

PROFILE OF CUTANEOUS ADVERSE DRUG REACTIONS IN PATIENTS ATTENDING THE DERMATOLOGY OUTPATIENT DEPARTMENT OF A TERTIARY CARE HOSPITAL, GANGTOK

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ABSTRACT

Objectives: The present study was undertaken to evaluate the frequency of occurrence of cutaneous adverse drug reactions (ADRs) in patients attending dermatology outpatient department (OPD) and to assess causality and severity of the reported cutaneous ADRs, using different scales.

Methods: The study involved descriptive through retrospective review of patient medical records for patients who attended dermatology OPD for a period of 9 months. Patients' records specifying with cutaneous ADRs were taken for the study.

Results: The record of 30 patients reported with cutaneous ADRs with certain exclusions was studied. Higher incidence was found among females with 20–40 years of age. The most common presenting symptom was found to be erythematous rash (33%) and the drug groups involved in reactions were NSAIDs, beta-lactams, antitubercular drugs, and antifungals (16.7% each). The most common drug associated with cutaneous ADRs (CADRs) was itraconazole and aceclofenac (16.7% each). On the Naranjo scale, 86% reactions were labeled as "possible" while others as "doubtful". All the reactions were labeled as mild on Hartwig's Severity Assessment Scale.

Conclusions: Lack of post-treatment follow-up could be a reason for the difference in the causality result as compared to other studies. The data recorded in this study can be utilized as reference for future studies with large population.

Keywords: Cutaneous adverse drug reactions, Erythematous rash, Naranjo scale, Hartwig's Severity Assessment Scale.

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INTRODUCTION

Drugs, no matter how safe and efficacious, are subject to an inescapable risk of adverse reactions with their use [1]. Adverse drug reactions (ADRs) are considered as one among the leading causes of morbidity and mortality and a major problem of drug therapy. According to the World Health Organization, an adverse drug reaction is defined as "a response to a drug that is noxious and unintended and occurs at doses, used in man for prophylaxis, diagnosis, or therapy of a disease or for modification of physiological function [2]. ADRs may also lead to a diminished quality of life, increased doctor visits, hospitalizations, and may even cause death [3].

A wide range of cutaneous manifestations ranging from maculopapular rashes to toxic epidermal necrolysis (TEN) can be caused by different classes of drugs [4]. The mechanism is either immune or non-immune mediated, cumulative toxicity, photosensitivity, drug interaction, etc. [5]. TEN is the most serious form of adverse reaction with an acute onset involving more than 30% of body surface area and is differentiated from Stevens–Johnson syndrome (SJS) by a total surface area of <10% involved [4]. Most of the time, the diagnosis of ADR is difficult because of the similarity of signs and symptoms of different diseases [6]. Therefore, dermatologists and practicing physicians should be familiar with these types of conditions to enable early diagnosis and prompt withdrawal of the causative agent (s) to prevent mortality.

Underdiagnosing patients can encounter the risk of developing life-threatening reactions while at the other end of the spectrum, over-diagnosing them can lead to an unnecessary burden to the monetary position of patients and the existing medical infrastructure [7], in addition to the risk of mortality and morbidity. In the United States, ADRs contribute to an estimated additional US\$ 1.56–4 billion in direct hospital costs per year, and 5–9% of hospital costs in the United Kingdom are estimated to be related to ADRs [7].

The incidence of CADRs in developed countries is less (1–3%), than in the developing countries (2–5%). Most cases of cutaneous ADRs are mild or moderate and can be treated on OPD basis [8]. Sometimes, the data become less reliable for calculating incidence which is due to underreporting [9]. However, severe and life-threatening cases require prompt diagnosis and intensive treatment as in cases of Stevens–Johnson syndrome and TEN [4].

Sikkim is a small state in the northeastern part of India with a relatively small population of 610577 as per the census of 2011 [10]. The hilly terrain with the small population makes access to medical facilities due to various difficulties, resulting in very limited data.

Central referral hospital (CRH) of Sikkim Manipal Institute of Medical Sciences (SMIMS) with a medical college has an established peripheral ADR monitoring center, at department of Pharmacology. ADRs are hence collected and reported to monitoring center. Most of the drugs causing cutaneous ADRs are referred and treated at dermatology OPD. This study envisaged to estimate the frequency of occurrence, causality, and severity of cutaneous ADRs, using different scales.

