayawada to know the incidence, the clinical patterns of drug eruptions, the common drugs implicated and casuality assessment. Incidence of various cutaneous adverse drug reactions found to be 4.6 per thousand. Most of the reactions occurred in the age group 21-40yrs.Most common morphological types of cutaneous ADRs are maculopapular rash (28%) followed by fixed drug eruptions (25%) and exfoliative dermatitis(9.3%). Severe adverse reactions like SJS, TEN, DHS occurred in 19 cases (12%). The major incriminating drugs are Antibiotics(31.4%, mainly ciprofloxacin, cotrimoxizole) followed by Antiretrovirals (25%, mainly nevirapine), NSAIDS (15%, mainly diclofenac) and Antiepileptics (12% mainly phenytoin, carbamazepine).HIV positivity found in 31% cases and in them maculopapular rash was common,is mostly caused by nevirapine. In HIV negative patients (69% cases) FDE and MP rash were common and are due to antibiotics and NSAIDS. Degree of certainty of a CADR was found to be definite in 14 cases, probable in 119 cases and possible in 19 cases according to WHO –UMC criteria. Cutaneous adverse drug reactions pose considerable amount of diagnostic challenges. Maculopapular rashes and fixed drug eruptions are the most common morphological types with antimicrobials and antiretroviral drugs being the main culprits.
Keywords: CADRs, MPR, SJS, TEN, DHS, oral provocation, Re-challenge.

INTRODUCTION

An adverse drug reaction is "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function". Cutaneous adverse drug reactions (CADRs) are the most common manifestations of adverse drug reactions. Drugs are almost always coupled with inherent risk of adverse reactions no matter how safe and efficacious they are during clinical trials and subsequent widespread therapeutic use. The clinical spectrum and pattern of CADRs may vary from mild and transient macula papular rash to severe and potentially fatal Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Cutaneous manifestations of adverse drug reactions may be part of systemic manifestation with other organ system involvement or could be the only manifestation of the ADR. Drugs may also worsen preexisting skin disorders. The pattern of CADRs and the drugs responsible for them keep changing from time to time because of new drugs being made available for therapy, changing prescription pattern, increased use of drugs for treatment of diseases, drug interactions due to multiple drug therapy and also due to a growing tendency for self-medication in the population. With this background the present study was undertaken in Dept. of Dermatology, Venereology & Leprosy, Government General Hospital, Vijayawada to evaluate the clinical pattern and epidemiological spectrum of various types of cutaneous adverse drug reactions.

MATERIALS AND METHODS

The aim and objectives of the present study are as follows: To evaluate the clinical spectrum of various types of cutaneous adverse drug reactions and their causative drugs; to study the distribution and frequency of the various types of cutaneous adverse drug reactions in the study population. This study was conducted on 152 consecutive patients with suspected cutaneous adverse drug reactions attending the faculty of Dermatology, Venereology and Leprosy, Government

General Hospital, Vijayawada between Jan 2015 to June 2016.

Inclusion criteria

- Patients of all age groups and both sexes with or suspected CADRs.
- A causality assessment of suspected CADR based on the WHO algorithm was used, and only those with "certain", "probable", and "possible" association were included in the study.
- Willingness to give written informed consent and comply with the study procedure.

Exclusion criteria

- Patients with reactions in whom the drug details unknown or unclear drug history.
- Reactions to topical application of drugs.

A stepwise approach was taken to evaluate the patients. This included an exhaustive history and clinical examination. An accurate drug history was obtained. Names of all the drugs and the duration of intake were noted. Attention was also paid to the sequence of events, to rule out other diseases mimicking drug rash. History of any previous drug allergies in self and family members, were also noted. All patients were counseled and advised HIV testing. In HIV reactive people, CD4 counts were done. Routine blood investigations and skin biopsy in selected cases were done. Re-challenge in the form of oral provocation planned in selected cases. Based on the clinical and laboratory findings the rash was categorized into one of the various morphological types. The causal relationship with the offending / suspected drugs was established (as certain, probable, possible, unlikely, conditional or unclassifiable) as per the WHO-UMC causality assessment scale.

