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Original Article

Cutaneous morphological patterns of adverse drug reactions: a study of 50 cases

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Abstract

Background Adverse drug reactions are common complications in drug therapy. About 3-8% of all hospital admissions are the results of adverse drug reactions, and these can cause significant disability to patients.

Objectives To evaluate the clinical spectrum of all cutaneous adverse drug reactions and to establish the causal link between suspected drug and the reaction.

Patients and methods This observational cross-sectional study was done among the patients having cutaneous drug eruptions. 50 consecutive patients were enrolled. Purposive sampling was done. In every patient a detailed history was taken. Examination was carried out to find out the type of cutaneous reactions. Data were collected in a predesigned structured questionnaire. Statistical analysis was done with the help of SPSS.

Results Out of 50 respondents, 20% had a history of indigenous drug intake followed by 18% sulphonamides, 14% NSAIDs, 14% quinolones, 8% anticonvulsants, 8% cephalosporins, 6% penicillins, 4% antituberculous drugs, 4% metronidazole and 4% tetracyclines. 34% had maculopapular rash, 24% Stevens-Johnson syndrome, 12% exfoliative dermatitis, 10% urticaria, 8% fixed drug eruption, 8% erythema multiforme, 8% bullae, 6% vesicles, 2% lichenoid eruption and 2% scaly eruptions.

Conclusion Frequency distribution of the offending drugs and the adverse reactions revealed that cephradine was responsible for maculopapular rash, sulphonamides for Stevens-Johnson syndrome, indigenous medicines for exfoliative dermatitis, NSAIDs for urticaria and paracetamol for fixed drug eruption.

Key words
Drug eruptions, Stevens-Johnson syndrome, erythema multiforme, fixed drug eruption

Introduction

Adverse drug reactions are common with many drugs and these can cause significant disability to the patient.[1] A French study among 2067 adults, aged 20-67 years attending a health centre for a checkup reported that 14.7% gave reliable histories of systemic adverse reactions to one or more drugs. In a Swiss study of 5568 hospital inpatients, 17% had adverse reactions to drugs. Fatal drug reactions occur in 0.1% medical inpatients and 0.01% of surgical inpatients.[2] Cutaneous drug reactions occur in 2-3% of all hospitalized patients. Furthermore, the

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development of a skin eruption is frequently cited as a reason for discontinuation of treatment before the completion of a therapeutic course. Cutaneous drug eruptions account for a large proportion of burden on the general population and health care system.[1]

Certain patient groups seem to be at increased risk of developing a cutaneous drug reaction. The incidence of developing a cutaneous reaction increases with the number of the drugs taken. In addition, some drug interactions may contribute to the development of a skin eruption. The age of the patient also correlates with an increased risk of a cutaneous drug eruption; older patient, boys younger than 3 years, and girls older than 9 years have been found to be more prone to drug eruptions. Women are more likely than men to develop a skin eruption.[1]

Viral infections have been shown to increase the risk of a drug rash; infectious mononucleosis, cytomegalovirus, human immunodeficiency virus and human herpes virus 6 have all been incriminated.

Moreover, some intrinsic factors influence the risk of a cutaneous drug eruption. Individual genetic variations in the metabolism of a drug and HLA association are part of these factors. For example the slow N-acetylation phenotype may predispose to sulfonamide reactions, HLA-DR4 type may predispose to drug-induced pemphigus, HLA-B7 to insulin allergy, and HLA-B22 to fixed drug eruptions. Finally, concurrent disease like systemic connective tissue disease may lead to immune disturbance and enhance the risk of a cutaneous drug eruption, as impaired renal and liver function increase risk of cutaneous rashes.[1]

Although most drug-induced skin eruptions are not serious but some are severe and potentially life threatening. Serious reactions include angioedema, erythroderma, Stevens-Johnson syndrome and toxic epidermal necrolysis. Drug eruptions can also occur as part of a spectrum of multiorgan involvement, for example in drug-induced SLE. A cutaneous drug reaction should be suspected in any patient who develops a rash during a course of drug therapy. The reaction may be due to any medicine the patient has been currently taking or has recently been exposed to, including prescribed and over the counter medicine, herbal or homeopathic preparations, vaccine or contrast media.[3]