METHODS

This descriptive study was based on the retrospective records of the patients. The medical record of the patients diagnosed with cutaneous ADRs was retrieved from the medical record department, in accordance with the OPD register maintained by nurse at dermatology department. The data were collected at the end of each month from the record section during the study period. From the OPD record, patients of all age groups with a history of medication before the development of cutaneous ADRs were noted and included for further study. Record of over-the-counter medication was also included. However, the patients with a history of viral and bacterial infections, infectious mononucleosis, family or personal history of skin diseases, environmental or occupational

exposure to substances, and comorbidities (Cushing's disease, systemic lupus erythematosus, and peripheral vascular diseases) were excluded from the study to avoid the misdiagnosis due to similar manifestation as that of CADRs. The study population consisted of all cases registered between January and September 2018 (9 months) at dermatology outpatient department (OPD), CRH, Gangtok.

Ethical statement

The study was commenced upon approval of the study protocol and case record form (CRF) by the Institutional Ethics Committee (IEC) bearing SMIMS/IEC/2018-96 number. The ADR monitoring center of the institute (Pharmacology department) sensitized the treating physicians for inquiry and recording of suspected ADRs before the commencement of the study.

Operational modality

The details of the patients' information recorded on the OPD record presented with cutaneous adverse drug reactions were collected in "suspected adverse drug reaction reporting form" and voluntary reporting of adverse drug reactions by health-care professionals (doctors, nurses, pharmacist, etc.) as circulated by Central Drugs Standard Control Organization (CDSCO), Ministry of Health and Family Welfare, Government of India [11]. Sociodemographic information was taken in the pre-designed record form. Sociodemographic data and adverse drug reaction data were transferred to secure excel data file and paper forms were kept securely after authentication.

Data analysis

Patients were classified by occurrence of ADRs with the aid of the Naranjo algorithm, comprising ten questions, each of which received a score. The algorithm enables ADRs to be classified. The data analyses were performed using the statistical package SPSS for Windows, Version 20.0 as "definite", "probable", "possible", or "doubtful". ADRs were classified by Hartwig's severity scale based on the severity of the reactions as "mild", "moderate", and "severe". The data thus received were expressed in the forms of charts, histograms, and bar diagrams.

RESULTS

The data including, sociodemographic information, suspected drug and their class, type and total number of ADRs, causality and severity, and any pre-existing co-morbidities were recorded.

In the study period, a total of 30 patients (53.3% female and 46.7% male) were found to be presented with cutaneous adverse reaction.

Most affected age group was found to be between 20 and 40 years (17 cases) and the least was <20 years (2 cases). Among other age groups, 6 cases were reported from more than 60 years and five cases were reported from 41-60 years group. The youngest case was of 14 years and the oldest was 75 years of age as shown in (Fig. 1).

The majority (26 out of 30) were urban residents with different religious faith, namely Hinduism (n=22, 73.3%) followed by Buddhism (n=6, 20%) and Christianity (n=2, 6.7%).

The most common group of drugs associated with CADRs was antimicrobials. Among the drug class associated with CADRs, beta-lactams (n=6, 20.00%), NSAIDs antitubercular drugs (ATTs), and antifungals (n=5, 16.7% each) were the most common (Fig. 2). The most common drug associated with cutaneous ADRs was itraconazole and aceclofenac (n=6, 20% each). Other drugs included ceftriaxone (n=3, 10%), amoxicillin (n=2, 6.7%), ethionamide (n=3, 10%), pyrazinamide (n=1, 1%), and zidovudine (n=2, 6.7%) as shown in (Fig. 3).

The reported CADRs were that of erythematous rash (n=10, 33.3%) followed by maculopapular rash (n=6, 20%) and acneiform eruptions (n=3, 10%). FDE, general pruritus, photodermatitis, and urticarial rash in 2 cases (6.2%) each, respectively, while excessive dryness, exfoliative dermatitis, and petechial rashes formed the other symptoms seen in 1 patient (3.3%) each as shown in Fig. 4.

On the Naranjo scale, 26 (86%) of the reactions were labeled as "possible" while 2 were labeled as "doubtful", whereas 2 cases were not accessible. All the reactions were labeled as mild on Hartwig's Severity Assessment Scale.

Comorbidities such as jaundice were present in two cases, and hepatitis, urticarial, melasma, brain tumor, gout, penile cancer, and diarrhea were also observed in one case each. However, they were not enough to show an association between the various ADRs seen in the study populations.

