Patterns and Outcomes of Cutaneous Adverse Drug Reactions in a Hospital Based Study

Paudel U[1], Parajuli S[2], Pokhrel DB[3]

[1,2]Assistant Professor, [3]Professor, Department of Dermatology, Maharajgunj Medical Campus, Maharajgunj.

Address for correspondence
Dr. Upama Paudel
Phone: 9841256983
E-mail : upama_ups@yahoo.com

Abstract

Introduction : Drug reactions are one of the common reasons for admission in the Dermatological beds. Data on the culprit drugs and patterns of reaction are very scarce in Nepal.

Objective: To determine the patterns of drug reactions admitted in Tribhuwan University (TU) Teaching hospital, the causes of drug reactions, duration of hospital stay, duration of steroid use and the outcome of the treatment.

Material and Methods: This was a retrospective study done in TU Teaching Hospital. The admissions and discharge record of admitted patients from 15th April 2008 to 14th April 2012 were analyzed for the variables mentioned above.

Results: There were 61 new patients of drug reactions; however only files of 42 patients could be studied.The mean age of the patients was 32.26 +/- 15.26 with male to female ratio of 1.8:1. Stevens Johnson's syndrome (35.7%) was the commonest cause of admission followed by drug induced erythroderma (16.7%) and toxic epidermal necrolysis (11.9%). Carbamazepine, Phenytoin and allopurinol were the most common drugs for the reactions. The median time for the appearance of the lesions was 20.07 days. The median duration of hospital stay was 7 days. Steroids were used for initial treatment for around 4.9 +/-1.7 days. 83.3% of the patients improved while 11.9% succumbed despite optimal management.

Conclusion: Severe drug reactions were the common reasons for admissions in our hospital. Anti-epileptics were the leading cause for the reactions. Steroids were used for initial period and rapidly tapered off in short duration. Overall, the outcomes of the treatment were good.

Key words: cutaneous drug reactions; steroids; steven-johnson syndrome; toxic epidermal necrolysis

Introduction

Drugs can cure, suppress or prevent a disease and are usually beneficial to humans.

However, they can also produce undesirable/harmful effects, which are known as adverse drug reactions (ADRs). Cutaneous adverse drug reactions (CADRs) can be defined as noxious, unintended morphological skin changes with or without systemic involvement, developed after local or systemic administration of drugs in dosages commonly used for prevention, diagnosis or treatment of disease or modification of physiological functions, in accordance with the World Health Organization's general definition of adverse drug reactions (ADRs).[1]

Cutaneous ADRs can be caused by a wide variety of agents. The spectrum of Cutaneous ADRs ranges from a transient maculopapular rash to fatal reactions like SJS, TEN and DRESS.[2,3] They account for about 5 % of all hospital admissions in the UK.[4] The incidence of cutaneous ADRs among inpatients in developed countries ranges from 1 - 3% whereas in India it is 2-5%[5], however, the data from our country is limited.

ADRs are reportedly responsible for up to 7% of hospital admissions, and cutaneous ADRs alone contribute to 2-3% of the overall hospital admissions.[6,7] Up to 30-45% of the ADRs are reportedly cutaneous in nature, 2% of which may be severe and few may even end in fatalities.[8,9] Incidence of fatal cutaneous ADRs in the US is 0.32%.[10]

The most common CADR is morbilliform exanthema (ME), but it is also the least specific manifestation.

Other potentially severe forms are more specific, but they are less frequently encountered.[11]

The aim of this study is to report the various reaction patterns of the severe cutaneous adverse drug reactions and their putative drugs, as well as the outcome among the patients who were managed in a tertiary hospital of Nepal from 15th April 2008 to 14th April 2012.

Material and Methods

In this mono centric study, a retrospective analysis of all hospital records of severe cutaneous adverse drug reactions admitted in the dermatology ward of the TUTH from 15th April 2008 to 14th April 2012 was conducted. The age and sex of the patient, the offending drug, the time interval between the drug intake and the eruption, duration of hospital stay, outcome and sequel were recorded. Based on morphology, distribution of the lesions, and clinical examination of the CADR, toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS); Erythroderma (ED); and drug hypersensitivity syndrome (DHS) were distinguished.

Results

There were a total of 283 new admissions in the Dermatology ward, out of which 61 patients (21.6%) were having drug reactions, in a four years period, but only 42 files could be retrieved. There were 27(64.3%) males and 15(35.7%) females. The mean age of the patients was 32.26+/-15.26 (ranging from 11 to 75 years). The commonest age group to be affected by drug reactions was 26-35 years. (Table 1).