A wide spectrum of cutaneous manifestations ranging from maculopapular rash to severe toxic epidermal necrolysis can be produced by different classes of drugs. Severe adverse drug reaction may result in serious morbidity and even death. Prompt identification and withdrawal of the offending agent help to limit the toxic effects associated with drug.[4]

This study was, therefore, designed to evaluate the clinical spectrum of all cutaneous adverse drug reactions and to establish the causal link between suspected drug and the reaction.

Patients and methods

This observational type of cross-sectional study was done in the Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka from January 2006 to February 2007 among the patients suspected of having cutaneous drug eruptions. Fifty consecutive patients were enrolled from the inpatient and outpatient departments. Purposive sampling was done. Patients of any age, sex and having a definite relationship of a drug intake and the appearance of skin eruption were included. The criteria for the diagnosis of

Adverse Drug Reactions (ARDs) followed in the present study were as below:

1. The reaction was considered as drug induced if the drug was administered at least within 8 weeks of onset of cutaneous eruption.
2. Improvement of the condition of the patient after withdrawal of the suspected drug.
3. The patient with a history of taking more than one drugs, recently added drug was considered as the offender.
4. The ADRs cases with the history of several drugs causing similar reaction were diagnosed on the basis of probability of similar cases in other studies.

In every patient a detailed history regarding drug intake, reaction time, history of previous drug reaction were taken. Meticulous examination was done to find out the type of cutaneous reactions. Data including socio-demographic variables were collected in a predesigned structured questionnaire. All the data were checked and edited after collection. Then data were analyzed with the help of statistical package for social sciences (SPSS) and p <0.05 was considered as a level of significance.

Results

Out of 50 patients, 44% were males and 56% were females with a male to female ratio of 1:1.14. The age varied from 5 to 75 years with a mean of 30.05±15.15 years. 82% patients are adult (≥19 years) and rest 18% were in pediatric age group.

Out of all respondents, 20% had history of indigenous drug intake followed by 18% sulphonamides, 14% NSAIDs, 14% quinolones, 8% anticonvulsant, 8% cephalosporin, 6% penicillins and related drugs, 4% each of antituberculous drugs, metronidazole and tetracyclines intake (**Table 1**).

Table 1 Frequency distribution of drug intake among the patients (n=50)

Group	*n (%)*
Indigenous drugs	10 (20%)
Sulphonamides	9 (18%)
NSAIDs	7 (14%)
Quinolones	7 (14%)
Anticonvulsants	4 (8%)
Cephalosporin	4 (8%)
Penicillins	3 (6%)
Antituberculous drugs	2 (4%)
Metronidazole	2 (4%)
Tetracyclines	2 (4%)

Table 2 Time interval between drug intake and onset of eruption.

Type of lesion	*Mean time of eruption (days)*
Exfoliative dermatitis	18 ±12.67
Bullae	13.25±13.33
Vesicles	10.67±15.04
Maculopapular/ morbilliform reaction	10.53±11.76
Fixed drug eruption	10±2.83
Stevens-Johnson syndrome	9.25±8.38
Scaly eruption	7±6.37
Erythema multiforme	5.5±4.51
Urticaria	3±1.41
Lichenoid eruption	2±1.21

Table 3 Frequency distribution of different types of lesions

Lesion	*n (%)*
Maculopapular/morbilliform eruption	17 (34%)
Stevens-Johnson syndrome	12 (24%)
Exfoliative dermatitis	6 (12%)
Urticaria	5 (10%)
Fixed drug eruption	5 (10%)
Erythema multiforme	4 (8%)
Bullae	4 (8%)
Vesicles	3 (6%)
Lichenoid eruption	1 (2%)
Scaly eruption	1 (2%)

Table 2 enlists the mean interval between drug intake and the onset of eruption. It ranged from 2±1.21 days for lichenoid drug eruption to 18±12.67 days for exfoliative dermatitis.

