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Original Article

Analysis of clinico-etiological pattern of adverse cutaneous drug reactions

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Abstract

Objective To determine the frequency of various adverse cutaneous drug reactions and drugs causing these reactions in patients presenting to a tertiary care hospital.

Methods This cross-sectional survey was carried out at Dermatology Department of Services Hospital, Lahore for six months. Patients who fulfilled the inclusion criteria were enrolled. Adverse drug reactions were assessed for causality, using Naranjo Algorithm. Patients were evaluated clinically for the type of drug reaction. Patients were asked for drugs/medicine used before appearance of adverse cutaneous drug reactions. Data was stratified for age, gender and duration of symptoms to address the role of effect modifiers. Post-stratification, chi-square test was applied to compare types of adverse drug reaction and medicines involved.

Results Among 150 patients, 71 (47.3%) were males and 79 (52.7%) were females. Age range in this study was from 10 to 70 years with mean age of 44.3±8.7 years. According to type of adverse drug reaction, 37 (24.7%) patients had maculopapular rash, 23 (15.3%) had urticarial drug reaction, 20 (13.3%) had acneiform eruption, 19 (12.7%) had fixed drug eruption, 13 (8.7%) had Erythroderma, 11 (7.3%) had DRESS, 9 (6.0%) had Stevens-Johnson syndrome, 8 (5.3%) had erythema multiforme, 7 (4.7%) had toxic epidermal necrolysis and 3 (2.0%) had drug-induced hyperpigmentation. Phenytoin and diclofenac were the commonest offending drugs.

Conclusion Knowledge of pattern and causative drugs of adverse cutaneous drug reactions is of utmost importance for any clinician as their consequences can be life threatening as well.

Key words
Cutaneous, adverse, drug reactions, dress.

Introduction

World Health Organization has defined Adverse Drug Reactions (ADRs) as a response to a drug used to treat a person that is harmful and inadvertent.[1] Most of these are preventable and are quite common with a prevalence of around 12 to 40%.[2] These reactions may involve any organ including cardiovascular system, nervous system and gastrointestinal tract.[3] Adverse cutaneous drug reactions (ACDRs) constitute a majority of these reactions and may vary from mild rashes to life threatening sequelae.[4] They are a cause of considerable morbidity and complications among hospitalized and outdoor patients.[5]

Most of the drug reactions are dose-dependent and predictable and are mediated by non-immunological pathways. However, about 20 to 25% are unpredictable and may be immune-mediated. These immunological mechanisms may involve immediate or delayed hypersensitivity pathways involving cellular or humoral immunity.[6] Naranjo with his team

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developed a scale to determine the probability of adverse drug reaction in 1991. The Naranjo scale helped in assessment of causality of a drug reaction. It is composed of ten questions which are answered as yes, no or don't know. Values of -1 to +2 are assigned to the answers. Final score varies from -4 to +13, where a total score of 9 or more makes a reaction definite, 5 to 8 is probable, 1 to 4 possible and 0 or less makes it doubtful.[7]

Cutaneous adverse reactions vary in severity from mild to severe, life-threatening reactions. The milder forms include itching, acneform eruption, maculopapular rash, urticaria etc. These closely mimic many other diseases especially viral exanthems, for which the drug might have been taken. This makes the diagnosis particularly problematic. The potentially lethal reactions are termed as SCAR (severe cutaneous adverse reactions). These include acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS).[4]

According to literature, the common groups of culprit drugs causing adverse drug reactions include antibiotics, anti-epileptics, non-steroidal anti-inflammatory drugs and anti-gout medications.[8] Knowledge of potentially culprit drugs may help clinicians select safer drugs. The risk of developing these reactions rises with the number of drugs taken. Certain patient groups are more liable to develop these reactions compared to others.[9]

Despite being common and potentially lethal, not much data is available about the prevalence, pattern, morbidity and mortality of these adverse reactions. This is because most of these reactions remain unreported.[10] Since these reactions are commonly seen by both clinicians and dermatologists, they must be familiar with the pattern and culprit drugs to avoid delay in diagnosis and help immediate withdrawal of the offending drugs. These patterns are continuously changing with the introduction of new drugs. Therefore, this study was planned to know the prevalence of these reactions in our population and to identify the culprit drugs. This would help in better understanding of these adverse reactions and help in their prompt and adequate management reducing burden on healthcare system.