DISCUSSIONS

In this study, the prevalence of various CADRs and its distribution in the population with respect to age, sex, etc., has been described and the same has been correlated with the findings of the different studies. The occurrence of ADRs in the community was more among females than males [12-14]. As discussed in many other literatures, the reason for gender-wise variation in the occurrence of ADRs could be due to

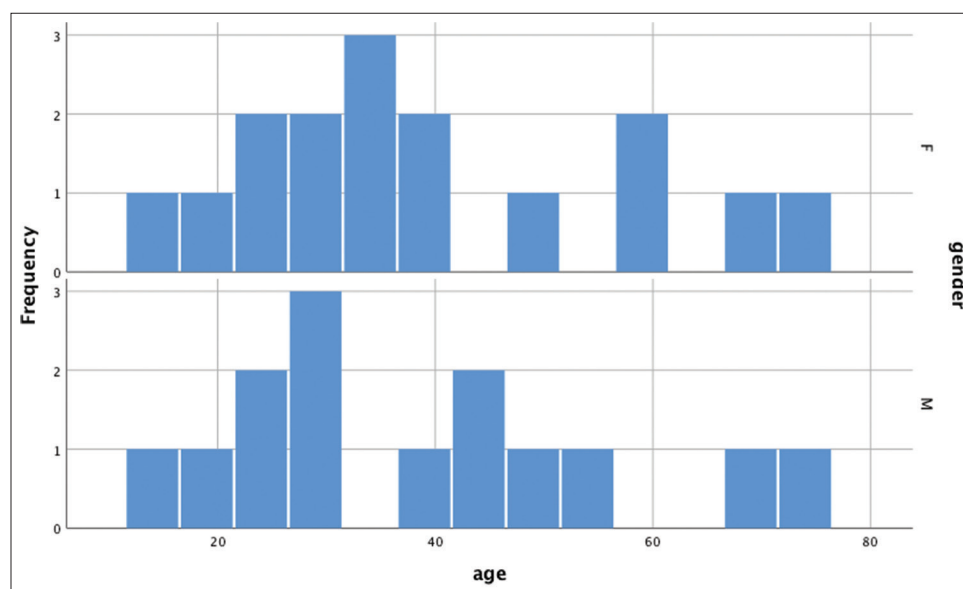


Fig. 1: Age and gender of cutaneous adverse drug reactions patients encountered during the study

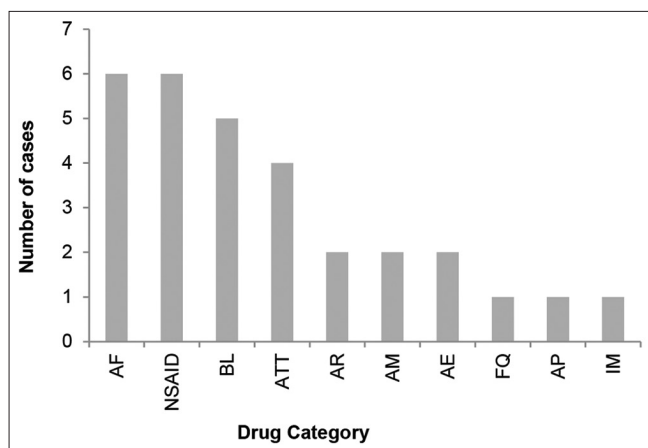


Fig. 2: Categories of drugs involved in the development of cutaneous adverse drug reactions

AF: Antifungal; NSAIDs: Non-steroidal anti-inflammatory drugs; BL: Beta-lactam; ATT: Antitubercular drugs; AR: Antiretroviral; AM: Ayurvedic medicine; AE: Antiepileptic, FQ: Fluoroquinolone; AP: Antiparasite; IM: Immunomodulator