Exanthematous/maculopapular/morbilliform drug eruption was the commonest morphological pattern of cutaneous ADR. Other patterns of cutaneous ADRs in decreasing frequency are shown in **Table 3**.

The causative drugs in different morphological drug reactions are shown in **Table 4**. It is pertinent to note that one group of drugs could give rise to different morphological patterns of ADRs. Sulphonamides were responsible in 41.7% cases of Stevens-Johnson syndrome, followed by each of indigenous medicines and anticonvulsant drugs in 25% cases. 8.3% cases were caused by quinolone.

Out of all patients of exfoliative dermatitis, 4 (66.7%) had taken indigenous drug, 1 (16.7%) had anticonvulsant drug and 1 (16.7%) had quinolone intake history (**Table 4**).

Out of all patients of urticaria, 40% had a history of taking NSAIDs, 20% in each group had a history of penicillin and related drugs, cephradine and quinolone intake (**Table 4**).

Out of all patients of fixed drug eruption, 40% had history of taking NSAIDs. 20% of each has history of sulphonamides, metronidazole and tetracycline (**Table 4**).

Table 4 Frequency distribution of drugs causing different drug reactions.

Drugs	*N (%)*
Stevens-Johnson syndrome (n=12)	
Sulphonamides	5 (41.7%)
Indigenous medicine	3 (25%)
Anticonvulsant	3 (25%)
Quinolone	1 (8.3%)
Exfoliative Dermatitis (n=6)	
Indigenous medicines	4 (66.7%)
Anticonvulsant	1 (16.7%)
Quinolone	1 (16.7%)
Urticaria (n=5)	
NSAIDs	2 (40%)
Penicillins	1 (20%)
Cephradine	1 (20%)
Quinolone	1 (20%)
Fixed drug eruption (n=5)	
NSAIDs	2 (40%)
Sulphonamides	1 (20%)
Metronidazole	1 (20%)
Tetracycline	1 (20%)

Discussion

This descriptive type of cross sectional study was undertaken to observe the cutaneous manifestations of drug reactions. Out of 50 patients studied 56% were females and 44% males with a male female ratio of 1:1.14. Age varied from 5 year to 75 years. 82% were of 19 and above age group falling into category of adults. The rest 18% were found in the group of children and adolescents. Vervloet and Durham had reported similar findings.[2]

Drugs most frequently involved were indigenous 20%, sulphonamide 18%, NSAIDs and quinolones 14% each, anticonvulsants and cephalosporin 8% each, penicillins 6%, antituberculous drugs, metronidazole and tetracyclines 4% each (**Table 2**). In the Boston collaborative drug surveillance programme almost similar results were obtained by Shear.[1]

The time interval between the introduction of drug and the onset of reaction (mean time) of exfoliative dermatitis was 18 days, maculopapular rash 10 days, fixed drug eruption 10 days, Steven-Johnson syndrome 9 days, erythema multiforme 5 days, urticaria 3 days, lichenoid eruption 2 days and scaly eruption 7 days. Breathnach has reported the development of exfoliative dermatitis within 2-3 weeks, maculopapular rash within 2 weeks, Stevens-Johnson syndrome in 7±6 days, fixed drug eruption in 16 hours and urticaria in 1.5 days after initiation of drug therapy.[5] Noel *et al*.[4] had reported the time taken for the reaction to appear since the last exposure to suspected drug to be 2-7 days for the maculopapular rash, 1-3 weeks for

Stevens-Johnson syndrome, 2-3 weeks for toxic epidermal necrolysis, 1-3 days for urticaria, 1-2 weeks for erythema multiforme, 6 weeks for exfoliative dermatitis and 1 day for fixed drug eruption. These observations were quite similar to those of our study except that for fixed drug eruption.