Methods

This cross-sectional survey was conducted at Dermatology Department of Services Hospital, Lahore for six months from October 10, 2020 to April 10, 2021, after getting approval from Ethical Review Board. After taking informed consent, 150 patients suffering from ACDRs were selected by non-probability consecutive sampling. Patients of both genders and ages between 10 and 70 years were enrolled in the study. Patients with other skin problems (bacterial, viral, fungal infections and systemic diseases) before using drug/medicine (on history, examination) which may mimic ACDRs, were excluded.

Demographic data of patients (name, age, gender, duration of symptoms) were recorded on a predesigned proforma. Adverse drug reactions were assessed for causality, using Naranjo Algorithm scale. Patients were evaluated for the type of drug reaction including maculopapular rash, urticarial drug reaction, fixed drug eruption, Acneiform eruptions, Erythema multiforme, erythroderma, dress, Stevens-Johnson syndrome, toxic epidermal necrolysis or drug-induced hyperpigmentation. Patients were asked for drugs/medicine they used before appearance of symptoms of adverse cutaneous drug reactions like diclofenac, isoniazid,

efavirenz, prednisolone, phenytoin, cefixime, metoclopramide, carbamazepine, levetiracetam, ethambutol, methotrexate, allopurinol, cephalexin, non-steroidal anti-inflammatory drugs (other than diclofenac), etc. Patients were managed as per standard protocol. Data was collected on the proforma. Data was analyzed in SPSS version 27. Quantitative variables like age and duration of symptoms were presented as means±SD. Qualitative variables like gender, type of adverse reaction and drugs causing adverse drug reaction were presented as frequencies and percentages. Data was stratified for age, gender and duration of symptoms to address the role of effect modifiers. Post-stratification, chi-square test was applied to compare type of adverse drug reaction and medicines involved in stratified groups with p-value ≤0.05 taken as significant.

Results

Total 150 patients were included in the study. Age range of patients in this study was from 10 to 70 years. Mean of the ages of the patients was 44.3±8.7 years. Most of the patients 51 (34%) were in >50 years' age group, while 30 (20%), 42 (28.0%) and 27 (18.0%) were in <20 years', 21-35 years' and 36-50 years' age groups respectively. 71 (47.3%) were males and 79 (52.7%) were females. Most of the patients (77 i.e. 51.3%) had duration of symptoms for <2 months, while 73 (48.7%) had duration of symptoms for >2 months.

According to type of adverse cutaneous drug reaction, 37 (24.7%) patients had maculopapular rash **(Figure 1A)**, 23 (15.3%) had urticarial drug reaction **(Figure 1B)**, 20 (13.3%) had acneiform eruptions **(Figure 1C)**, 19 (12.7%) had fixed drug eruption **(Figure 1D)**, 13 (8.7%) had erythroderma **(Figure 1E)**, 11 (7.3%) had DRESS, 9 (6.0%) had Stevens-Johnson syndrome **(Figure 1F)**, 8 (5.3%) had erythema multiforme, 7 (4.7%) had toxic epidermal necrolysis and 3 (2%) had drug-induced hyperpigmentation.

