Brief Communication

Cutaneous adverse drug reactions in a tertiary care teaching hospital: A North Indian perspective

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Abstract

Background: Cutaneous manifestations of adverse drug reactions are a common occurrence and need to be differentiated from other causes of similar manifestations. Active search is essential for identification of these as patients may tend to downplay the causal association between drug use and the subsequent cutaneous manifestation. **Purpose:** To study the incidence of Cutaneous Adverse Drug Reactions (CADRs) in a tertiary care teaching hospital in North India. **Methods:** A prospective, observational study was conducted over a period of 6 months; using self-reporting method for selection of cases. The CADRs were graded as definite, possible and probable. **Results:** During the study period, 91 cases of CADRs were observed. Maximum incidence of CADRs was seen with antimicrobials (48.30%), followed by nonsteroidal anti-inflammatory drugs (21.90%). Maculopapular rash was the most common cutaneous manifestation of ADRs (42.85%). **Conclusion:** CADRs are a common occurrence and awareness about the same is essential for diagnosis and prevention.

Key words: Cutaneous adverse drug reactions, drug rash, drug reaction, pharmacovigilance

Introduction

Adverse drug reactions (ADRs) are important cause of morbidity, hospitalization, increased health expenditure and even death.[1] A meta-analysis found serious ADRs accounting for 6.7% of hospitalized admissions in USA.[2] ADRs accounted for 0.7% of total admissions and 1.8% of total deaths in a South Indian hospital.[3] Cutaneous ADRs (CADRs) are among the most frequent ADRs. Studies have found the incidence of CADRs in developed countries as 1–3%, while the incidence in developing countries is supposed to be higher between 2 and 5%.[3-5] ADR reporting leads to an increased general vigilance and may influence the recommendations for drug use through regulatory authorities.[6]

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Materials and Methods

A prospective, observational study over a period of 6 months (January–June, 2008) was conducted after the approval of the Institutional Ethics Committee at a tertiary care teaching hospital located in North India. The study was conducted by the Department of Pharmacology with the help of Dermatology Department and used spontaneous reporting of ADR for the collection of data. All patients presenting to the dermatology OPD with cutaneous manifestations after drug consumption and those referred from other departments were included in the study. Referrals and OPD patients when necessary were hospitalized for further management. The diagnosis of the CADR was done by the senior dermatologist on duty. Causality assessment of the reported ADR was done by establishing the drug use with elaborate elicitation of the history, temporal association with ADR, response following stoppage and rechallenge. Rechallenge was done after taking patient's consent. It was performed following stoppage of the drug for certain period of time depending upon the clinical status of the patient and considering the risk–benefit ratio. ADRs were graded as definite, possible and probable according to WHO causality assessment scale.

Cutaneous reactions due to drug abuse, errors in drug

administration and in patients with incomplete history were not included in the final analysis. Patients were specifically asked about the intake of any alternative medicine as they do have high potential to cause CADRs. Such patients were also excluded from the study. All reactions were classified into dermatologically distinct morphological patterns by a senior dermatologist on duty and recorded by a pharmacologist in a prefixed proforma for the study. All the patients were given adequate treatment (soothing lotions, local/oral antibiotics or steroids) depending upon the severity of CADR. Descriptive statistics was used for data analysis and results were expressed as percentages.

Results

Of the total 91 cases reported during the study, 47 (51.7%) were females and 44 (48.3%) were males. The male to female ratio was 0.93:1. The maximum number of cases was seen in the age group 21–30 years (25.27%) followed by the age group 31–40 years (23.07%) [Figure 1].

The drugs most commonly responsible for CADRs were antimicrobials (48.30%), followed by nonsteroidal anti-inflammatory drugs (NSAIDs) (21.90%) and anti-epileptics (13.20%) [Figure 2]. Other drugs presenting with CADRs included ramipril (*n* = 1, 1.09%), enalapril (*n* = 1, 1.09%), amlodipine (*n* = 1, 1.09%), steroids (*n* = 2, 2.19%), lithium (*n* = 2, 2.19%), oral contraceptives (*n* = 1, 1.09%), folic acid (*n* = 1, 1.09%), benzoylperoxide (*n* = 1, 1.09%), and chlorpromazine (*n* = 1, 1.09%). Fixed drug combinations causing cutaneous manifestations included tetracycline and ibuprofen (*n* = 1, 1.09%), diclofenac and allopurinol (*n* = 1, 1.09%), rifampicin and isoniazid (*n* = 1, 1.09%), and dapsone and clofazimine (*n* = 1, 1.09%). One fatal CADR, toxic epidermal necrolysis (TEN), was seen with ciprofloxacin which was prescribed for a case of suspected enteric fever.

Maculopapular rash was the most common CADR (*n* = 39, 42.85%), followed by fixed drug eruption (FDE) (*n* = 19, 20.87%), urticaria (*n* = 11, 12.08%) and photosensitivity (*n* = 4, 4.39%). Bullous eruption, erythema multiforme, lichenoid eruption, and TEN were seen in 1 (1.09%) patient each. Other CADRs accounted for 14 (15.38%) cases [Tables 1 and 2].

The lag period between starting the drug and appearance of cutaneous reactions varied between 2 and 14 days in maximum number of cases (*n* = 73, 80.2%), within 2 days in 2 (2.19%) and between 15 and 30 days in 16 (17.58%) cases. Of all the 91 cases, 3.29% were classified as definite (*n* = 3), 76.98% as probable (*n* = 70) and 19.78% as possible (*n* = 18). Outcome of CADR showed 65 (71.42%) patients cured, 25 (27.47%) improved and 1 (1.11%) expired.