Cutaneous adverse drug reactions vary in their patterns of morphology and distribution. In the present study, maculopapular rash was the most common manifestation of cutaneous ADRs accounting for 34% of patients, followed by Stevens-Johnson syndrome 24%, exfoliative dermatitis 12%, urticaria and fixed drug eruption 10% each, erythema multiforme and bullous eruption 8% each, vesicular eruption 6%, lichenoid eruption and scaly eruption 2% each. Stern and Wintroub [6] reported the most common morphological patterns as exanthematous (maculopapular), urticarial and/or angioedema, fixed drug eruption and erythema multiforme. Noel *et al*.[4] had reported maculopapular rash in 35%, followed by Stevens-Johnson syndrome 15%, urticaria and erythema multiforme 7% each, and exfoliative dermatitis and fixed drug eruption 4% each. Jhaj *et al*.[7] had also reported maculopapular rash as the most common reaction in 50% patients, urticaria 21.5%, Stevens-Johnson syndrome 13.9% and toxic epidermal necrolysis in 10% cases. Other reactions included pruritus without a rash, contact dermatitis, purpura, erythema multiforme, fixed drug eruption and acneiform eruption.

Cephalosporins were responsible for 17.6% of maculopapular/morbilliform rash, followed by 11.8% each of quinolones, antituberculous drugs, indigenous medicines, metronidazole, NSAIDs and penicillins. Each of anticonvulsant and sulphonamides was responsible in 5.9% cases. Shear[1] had reported beta-lactam antibiotic cephradine as the most commonly implicated drug. Most common drugs causing maculopapular reactions as observed by Breathnach[5] were ampicillin and penicillin, sulphonamides, phenytoin and carbamazepine.

Sulphonamides were responsible in 41.7% cases of Stevens-Johnson syndrome, followed by indigenous medicine and anticonvulsant drugs each in 25% cases. 8.3% cases were caused by quinolone. Sehgal *et al*.[8] mentioned sulphonamides, thiacetazone, barbiturates, carbamazepine, lamotrigine, allopurinol as the causes of Stevens-Johnson syndrome.

Out of all patients of exfoliative dermatitis, 66.7% had history of taking indigenous drugs, and 16.7% had anticonvulsant drugs and quinolone intake history. This observation did not match with that of Sehgal *et al*.[8]

According to his study, the commonest associated drugs were isoniazid 20%, thiacetazone 15%, topical tar 15%, homeopathic medicine 20% while phenylbutazone, streptomycin and sulphadiazine each accounting for 5% of cases.

In our series, out of all patients of urticaria, 40% had history of taking NSAIDs while 20% had a history of penicillins, cephradine and quinolone intake. Shear[1] listed NSAIDs, cephalosporins, penicillin and its derivatives, narcotic analgesia, radio contrast dye as the commonly associated drugs with urticaria.

In a study of 113 patients with fixed drug eruption, co-trimoxazole caused the maximum incidence (36.3%) followed by tetracycline (15.9%), pyrazolone (naproxen and mefenamic acid) (14.2%), sulphadiazine (12.4%), dipyrine (a drug of aspirin group) (9.3%), paracetamol (acetaminophen) (7.9%), aspirin (1.7%),

thiacetazone (0.88%) and levamisole (0.88%).[9] We found in all patients of fixed drug eruption that 40% had history of taking NSAIDs. 20% in each group, had history of sulphonamides, metronidazole and tetracyclines intake. Stern and Wintrob[6] mentioned oral contraceptives, barbiturates, paracetamol, aspirin, naproxen, tetracycline, metronidazole and sulphonamides as the drugs associated with fixed drug eruption.

Conclusion

Cutaneous adverse reactions occurred mostly by indigenous drug, sulphonamides, NSAIDs and quinolones. Maculopapular rash and Stevens Johnson Syndrome were the most common morphological types.

The pattern of toxicity is likely to change with the introduction of new biotechnology products. A better understanding of the mechanisms underlying ARDs is important in drug development and in patient care.

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