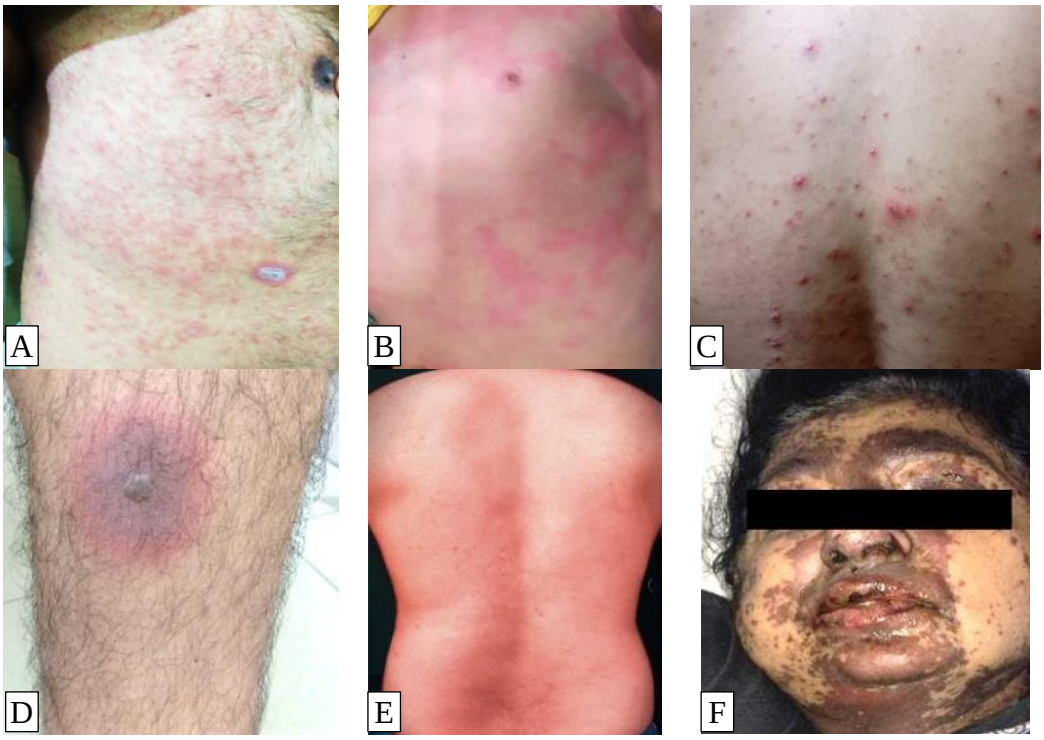

Figure 1 Photographs of patients showing A: Maculopapular rash; B: Urticarial drug reaction; C: Acneiform eruption; D: Fixed drug eruption; E: Erythroderma and F: Steven Johnson Syndrome).

