Original Paper

Severe Cutaneous Adverse Drug Reactions in Bangladesh: A Review in a Tertiary Level Hospital

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Abstract

Introduction: The Severe Cutaneous Adverse Drug Reactions (SCADRs) are rare but life-threatening as these encompass drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalized exanthematous pustulosis (AGEP).

Objective: To estimate the incidence of SCADRs and to find out the cause in Bangladesh.

Materials and Methods: 50 patients with SCADRs were studied over a period of 1 year from January 2015 to December 2015 in the Department of Dermatology, Combined Military Hospital, Dhaka. Data were collected from the informant and recorded in structured Case Report Form. Quantitative data were expressed as mean and standard deviation and qualitative data as frequency and percentage.

Results: Clinical diagnosis of the study subjects recognized 46.0% cases as SJS, 28(19.0%) as TEN, 16.0% as DRESS and 10.0% as AGEP. The maximum incidence (46%) was seen in the age group of 31-50 years; mean age of the patient was 37.42+5.3 years. Male and female ratio was 2.84:1. Anticonvulsant group of drugs could give rise to maximum incidence of SCADRs. Carbamazepine was responsible in 22.0% cases of SCADRs, followed by Phenytoin in 16.0% patients and Phenobarbital in 14.0% cases.

Conclusion: SCADRs were seen mostly with the anti-convulsant drugs belonging to Carbamazepine and Phenytoin group. SCADRs deserve continuous monitoring to plan preventive strategies.

Key-words: Severe cutaneous adverse drug reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, anticovulsant drugs.

Introduction

Since time immemorial medications have been used to cure the sufferers; however the Adverse Drug Reactions (ADRs) are considered as one of the most serious medical challenges in terms of early recognition, proper management and their prevention[1]. These are rated as the fifth leading cause of death among all diseases; about 5–8% of all hospitalization worldwide is due to ADRs[2]. The Severe Cutaneous Adverse Drug Reactions (SCADRs) are rare but life-threatening as these encompass drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP). As per WHO, adverse drug reaction is a response to a drug that is noxious and unintended and occurs at doses, used in man for prophylaxis, diagnosis, or therapy for a disease or for modification of physiological function[3].

Genetic factors are crucial in examining patients[4]. The patients with history of drug allergy should be carefully examined while prescribing any drug especially those drugs which are commonly implicated in skin reaction[5]. Some diseases such as hepatic disease, renal disease, systemic lupus erythematosus (SLE) and acute immuno-deficiency syndrome (AIDS) are associated with an increased risk of skin reactions[6]. At the time of ADRs to confirm the over dose of drug, determination of serum or blood levels of drug could be useful[7]. Furthermore, dechallenge (improvement after stopping of drug) and rechallenge (recurrence or exacerbation of reaction after re-exposure to the offending drug) are also important to document[8].

With the advancement of modern medical science, new drugs are being launched every day. With the increased number of drugs taken, the incidence of developing cutaneous ADRs also increases. Severe ADRs account for 6.7% of drug reaction with 0.32% of these being fatal

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in hospitalized patients. The overall incidence of SJS and TEN was estimated at 1 to 6 cases per million person-years and 0.4 to 1.2 cases per million person-years, respectively. The estimated incidence of DRESS ranges from 1 in 1000 to 1 in 10,000 drug exposures. AGEP is rare with an incidence of 1-5 cases per million per year[9]. ADRs could also be occurred with the use of herbal drugs[10]. ADRs are ranked between the fourth and sixth leading causes of death in USA and it is responsible for 6.9% of total admissions in India[11]. However there is no structured available data regarding the incidence of ADRs as well as SCADRs among hospitalized patient in Bangladesh. Moreover, information on the market penetration of new drugs and on their rational and safe prescribing are also limited. Thus more recent and authentic data are required to estimate the incidence of serious and fatal SCADRs in hospitalized patients in Bangladesh. Therefore, this study was designed to monitor drug induced cutaneous adverse reactions in patients to estimate the incidence of serious and fatal SCADRs and the cause of such reactions in hospitalized patients in Bangladesh.

