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Original Article

Dermetology Section

Cutaneous Adverse Drug Reactions: A 6-Month Teaching Hospital Based Study from Mid-Western Nepal

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ABSTRACT

Background: Cutaneous adverse drug reactions (CADRs) are a frequent problem in dermatology, but only a few prospective studies on these have been reported. This study was done to (i) evaluate the incidence of CADRs from systemic drugs; (ii) study the characteristics of the patients with CADRs; (iii) describe the CADRs; and (iv) evaluate the drug reaction imputability and preventability.

Materials and Methods: This was a prospective, descriptive study which was conducted at the Department of Dermatology of Nepalgunj Medical College Teaching Hospital, Banke, Nepal. from May 2008 to October 2008. All the patients who attended the dermatology OPD and those patients who were admitted in the wards with suspected CADRs to systemic drugs were included in the study. Each case was assessed for its causality by using the WHO causality definitions. The data which was collected was subjected to descriptive analysis.

Results: Out of 2904 dermatology patients, 1.6% had a diagnosis of CADRs. The ages of the patients ranged from 9-years to 52-years, with a mean of 30-years. The male to female ratio was 1.08. A majority of the patients had taken the drugs for underlying infections (56%). The major drug group which was implicated in the CADRs was antibiotics, followed by anti-convulsants. Among the antibiotics, Cotrimoxazole accounted for the highest number of CADRs, in 5 cases. Fixed drug eruption was the most common type of reaction which was observed (in 6 cases). As a whole, 28% of the CADRs were severe, that included exfoliative dermatitis, erythema multiforme, the Stevens-Johnson syndrome and toxic epidermal necrolysis. There was mortality in one case of toxic epidermal necrolysis.

Conclusion: The commonest type of drug reaction which was noted was fixed drug eruption. Antibiotics were the most common drugs which caused the CADRs. Most of the drug reactions were caused by Cotrimoxazole.

Key Words: Cutaneous adverse drug reactions, Antibiotics, Fixed drug eruptions

INTRODUCTION

According to the WHO, an adverse drug reaction (ADR) is defined as any noxious, unintended or undesired effect of a drug, which occurs at doses which are used in humans for prophylaxis, diagnosis or therapy [1]. Cutaneous adverse drug reactions (CADRs) are a frequent problem in dermatology, but only few prospective studies have been done to evaluate their prevalence and to analyze their features in hospital settings [2-4]. Adverse drug reactions (ADRs) are among the major causes of morbidity, hospital admissions, increased health care expenditure, and even death [5]. This study was designed to (i) evaluate the incidence of cutaneous reactions from systemic drugs; (ii) study the characteristics of patients with cutaneous drug reactions; (iii) describe the adverse cutaneous reactions; and (iv) evaluate the drug reaction imputability and preventability.

MATERIALS AND METHODS

This was a prospective descriptive study which was conducted at the Department of Dermatology of Nepalgunj Medical College, Banke, Nepal. All the patients who attended the dermatology OPD and those patients who were admitted in the wards with suspected cutaneous adverse drug reactions to systemic drugs were included in the study. The study period was from May 2008 to October 2008. Adverse cutaneous reactions which were caused by the use of topical medications were excluded from the study. Informed consent was obtained from each patient in our study, and the protocol conformed to the ethics committee guidelines. The patients' data were recorded in a preset proforma that included: the patient's demographic data, their detailed clinical history, past history, any underlying disorders like HIV infection, connective tissue disease, liver disease, renal failure and malignancy, a detailed history of drug intake, reaction time, previous allergic history, duration of reaction, type of cutaneous reaction, and improvement after the dechallenge. Relevant investigations such as blood culture and serology were done to rule out any infectious aetiology. If a previous exposure to the suspected causative drug(s) or another drug of the same family had already caused an adverse skin eruption, the reaction was considered as preventable.

Only those cases were included that satisfied the following criteria [6]:

1. Those in which the diagnosis of the cutaneous adverse reaction was in accordance with the definition of ADRs which was provided by the WHO.
2. Those in which there was no alternate explanation for the reaction.
3. Those in which there was a plausible time relationship between the introduction of the drug and the onset of a reaction.
4. Those in which there was improvement in the condition of the patient after dechallenge/withdrawal of the suspected drug.

Each case was assessed for its causality by using the WHO definitions and was categorized as 'certain', 'probable', 'possible', and 'unlikely', as it was a very simple and widely accepted method to assess the causality. Only the 'certain' and 'probable' cases

were included for the analysis. The data which was collected was subjected to descriptive analysis.