Table 1: Age group of patients admitted with CADRs

Age Group	Number (%)
<14 years	4 (9.5%)
15-25years	11 (26.2%)
26-35 years	12 (28.6%)
36-45years	8 (19%)
46-55 years	3 (7.1%)
56-65years	2 (4.8%)
>65years	2 (4.8%)
Total	**42 (100%)**

Twenty four (57.1%) patients had history of intake of single medication and 18 (42.9%) had taken multiple medications. Among the multiple drugs, antibiotics with NSAIDs were common combinations.

Maximum number of cases were diagnosed as SJS (15 cases) followed by 7 cases each of erythroderma and extensive exanthematous drug eruption. There were 5 cases of TEN, 3 cases each of drug hypersensitivity syndrome and SJS-TEN overlap; 1 case each of FDE and EM (Table 2).

Table 2: Types of CADR

Diagnosis	Number(%)
SJS	15 (35.7%)
TEN	5 (11.8%)
SJS-TEN	3 (7.1%)
Erythroderma	7 (16.7%)
Exanthematous drug eruption	7 (16.7%)
Drug hypersensitivity syndrome	3 (7.2%)
Erythema multiforme	1 (2.4%)
Fixed drug eruption	1 (2.4%)
Total	**42 (100%)**

The median time for appearance of lesions after medication was 20.07 days.(ranging from 2 days to 90 days) (Table 3).

Table : 3 Latency period

Time interval	Number(%)
<7days	15 (35.7%)
7-14 days	8 (19%)
15-21 days	4 (9.5%)
>21 days	15 (35.7%)
Total	**42 (100%)**

Carbamazepine and phenytion were the two most common culprits for 8 and 7 cases of CADRs respectively. Various putative drugs and the clinical reaction patterns caused by them are depicted in Table 4.

Out of 42 cases, 26 patients were managed with tapering doses of IV corticosteroids, i.e. hydrocortisone, rest were managed with supportive and symptomatic therapy. Patients receiving corticosteroid therapy were all 5 cases of TEN, 3 cases of SJS-TEN, 13 out of 15 cases of SJS, 2 out of 7cases of erythroderma, 2 cases of exanthematous drug eruption and a case of EM. The average duration of steroid therapy was 4.88 days (SD 1.68), ranging from 2 days to 9 days.

The median duration of hospital stay was 7 days (minimum of 3 days to a maximum of 51 days). Despite of optimal management,11.9% (n=5) succumbed; however, 83.3% (n=35) cases improved. One case was referred to other speciality for management of co-morbidities and one case left against medical advice. Cases who succumbed were 3 cases of TEN (2 caused by unknown medication and 1 caused by allopurinol), 1 case of erythroderma caused by phenytion and 1 case of DRESS caused by leflunomide.

Table 4: Various putative drugs and their associated clinical reaction pattern

Drug	Diagnosis								Total
	SJS	TEN	SJS-TEN	Erythroderma	Exanthematous Drug Eruption	DHS	EM	FDE	
Carbamazepine	4	1	2		1				8 (19%)
Phenytoin	3			3	1				7 (16.7%)
Allopurinol		1	1	1	1				4 (9.5%)
Cotrimoxazole					2		1		3 (7.1%)
Ciprofloxacin	2			1					3 (7.1%)
Ceftriaxone	1			1					2 (4.8%)
Lamotrigine		1			1				2 (4.8%)
Amoxycillin	1								1 (2.4%)
ATT	1								1 (2.4%)
Cefixime								1	1 (2.4%)
Paracetamol	1								1 (2.4%)
Sulfasalazine						1			1 (2.4%)
Leflunomide						1			1 (2.4%)
Dapsone						1			1 (2.4%)
Unknown	2	2		1	1				6 (14.2%)
Total	**15**	**5**	**3**	**7**	**7**	**3**	**1**	**1**	**42 (100%)**

Discussion

Adverse drug reactions may affect any organ, and the skin is the commonly involved organ. CADRs are usually benign. Severe forms are rare, with an estimated proportion of 2%.[12,13] The course can be fatal in 0.2 to 29.3% of cases requiring hospitalization when a severe evolution is predicted.[12] The recognition of the dermatological reaction patterns and the exclusion of differentials are of primary importance for which history and clinical examination form the cornerstone of diagnosis.[10] These various reaction patterns have different temporal relationships between the time of administration of the medication and the onset of dermatoses, although this latency may be shortened in the event of a re-exposure. Retrospective studies of drug eruptions have been reported by many countries and regions but retrospective study of inpatients with CADRs in Nepal has not previously been reported, to our knowledge.