RESULTS

A total of 40,126 patients attended the Dermatology OPD during the study period. The incidence of CADRs was 4.63 per thousand. The male to female ratio was 72:80 (47%:53%). The majority of affected patients (62%) were between 21 to 40 years old with a mean age of 32 years (range 10 to 70 years).Main presenting symptoms were rash (77%), itch (66%), fever (22%), pigmentation (14%) and vesicle formation (10%). The most common cutaneous adverse reaction seen was maculopapular rash (44 cases,28.2%) followed by fixed drug eruptions (39 cases, 25%), exfoliative dermatitis(14 cases,9%), Stevens Johnson syndrome (11 cases,7%), erythema multiforme (10 cases,6.5%), urticaria (9 cases,5.7%), acneform eruptions (6 cases,3.8%), phototoxic dermatitis(6 cases,3.8%), toxic epidermal necrolysis (5 cases, 3.2%), drug hypersensitivity syndrome (3 cases,2%), acute generalized pustular exanthematosis (3 cases,2%) and others. Mean onset time of rash after drug exposure for the top ten reaction patterns were i) 9 days (range: 2-28 days) for maculopapular eruption, ii) 1.5 days (range: 2hr-3days) for FDE, iii) 18days (range: 10-26days) for exfoliative dermatitis, iv) 15 days (range: 2-30 days) for SJS, v) 5 days (range:1-13 days) for erythema multiforme, vi) 1.8 days (range:6hr -4days) for urticaria, vii)16 days (range:13-24 days) for acneform eruptions, viii) 16days(range:3-28 days) for photodermatitis, ix) 9 days (range:7-12 days) for TEN, x) 13 days (range:6-23 days) for DHS. Antibiotics were the most commonly implicated drug group (50 cases, 31.4%) followed by antiretrovirals (40 cases, 25%), NSAIDS (24 cases, 15%) anticonvulsants (19 cases, 12%), antitubercular drugs (6 cases, 3.7%), antifungals (5 cases,3%), steroids (5 cases,3%), antimalarial drugs(4 cases,2%) and others. The most common culprit drug was nevirapine (39 cases, 24.5%), followed by diclofenac (16 cases, 10%), cotrimoxazole (12 cases, 7.5%) and phenytoin (10 cases, 6.3%). Maculopapular rashes were mainly due to antiretrovirals especially nevirapine (23of 48 cases,48%), followed by antimicrobials (19 cases,40%) and analgesics (4.16%). Quinolones (6 cases), cotrimoxazole(6 cases) and b-lactams(6 cases) were the common antibiotics to cause the exanthematous rash. Fixed drug eruptions were mainly due diclofenac (13 of 41 cases, 32%), ciprofloxacin (8 cases, 19%), cotrimoxazole(6 cases, 15%). Exfoliative dermatitis was mainly due to nevirapine (8 of 14 cases, 57%), and phenytoin (3 cases,21%). Nevirapine was the main culprit drug in causing Stevens Johnson syndrome (6 of 11 cases, 55%) followed by antiepileptics (phenytoin-2, carbamazepine-2). Five cases of toxic epidermal necrolysis were seen in the present study. Of them, three cases were due to antiepileptics (60%), one due to nevirapine and in another, ciprofloxacin was the causative drug. Phenytoin induced DHS seen in 2 patients and in one case nevirapine caused it. Antibiotics were the main offending drugs in erythema multiforme (3 of 10 cases,30%), followed by antiepileptics (20%) and analgesics. The most common cause of urticarial lesions were NSAIDS (4 of 10 cases, 40%), followed by antibiotics (30%). Steroids were the main culprit drugs in acneform eruptions (5 of 6 cases, 80%).Of the total 152 patients, 47 were reactive to HIV infection (31%). Among HIV positive patients, the most common drug reaction was maculopapular rash (27 cases,55%) followed by exfoliative dermatitis (9 cases,18%). Nevirapine is main offending drug (39 cases, 77%) followed by cotrimoxazole (6 cases,12%). Re-challenge in the form of oral provocation done in 16 patients, with 14 positive results. De-challenge attempted in 143 cases and 141 patients improved.

DISCUSSION

Drugs no matter how safe and efficacious, are always coupled with inescapable risk of adverse reactions. Adverse drug reactions are a cause of significant morbidity and mortality in patients of all areas of healthcare today. Healthcare professionals have a responsibility to their patients, who themselves are increasingly aware of the problems associated with drug