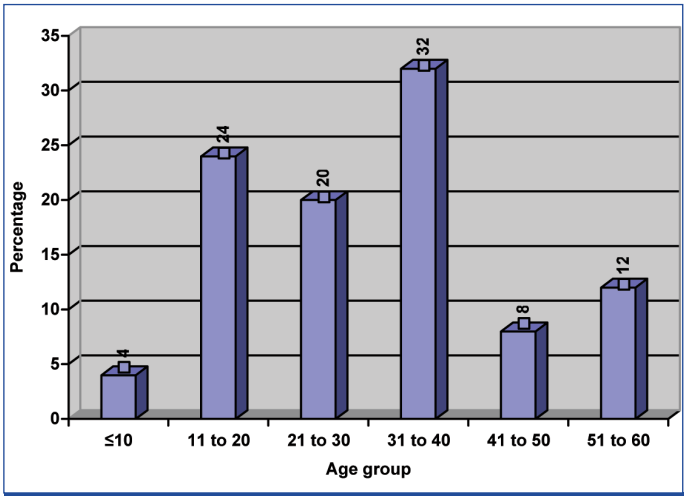
RESULTS

Of the 2904 dermatology patients, 25 patients (1.6%) had a diagnosis of cutaneous adverse drug reaction. Among them, 7 patients with severe cutaneous ADRs were hospitalized and the rest were managed on an outpatient basis. The ages of the patients ranged from 9-years to 52-years, with a mean of 30-years. Most of the patients were in the 21-40 years (52%) age group and only a small number was there in the ≤ 10 yrs age group (only one case) [Table/Fig-1]. There were 13 (52 %) males and 12 (48%) females with male to female ratio of 1.08.

Out of the 25 patients with adverse cutaneous drug reactions, 14(56%) had taken the drug for underlying infections, 5(20%) had taken it for seizure disorder, 3(12%) had taken it for pain management and 1(4%) each had taken it for heart disease, family planning and COPD. One patient with toxic epidermal necrolysis was HIV positive (4%). His CD4 count was 70 and he had been given cotrimoxazole prophylaxis. Otherwise, none of the other patients had HIV infection, underlying connective tissue diseases, liver disease, renal failure or malignancy.

The major drug group which was implicated in the adverse cutaneous drug reactions was antibiotics, which accounted for 14 cases (56%) of CADRs, followed by anti-convulsants, non-steroidal anti-inflammatoy drugs (NSAIDs), beta-2 agonists and hormones [Table/Fig-2]. Among the antibiotics, cotrimoxazole accounted for the highest number of CADRs, in 5 cases (20%), followed in a decreasing order by tetracyclines (3 cases), aminopenicillins (3 cases) and cephalosporin, metronidazole and antitubercular drugs (combination of isoniazid and ethambutol) accounting for one case each. Anticonvulsants were the second most common drugs which caused CADRs, which were implicated in 6 cases (24%). Among these, 4 cases were caused by carbamazepine and 2 cases were caused by phenytoin. Three cases (12%) were caused by NSAIDs, which included two cases which were caused by ibuprofen and one which was caused by aspirin. One case each was caused by β_2 agonists (salbutamol) and hormones (oral contraceptive pills).

The maximum number of the reactions in our study consisted of fixed drug eruptions which accounted for 24% (6 cases) of the total CADRs. This was followed by exanthematous drug reactions, acute urticaria and the Stevens-Johnson Syndrome [three cases (12%) each]. Exfoliative dermatitis and drug induced pigmentation constituted 2 cases (8%) each. Erythema nodosum, erythema multiforme, toxic epidermal necrolysis, pityriasis rosea, photosensitivity and acneiform eruptions were less common (one case or 4% each). As a whole, 28% of the CADRs were severe, which included exfoliative dermatitis, erythema multiforme, the Stevens-Johnson Syndrome and toxic epidermal necrolysis [Table/Fig-3].



[Table/Fig-1]: Age distribution of the patients

Drugs involved	Frequency	Percentage
Antibiotics	14	56 %
Anticonvulsants	6	24%
NSAIDs	3	12%
β_2 Agonist	1	4%
Hormone	1	4%

[Table/Fig-2]: Drug groups involved in adverse cutaneous drug reactions

Clinical type	Frequency	Percentage
Fixed Drug Eruption	6	24%
Exanthematous drug reaction	3	12%
Exfoliative Dermatitis	2	8%
Acute urticaria	3	12%
Pityriasis rosea	1	4%
Acneiform eruptions	1	4%
Pigmentation	2	8%
Photosensitivity	1	4%
Erythema nodosum	1	4%
Erythema multiforme	1	4%
Stevens-Johnson Syndrome	3	12%
Toxic Epidermal Necrolysis	1	4%

[Table/Fig-3]: Clinical pattern of cutaneous adverse drug reactions

Clinical types of ACDRs	Drugs implicated	No. of cases
Fixed drug eruption	Cotrimoxazole	2
	Doxycycline	1
	Ibuprofen	1
	Metronidazole	1
	Salbutamol	1
Exanthematous drug reaction	Ampicillin+Cloxacillin	1
	Amoxycillin	1
	Cefadroxil	1
Acute urticaria	Amoxycillin	1
	Aspirin	1
	Cotrimoxazole	1
Stevens-Johnson Syndrome	Carbamazepine	1
	Cotrimoxazle	1
	Ibuprofen	1
Exfoliative dermatitis	Carbamazepine	1
	Phenytoin	1
Pigmentation	Minocycline	1
	Carbamazepine	1
Erythema multiforme	Carbamazepine	1
Erythema nodosum	OCP	1
Photosensitivity	Doxycycline	1
Toxic epidermal necrolysis	Cotrimoxazole	1
Pityriasis rosea	Isoniazid/Ethambutol	1

[Table/Fig-4]: Correlation of drug with type of CADR

A single type of CADR was caused by different groups of drugs in different individuals. Similarly, a single drug was responsible for different types of reactions in different individuals. In this way, heterogeneity was observed [Table/Fig-4].