Comparing the incidence of CADRs by gender, we found our inference to be conflicting with some studies reporting a female preponderance [14,15,16] and was in line with other studies with male preponderance. [3,17,18] This study showed male preponderance with male female ratio of 1.8. Our study revealed 54.8 % cases of CADRs being in age group of 15 to 35 years and similar age groups were affected by CADRs in few other studies. [3,14,17,18] Literatures suggested maculopapular eruptions as the most frequent reaction pattern [3,15,19,20] while according to our study SJS (35.7%) was the most common CADR, while maculopapular eruptions and erythroderma were second highest reactions with 16.7% each. The reason behind this may be the management of less severe exanthematous drug reactions in outpatient basis. In our study the latency was 2 – 90 days with an average of 20.07days, this was similar to the latency of 3 to 60 days in Tunisia.[15] However, one study revealed the latency for SJS/TEN to be few hours to one week[3] where as in another study 71.3% of CADR cases had a latency of less than a week.[17] It was 2 – 14 days in 80% cases in a North Indian study.[21] Almost 36% cases had latency of less than a week in our study as well, this reduction in latency may be due to repeated exposure to medications. Common drugs associated with CADR were anticonvulsants namely carbamazepine (n=8) and phenytoin (n=7) followed by different antibiotics and unknown medications. This result was similar to a Tunisian study but in contrast to many other studies where antibiotics were the common culprits followed by anticonvulsants.[5,10,12,14,18,20] However unknown medication made second largest group in a study[17] and it was 14.4%(n=6) in our study. Carbamazepine accounted for 24% SJS/TEN in a study from Malaysia.[19] Recently, many studies on allele associations with cutaneous ADR induced by aromatic amine anticonvulsants have been reported in Asian and European populations. Current studies indicate that HLAB*1502 is a marker for carbamazepine-induced SJS⁄TEN in Southeast Asian populations, where the prevalence of HLA-B*1502 is relatively high.[22]

The role of corticosteroids in the treatment of SJS/TEN is controversial. Earlier studies suggested increased morbidity and mortality.[23,24] A retrospective analysis of 289 patients from the Euro SCAR study found no benefit from corticosteroids or IVIg compared to supportive care alone.[25] There are, however, few studies suggesting benefits in administering high-dose corticosteroids early in the course of disease.[26,27,28] Possible explanation for this contradictory evidence may be due to the unfavourable outcomes from the use of corticosteroids resulting from inadequate doses, a delay in the initiation of treatment and the increased risk of mortality from sepsis from prolonged courses of therapy. However, in our study, the use of systemic corticosteroids with rapid tapering has given favorable results with median duration of hospital stay being 7 days, (minimum of 3 days to a maximum of 51 days) which was similar to a Chinese study[16] but slightly higher than that of Singapore[10] where it was 2-24 days (average 9days). Despite optimal management, there was 11.9% mortality; cases who succumbed were 3 cases of TEN(2 caused by unknown medication and 1 caused by allopurinol) 1 case of erythroderma caused by phenytion, 1 case of DRESS caused by leflunomide. In general, the mortality rate in Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) is high; approximately 5% for SJS and 30% for TEN.[29] In one of the studies, 4 out of 7 cases of TEN expired, which comprised 40% of all ADR related mortalities.[20] In another study, 5 out of 12 cases of TEN and 2 out of 3 cases of erythroderma succumbed.[15] Overall mortality of CADR in another study was 5.1%, which consisted of 2 mortalities of SJS/TEN and 3 of TEN.[10] Mortality rate was 15.6% among all cases; 9% in SJS and 26.7% in TEN in another study.[30]

Conclusion

Most of the results obtained in our study are comparable to what are reported in the literatures. The role of corticosteroids is currently under revision. Some earlier studies have shown their lack of efficacy or increased mortality in their use but the use of high doses early in the course of the disease may actually reduce morbidity and mortality, which has been shown in our study too.

A retrospective study has several limitations. Our data may not include all the patients with CADRs because some of them may not have been admitted to our hospital, in addition all data could not be retrieved due to poor record keeping.

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