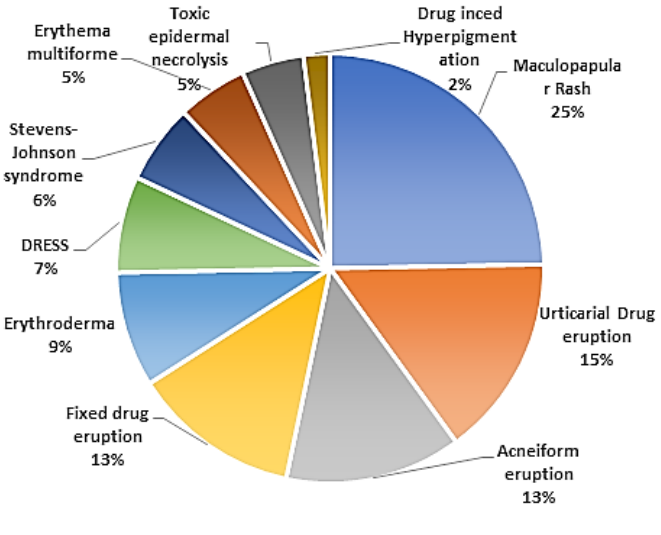

Figure 2 Frequency of types of drug reaction

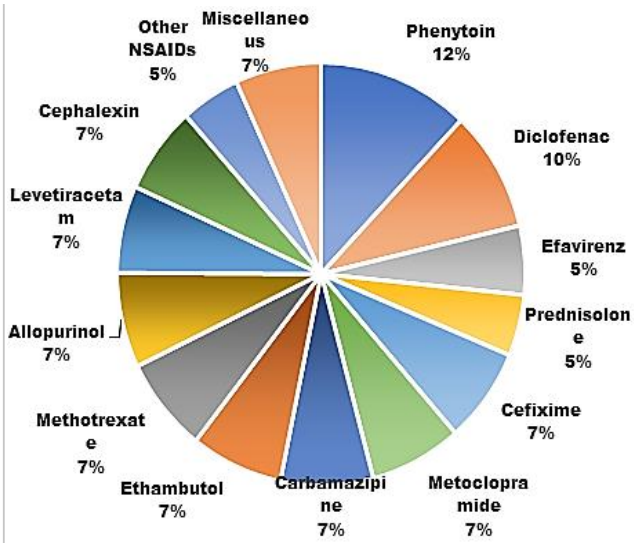

Figure 3 Drugs causing ACDRs

According to drugs causing adverse reaction, the most common drugs causing adverse cutaneous drug reactions were phenytoin (12%) followed by diclofenac (9.3%), efavirenz (5.3%), prednisolone (4.7%), cefixime (7.3%), metoclopramide (7.3%), carbamazepine (7.3%), ethambutol (7.3%), methotrexate (7.3%), allopurinol (7.3%), levetiracetam (6.7%), cephalexin (6.7%), other non-steroidal anti-inflammatory drugs (4.7%) and miscellaneous drugs (6.8%).

Miscellaneous drugs included antibiotics, anti-malarial and anti-hypertensive and anti-diabetic drugs, constituting less than 0.5% of total. No significant effect of age, gender or duration of disease was noted on frequency of various types of drug eruptions (p value > 0.05). Frequencies of various types of drug reactions and commoner culprit drugs are shown in **Figure 2 and 3** respectively.

Out of 150 patients assessed, 71 were males while 79 were females. This female preponderance was also reported by other studies around the world.[11,12] According to Alomar *et al.*, females have an anatomical and physiological propensity to develop drug reactions.[13] This might be the reason for more females developing these reactions.

Age of the patients in our study varied from 10 to 70 years while mean was 44.3±8.7 years. Most of our patients were >50 years old. Hina *et al.*[9] also made this observation. This can be attributed to the age-related altered physiological and metabolic profile in this age group which affects metabolism of drugs. Secondly, poly pharmacy is quite common in this age group, since elderly suffer from more chronic ailments than younger age groups.[14]

Regarding the type of drug reaction, maculopapular rash was the commonest pattern we observed, seen in about a quarter of cases. A number of other studies also reported it to be the most frequent clinical variety seen.[9,11,15,16] However, Kumari *et al.*[12] reported acneiform eruption as commonest ACDR in Indian population, Sultana *et al.*[17] found fixed drug eruption as commonest in Bangladesh while DRESS was the commonest clinical presentation in Malaysia.[18] This difference can be attributed to the variation in usage of drugs as well as

ethnic variation between the study populations.

We found urticarial drug eruption to be the second most commonly seen reaction pattern in 15.3% patients. However, Urticaria was the commonest ACDR reported by Anant *et al.*[19] and Panneerselvam[20] in India. This could again be attributed to social and ethnic variations of the two communities.

Regarding the drugs causing adverse reaction, phenytoin was the commonest culprit (12%) followed by diclofenac (9.3%), and efavirenz (5.3%). Nayak *et al.*[21] also reported anticonvulsants as commonest causative drugs along with others.[17] Sharma *et al.*[15] also found phenytoin to be the most commonly encountered culprit. However, other authors reported antibiotics as the most frequently implicated drugs in cutaneous reactions.[19,21] This variation may be due to different genetic and ethnic background of patients.

This study is one of the few done in our part of the world regarding adverse cutaneous drug reactions. Since our study was based on a single center, our patients were not exposed to newer and varied medicines; this may hinder generalization of our results. Secondly, since our population is prone to polypharmacy, exact causality of drug reaction could not be assessed accurately.

Personalized medicine is a patient specific approach adopted by health care providers where they alter treatment options for every patient in order to get most benefit and reduce risk of probable drug reactions.[22] Moreover, drug reactions may be a significant cause of non-compliance to therapy and reduce patient's confidence in treating physician. Legal implications may also complicate the doctor patient relationship and overall efficacy of health care system of a community.

Conclusion

Knowledge of a population's susceptibility to specific drug reactions is of utmost importance in order to formulate adequate, effective and safe treatment plans for patients. This would help reduce or minimize the extent of iatrogenic morbidity and mortality. Prescribing a drug to an already sensitized individual may have serious consequences for both the patients and the health care provider. Since, a majority of these reactions involve the skin, so it is inevitable for dermatologists to have updated knowledge of their spectrum amd prevalence in order to provide safe and efficient care to patients.

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