Materials and Methods

This is an observational cross sectional study. 50 admitted patients (37 males and 13 females) with severe cutaneous drug reactions were studied over a period of 1 year from January 2015 to December 2015 in the Department of Dermatology in collaboration with the Department of Medicine at Combined Military Hospital, Dhaka Cantonment, Dhaka. Samples were selected by purposive technique. Data were collected from the informant and recorded in structured Case Report Form. Patient data such as age, sex, clinical presentation, history of drug intake and allergic reactions, previous drug interactions, investigations and the treatment given to the patients were recorded. The patients were kept under follow up daily until their discharge from the hospital. Clinical examination and relevant investigation were done meticulously. All collected questionnaire were checked carefully to identify the error in the data. Data processing work consisted of registration schedules', editing's computerization, preparation of dummy table, analyzing and matching of data. Data was processed and analyzed with the help of computer programme SPSS and Microsoft excel. Quantitative data were expressed as mean and standard deviation and qualitative data as frequency and percentage. Comparison was done by tabulation and graphical presentation in the form of tables, pie chart, graphs, bar diagram and charts etc. The patients were briefed about the objectives of the study, risk and benefits, freedom for participating in the study and confidentiality. A written informed consent was taken from patient or attendant prior to the study.

Results

Total 50 (37 males and 13 females) patients with severe cutaneous ADRs were included in the study. The maximum incidence (46%) was seen in the age group of 31 to 50 years and the mean age of the patients was 37.42+5.3 years (Table-I). 74.0% cases were male and 26.0% were female. Frequency of severe adverse drug reactions was highest at middle age group in both sexes, but predominantly in female. Large numbers of respondents (70%) came from urban area and professionally, maximum were service holders (54.0%). Table-II shows that febrile illness and rapid progressive painful skin presentation were the commonest features in 100% cases. Purpuric lesions (86.0%), bulla (72.0%) and pustular eruption (50.0%) were the other common clinical presentations.

Laboratory findings and clinical examination revealed that leucocytosis was present in 64.0% patients, followed by lymphocytopenia in 58.0% patients, neutropenia in 50.0% patients, epidermal necrosis involved <10% of body surface area in 46.0% cases and neutrophilia was found in 34.0% of patients (Table-III). It is pertinent to note that anticonvulsant group of drugs could give rise to maximum incidence and different morphological patterns of ADRs. Carbamazepine was responsible in 22.0% cases of severe cutaneous adverse drug reactions, followed by Phenytoïn in 16.0% patients and Phenobarbital drugs in 14.0% cases. However others drugs like antimicrobials, NSAIDS and Herbal medicine were also the offending agent (Table-IV).

Clinical diagnosis of severe cutaneous adverse drug reactions (SCADRs) showed that stevens-Johnson syndrome (SJS) was found in 46.0% patients, toxic epidermal necrolysis (TEN) was in 19.0% of patients, drug reaction with eosinophilia and systemic symptoms (DRESS) in 16.0%, and acute generalized exanthematous pustulosis (AGEP) in 10.0% of patients (Table-V). In this study <10% body surface area was involved in 23 (46%) patients, 10 to 30% body surface area was involved in 13 (26%) and >30% body surface area in 14 (28%) patients (Figure-1).

From hospital admission to discharge, proper workup and evaluation were performed in all patients (Table-VI). Among 50 patients, 39(78.0%) were uneventful and recovered without any complication. However, 11(22.0%) patients developed some complications such as septicemia (6 patients), hepatitis (2 patients), pneumonia (single patient) and renal failure (2 patients). The study shows that recovery rate of patients with stevens-Johnson syndrome (SJS) was 78.2% (18/23), toxic epidermal necrolysis (TEN) was 35.7% (5/14), Drug reaction with eosinophilia and systemic symptoms (DRESS) was 75.0%

(6/8) and in Acute generalized exanthematous pustulosis (AGEP) 100%. More complications and fatal outcome were observed in patients with toxic epidermal necrolysis (TEN); patients died due to complications arising from a septic shock which developed into multiple organ disorder syndrome (MODS) leading to death.