Among seven cases of severe CADRs, mortality was seen in one case of toxic epidermal necrolysis. That came to 4% mortality as a whole among all the drug reactions or to 14% among all the severe CADRs.

DISCUSSION

There is no gold standard investigation for the confirmation of a cutaneous ADR. Instead, the diagnosis involves the analysis of factors such as timing of the drug exposure and the reaction time, the course of the reaction with drug withdrawal/ discontinuation, the timing and nature of a recurrent eruption on rechallenge, a history of a similar reaction to the suspected drug, and previous reports of similar reactions to the same drug [7]. In this study, the WHO causality definitions were used to categorize the ADRs into 'certain', 'probable', 'possible', and 'unlikely' categories, as it is a very simple and widely accepted method which is used to assess the causality.

The incidence of cutaneous ADRs in our study was 1.6%, which was lower than that which was reported from India [8] (11.4%) but it was higher than that of a French survey (0.36%) [9]. Both the studies had included only the hospitalized patients. The incidence of severe adverse cutaneous ADRs in our study was 0.45%, which is higher as compared to that of a Chinese study (0.032%). The Chinese study was based only on severe cutaneous adverse drug reactions, not including the mild cutaneous ADRs. A slight male preponderance which was noticed in our study was similar to the findings of other studies [8,9,10,11,12]. The most common age group in our study was the 21 to 40 years age group , which was similar to that in other studies in our subcontinent [8,10]. But one of the studies had noticed two peaks, one in the 21–40 years age group and the other in the 61– 70 years age group [13].

The infections comprised of 56% of all the underlying diseases, which justified the use of the drugs, which was consistent with the findings of other studies [9,13,14,15,16,17]. Among 14 cases of infections, 4 cases (28.5%) were upper respiratory tract infections. Antibiotics were the most common drugs which caused cutaneous ADRs, followed by anti-convulsants and NSAIDs, which was consistent with the findings of other studies [10,18]. Antibiotics, followed by anticonvulsants have also been implicated as the commonest causative agents for the severe CADRs [13,14,15,16,17]. A wide clinical spectrum of cutaneous ADRs was noticed in our study. Cotrimoxazole and cabamazepine caused a wide spectrum of cutaneous ADRs (4 types each). These two drugs were also responsible for most of the severe cutaneous ADRs. Cotrimoxazole is easily available in the rural health centers of Nepal and it is widely used for various infective disorders. Carbamazepine is predominantly used for seizure disorders. Carbamazepine is a drug which has been approved for epilepsy, trigeminal neuralgia, neuralgia of diabetes mellitus, glossopharyngeal neuralgia and post herpetic neuralgia. Our patients were given carbamazepine predominantly for seizure disorders and in one case, it was given for post-herpetic neuralgia. We could not know the total number of prescriptions of cotrimoxazole and carbamazepine at the same time, to calculate the risk of the drug reactions which were caused by the drugs.

Several studies have found exanthematous drug eruptions to be the most common drug reactions [8,19,20], but we had fixed drug eruptions as the commonest type, followed by exanthematous drug eruptions, acute urticaria and the Stevens-Johnson Syndrome, in equal frequency. Our study highlights the high proportion of severe cutaneous ADRs (28%). A similar higher incidence of severe cutaneous ADRs was also found in studies which were conducted in India [8] and France [9], but a lower incidence has been reported from other western countries [21,22].

In a study which was conducted by Fiszenson-Albala F et al [9], one-third of the patients were found to have a previous allergic skin reaction to another drug, but none of our patients gave such history. Hence, the CADRs in our study were not preventable.

Four percent of our patients had concomitant HIV infection. A higher percentage (19 %) of the HIV infection was shown in another study [9]. Other associated disorders in that study were immunosuppression, including HIV infection (25%), connective tissue disease (10%), viral or auto-immune hepatitis (12.5%) and diabetes mellitus (10%). None of our patients had such concomitant illnesses. In most of our cases [19 out of 25 cases (76%)], the culprit drug was stopped.

CONCLUSION

The commonest type of CADR which was noted in our study was fixed drug eruption. Antibiotics were the most common drugs which were implicated for CADRs in our study, followed by anticonvulsants and NSAIDs. Most of the drug reactions were caused by cotrimoxazole. Cotrimoxazole and cabamazepine caused a wide spectrum of cutaneous ADRs. These two drugs were also responsible for most of the severe CADRs.

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