therapy. Newer insights have been developing in the field of factors affecting CADRs and the need for studies in the Indian population regarding the newer trends in cutaneous adverse effects is immense. The incidence of cutaneous ADRs in this study was found to be 4.63 per thousand outpatients. Mehta *et al* reported an incidence of 10 per thousand[1], and Mani *et al* reported an incidence of 12 per thousand[2]. The lower incidence of CADRs in the present study as compared to above may be because of minor CADRs being dealt by physicians themselves. There were no significant differences in the male to female ratio. CADRs were seen most commonly in the 21-40 years age group with mean age of 32 years. There was progressive decline in the number of CADRs towards the extremes of age. Maculopapular rash was the most common adverse cutaneous reaction seen in 44 patients (28.2%) in this study. A study conducted by Ghosh *et al* [3] in manipal found that, maculopapular rash (21%) was the most common adverse cutaneous reaction and antibiotics (30%) were the offending drugs. In the study done by Jhaj *et al* [4], found that maculopapular rashes (50%) and urticaria (21.5%) were the common morphological CADRs and antibiotics were the main culprits (56%). The high number of antiretroviral drugs as a cause of maculopapular rashes found only in our study could partially be explained by the fact that ART referral center situated proximity. Fixed drug eruptions were seen in 39 patients (25%). Bullous form of fixed eruptions seen in 13 of them. In concordance with studies done by Sharma *et al* [5], antimicrobials constituted the major causative drugs (58%), followed by NSAIDS.(31.2%). Female preponderance noted in FDE. Most of the common drugs causing FDE involved limbs (73%) and trunk (66%). A positive family history was found in 3 cases which may be due to genetic (HLA) linkage. In three patients, dual reactions to one drug were observed. Simultaneous appearance of bullous FDE and erythema multiforme seen in a HIV patient after taking ofloxacin for gastroenteritis. Rechallenge confirmed the dual reactions with appearance of FDE at the previous site and EMF over the palms. A reactive patient developed nevirapine induced EMF along with maculopapular rash. Both AGEP and FDE observed in an epileptic patient using phenytoin. Simultaneous dual drug eruptions to a single drug have been described in the studies carried by Sharma et al [6]. Although most of the adverse reactions were mild to moderate, severe reactions like SJS, TEN and DHS were seen in 19 cases (12.17%). Jhaj *et al* [4] reported serious CADRs in 19% and Raksha M Patel *et al* [7] in 5% of the total adverse cutaneous drug reactions in their studies. With expert care, the mortality and morbidity were drastically reduced. Of the 19 cases, two cases of SJ syndrome were severe and managed successfully in the ICU. One case of phenytoin induced TEN involving more than 85 % body surface area proved fatal. Amongst various drug rashes, 55 were found to be localized (36%) and comprised mainly of fixed drug eruptions, erythema multiforme, and acneiform eruptions, while 89 were generalized (58%) and included mainly maculopapular rashes, exfoliative dermatitis, TEN, SJS, and DHS. These tend to be more severe. Eight cases were found to have a photo distributed rash. Drug reactions were seen mostly to orally ingested drugs (81%), oral route being the most commonly employed route for drug administration, reactions were more with this route. Reactions caused by parenteral medications were mostly acute reactions like urticaria, angioedema and fixed drug eruptions, and required prompt discontinuation of the drug. Drug eruptions may be easily diagnosed from the history and clinical picture. However, most patients receive many drugs at the same time, and thus recognizing the exact cause, though very important becomes difficult. Drug dechallenge is required most of the times. Rechallenge in the form of oral provocation, patch tests,prick and intradermal tests are gaining importance.Re-challenge in the form of oral provocation done in 16 patients, with 14 positive results, where the certainty of the drug reaction proved. De-challenge attempted in 143 cases and 141 patients improved after withdrawal of the offending drug along with supportive treatment. In our study causality analysis was done by using WHO-UMC assessment scale. Thus a definite diagnosis of drug eruption due to a particular drug was certain in 14 patients (9.21%), 119 cases were probable (78.29%) where re-challenge could not be attempted and 19 cases were possible (12.5%), where more than one drug was implicated.

CONCLUSION

Maculopapular rash was the most common cutaneous adverse drug reaction observed in this study, followed by fixed drug eruptions. Unusual features like dual drug eruptions to a single drug were observed in three patients. The predominant causative drugs were antimicrobials mostly beta-lactams and fluoroquinolones. In HIV patients, nevirapine was the most common offending drug. When rashes were taken individually, antimicrobials are the most common cause of fixed drug eruptions, erythema multiforme, and urticarial lesions. Antiretroviral drugs were the most common cause of maculopapular rash, exfoliative dermatitis, and Stevens Johnson syndrome. Analgesics mainly implicated in urticaria, angioedema and FDE. Severe reactions like DHS, SJS and TEN were mainly caused by anticonvulsants and antiretrovirals.

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