Table-I: Demographic characteristics of the patients (n=50)

Age (years)	Frequency		Total
	Male (n= 37)	Female (n= 13)	
16-30	12(32.43%)	4(30.76%)	16
31-50	15(40.54%)	8(61.53%)	23
51-70	7(18.91%)	1(7.69%)	8
>70	3(8.10%)	0	3
Mean ± SD	37.42 ±5.3		

Table-II: Clinical presentation of study subject

Clinical symptoms	No of Patients	(%)
Febrile illness	50	100.0
Purpuric lesions	43	86.0
Bulla	36	72.0
Detachment of epidermis of skin	37	74.0
Pustular eruption	25	50.0
Painful skin	50	100.0
Skin Rash	16	32.0

Table-III: Clinical signs and investigation findings in severe cutaneous adverse drug reactions

Clinical sign and investigation findings	No of Patients	%
Leucocytosis	32	64.0
Epidermal necrosis involving >30% of body surface area	14	28.0
Epidermal necrosis involving <10% of body surface area	23	46.0
Neutrophilia	17	34.0
Eosinophilia	13	26.0
Lymphocytopenia	29	58.0
Neutropenia	25	50.0
Thrombocytopenia	13	26.0
Lymphadenopathy	12	24.0
Pneumonia	7	14.0
Tachycardia	14	28.0
Jaundice	5	10.0
Hepatomegaly	8	16.0

Table-IV: Name of the offending drugs causing severe cutaneous adverse drug reactions (n=50)

Offending drugs	Affected Patients	Percentage
Carbamazepine	11	22.0
Phenytoïn	8	16.0
Phenobarbital	7	14.0
NSAIDs	5	10.0
Sulfonamides	4	8.0
Herbal medicine	4	8.0
Olanzepine	3	6.0
Ceftriaxone	3	6.0
Levoxin	2	4.0
Malacide	2	4.0
Fluconazole	1	2.0

Table-V: Clinical diagnosis of severe cutaneous adverse drug reactions (n=50)

Clinical Diagnosis	Frequency	%
Stevens-Johnson syndrome (SJS)	23	46.0
Toxic epidermal necrolysis (TEN)	14	28.0
Drug reaction with eosinophilia and systemic symptoms (DRESS)	8	16.0
Acute generalized exanthematous pustulosis (AGEP)	5	10.0

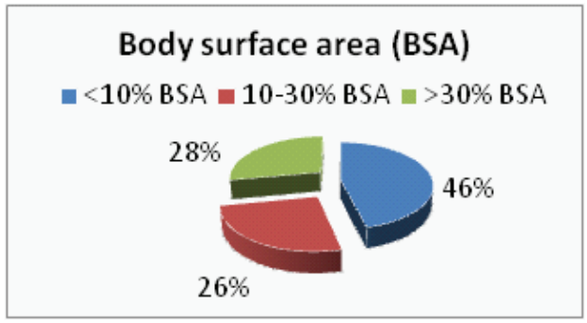

Fig-1: Involvement of body surface area (n=50)

Table-VI: Outcome and fate of patients with severe cutaneous adverse drug reactions (n=50)

Severe cutaneous adverse drug reactions	Outcome		
	Recovered	Recovered with sequele	Fatal
Stevens-Johnson syndrome (SJS)	18	2	3
Toxic epidermal necrolysis (TEN)	6	3	5
Drug reaction with eosinophilia and systemic symptoms (DRESS)	6	2	0
Acute generalized exanthematous pustulosis (AGEP)	5	0	0

Discussion

In this study, frequency of severe cutaneous adverse drug reactions was highest at middle age group in both sexes, but predominant in female (Table-I). Higher incidences of cautaneous ADRs in adult age groups ranging from 21-40 years were reported in previous studies[12-15]. However, few findings for example male female ratio is different than that of a prospective study by Hassan R Akhter et al[16]. This is because this study used spontaneous reporting system as the only method for detecting ADRs. ADRs were identified by prospective manner by using patient chart (medical notes, laboratory findings etc) as source of information.