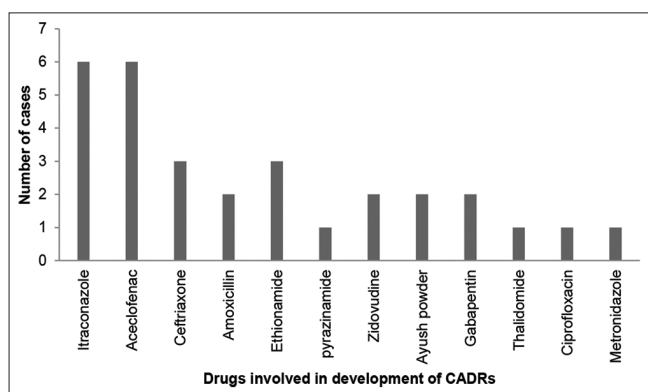


Fig. 3: Drugs involved in the development of cutaneous adverse drug reactions

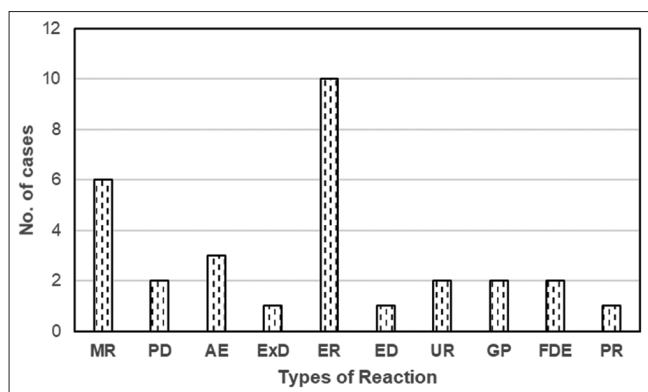


Fig. 4: Types of reactions observed prevailed among the cutaneous adverse drug reactions population under study.

MR: Maculopapular rash; PD: Photodermatitis; AE: Acneiform eruption; ExD: Exfoliative dermatitis; ER: Erythematous rash; ED: Excessive dryness, UR: Urticarial rash; GP: General Pruritus; PR: Petechial rash

more body fat, lower organ size, and low glomerular filtration rate in females as compared to males that can affect the pharmacodynamics and pharmacokinetics of drugs [15]. In the present study, affected

group was found to be 21–40 years and many other studies [9,16,17] also reported the same age group. However, there have been studies to show that there might not be a gender or age preponderance when it comes to cutaneous adverse drug reactions [8].

The drug most commonly associated with the reactions was itraconazole and aceclofenac. Other drugs included ceftriaxone, ethionamide (n=3, 10%), and zidovudine which corroborate other studies [17]. The previous reports [17,18] are in agreement with the result of present study, where antimicrobials and NSAIDs were the most common offenders, the reason behind which could be that they are the most frequently prescribed medications by prescribers [17].

In other two studies [19,20], maculopapular rash was seen as the most common reaction in the patients, followed by FDE in 20.8% and urticarial in 12.08%. In study in the UK, rashes were the most common ADRs caused by different categories of drugs [21]. This finding is in agreement with their findings although, the most common ADRs were that of erythematous rash followed by maculopapular rash and acneiform eruptions. In contrary to this study, urticaria forms the most common CADR [22]. A study from south India also showed cutaneous as the common type of ADRs [23].

The causality assessment reported in one study [9] reveals the distributions of “certain,” “probable,” and “possible” categories in Naranjo scale with 2.92 and 35.08, respectively, whereas 38.01%; 24% were termed as inaccessible. However, in this study, 86% were labeled as “possible”, which supports one finding [17], whereas 6.7% were reported as “doubtful” and 6.7% as “inaccessible” which could be due to the lack of follow-up of patients after getting treated for the reaction. Most of the reactions were non-serious therefore manageable at OPD basis.

The majority of the reaction occurred on the people from urban residence as compared to rural. This may be due to the ease of access to health-care facility in the urban area as compared to rural. The Hindu population was affected more than Buddhists and Christians which could suggest that majority of population belong to Hindu religion which is reflected in hospital attendance.

CONCLUSION

The present study focuses on the frequency of occurrence of cutaneous adverse drug reactions in the dermatological OPD of tertiary care hospital and their assessment based on causality and severity of reactions. In this study, the cases were treated by simple withdrawal of offending drug and its replacement with another drug and no additional treatment except for proper counseling and guidance was given. NSAIDs, ATT, and antifungal were the most common offending drugs associated with the CADR; hence, proper awareness on the ADRs related to these drugs must be given to the patients during their visits. The long-term study involving larger number of population will give a clearer picture on the frequency of occurrence of CADR and causality, severity, and preventability of CADR. Hence, the data obtained from this study can be taken as a baseline for future studies.

Limitations

Preventability data were not recorded since the study was retrospective in nature. The suspected drug was not put on re-challenge or re-administration to confirm the ADRs. The possibility of collection bias could be present since the data were collected only from dermatology OPD records available in medical record department.

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AUTHORS CONTRIBUTIONS

Karma Tenzing Bhutia: Data collections and Compilation, Dr. Chandrakala Sharma - Research proposal writing, Preparing the manuscripts and publication, Dr. Rukmalal Sharma- Dermatologist involved in attending patients with their complaints.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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