Present study shows that febrile illness and rapid progressive painful skin presentation were the commonest features in all patients; present in 100.0% cases. Purpuric lesions, bulla and pustular eruption were the other common clinical

presentations (86.0%, 72.0% and 50.0% respectively). The diagnosis of SCADRs requires identification of skin eruption with high fever and severe constitutional symptoms that might have been caused by a medication and not by other cause like viral infection. Clinical diagnosis of SCADRs recognized SJS in 46.0% cases, TEN in 19%, DRESS in 16% and AGEP in 10% cases. A cross-sectional study in the Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, revealed that, out of total twenty patients, 9(45%) had fixed drug eruptions, 4(20%) urticaria, 3(15%) Stevens-Johnson syndrome, 2(10%) morbilliform rashes and 2(10%) had erythema multiforme[17] that study included all forms of cuteneous ADRs. The most common types of offending drugs causing the drug reactions were sulfur containing drugs in 8(40%) cases, followed by NSAIDs in 6(30%), quinolones 3 (15%), metronidazole and anticonvulsants in a few[17]. The study by Ghosh et al[18] reported that majority of adverse reactions were cases of SJS, erythema multiforme and urticaria among the 53 patients of adverse drug reactions. A study by Sharma et al13 also observed maculopapular rash in 34.6%, fixed drug eruptions in 30% and urticaria in 14% among 500 patients of adverse drug reactions in Chandigarh, India. Though ADRs are very common in drug therapy, but SCADRs is rare. Most of the previous studies dealt with ADRs and revealed that antibiotics were commonly responsible for ADRs; however, this study observed that anticonvulsant group of drugs could give rise to maximum incidence (52%) of SCADR. This hospital is a tertiary level hospital where mostly severe cases came. Carbamazepine was responsible for drug reaction in 22.0% cases followed by phenitoin in 16% and Herval drugs in 8.0% cases. Similar to this study, life threatening cutaneous ARDs was reported to 43.0% cases with anticonvalsants; Carbamazepine accounted for 24.0%, phenytoin 9.6% and Harbal medicine 6.0%[13].

A 100% patient follow-up was achieved in the present study. All patients were compliant with the proposed surveillance protocol. The total follow-up duration was from hospitalization to 90 days in the whole series. Study showed that recovery rate of patients of stevens- Johnson syndrome (SJS) was 78.2% (18/23), toxic epidermal necrolysis (TEN) was 35.7% (5/14), Drug reaction with eosinophilia and systemic symptoms (DRESS) was 75.0% (6/8), and Acute generalized exanthematous pustulosis (AGEP) was 100%. More complications and fatal outcome were observed in patients with toxic epidermal necrolysis. Patient died due to complications arising from a septic shock, which developed into multiple organ disorder syndrome (MODS) leading to death.

It is evident that SCADRs represented a considerable part of overall medical events. This study revealed that anticonvulsants accounted for 52% cases of SCADRs. This could be considered as an indication for a need for intervention and increase prevention level in SCADRs related health problems. To protect patients from unnecessary health hazards, appropriate knowledge of effective use of drugs to prevent SCADRs is essential. This can result in a considerable health resource savings and at the same time can help to improve the quality of health provision.

Conclusion

Severe cutaneous adverse drug reactions occurred mostly by anticonvulsant drugs. Stevens Johnson Syndrome was the most common morphological type. The pattern of toxicity is likely to change with the introduction of new biotechnology to prepare products. A better understanding of the mechanisms underlying SCADRs is important in drug development and in patient care. Despite being rare, SCADRs deserve continuous monitoring to accurately quantify the burden and to identify the related risk factors in hospitalized patients and to plan preventive strategies to minimize these drug-induced harms and improve the quality of patient care.

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