Discussion

Cutaneous reactions are the most common manifestations of ADRs.[7] A wide spectrum of cutaneous manifestations ranging from maculopapular rashes to TEN can be produced by different classes of drugs. Reactions include pruritis, maculopapular and morbilliform rashes, erythema multiforme,

Table 1: Incidence of different CADRs

Type of CADR	Number of patients (*N* = 91)	Percentage
Maculopapular rash	39	42.85
FDE	19	20.87
Urticaria	11	12.08
Photosensitivity	4	4.39
Bullous eruption	1	1.09
Lichenoid eruption	1	1.09
TEN	1	1.09
Erythema ultiforme	1	1.09
Others	14	15.38

CADR: Cutaneous adverse drug reaction; FDE: Fixed drug eruption; TEN: Toxic epidermal necrolysis

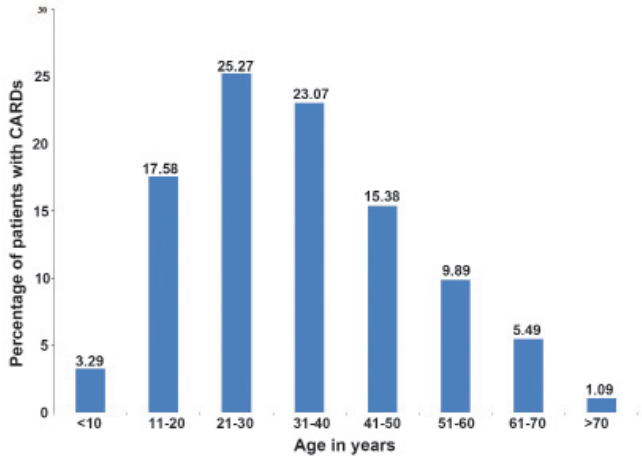

Figure 1: Relation of frequency of CADRs with age

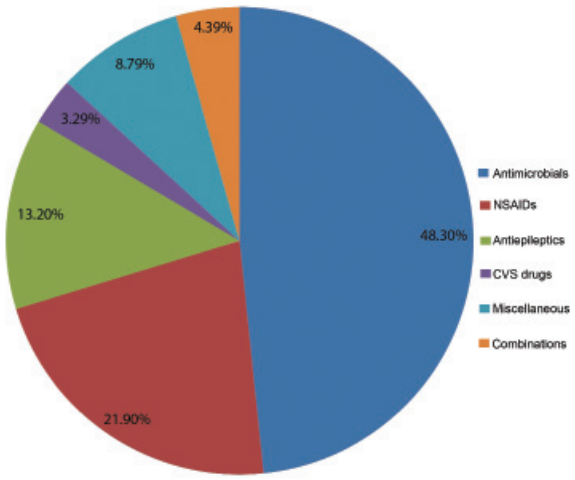

Figure 2: Drug groups causing CADRs

Table 2: Incidence of different CADRs with commonly used drugs

Drugs involved	Number of patients	Percentage	Type of morphology*
Cotrimoxazole	21	23.07	1, 2, 3, 9
Amoxicillin	8	8.79	1, 9
Fluoroquinolones	5	5.49	1, 3, 7
Tetracyclines	2	2.19	1, 9
Metronidazole	1	1.09	1
Chloroquine	2	2.19	1, 9
Fluconazole	1	1.09	9
Acyclovir	1	1.09	1
Ibuprofen	9	9.89	1, 2, 3, 4
Nimuselide	5	5.49	1, 2
Aspirin	4	4.39	2, 3
Diclofenac	2	2.19	1
Phenytoin	6	6.59	1, 5, 9
Carbamezapine	3	3.29	1, 6, 9
Valproic acid	3	3.29	1, 9

*Numbers in column 4 correspond with the type of reactions mentioned in Table 1

exfoliative dermatitis and others. Some severe CADRs may result in serious morbidity and even death.[8] Most drug-induced skin eruptions can be described as erythematous, morbilliform or maculopapular in nature.[9]

In the present study, a total of 91 CADRs were reported. This number may not represent the true prevalence of CADRs during this period as patients with incomplete history and doubtful diagnosis were not included. Moreover, the exclusion of many minor cutaneous reactions which do not require hospitalization and underreporting by patients might have contributed to the decreased prevalence of CADRs in this study. Mild predominance of CADRs was seen in females as compared to males in concordance with other studies.[5,10] This difference may be attributed to the fact that the females may be more conscious of any cutaneous reactions and report it, while males tend to ignore or not notice minor cutaneous reactions. Male preponderance has been seen in some other studies.[11,12] Antimicrobials have been implicated as the major causative factor for CADRs in this study. Similar results have been obtained in other studies where antimicrobials were responsible for 38.6% of CADRs,[10] while some have reported incidence of antimicrobials as a causative factor for CADRs as 56.9% and 55.88%.[5,13] In a study of hospitalized patients, antimicrobials as the causative factor for CADRs were reported in 32% cases.[14] Cotrimoxazole continues to be the drug commonly implicated in CADRs, with 23.07% of the cases in the study. Predominance of sulfonamides as causative agents for CADRs has been reported from a multicentric analysis from Italy and a 6-year study from Chandigarh, India.[10,12] There was one fatal CADR in the form of TEN due to ciprofloxacin in the present study. A higher incidence of fatal CADRs – TEN and Steven Johnson Syndrome (SJS) – as 11.4% was found in the study by Sharma *et al*.[12] The incidence of TEN and SJS was reported to be 0.2% and 1.82%, respectively, by the Italian study.[10] The difference in incidence may be attributed to the variation in prescription patterns. NSAIDs were the second leading cause (21.90%) of CADRs in this study. The study by Sharma *et al.* reported NSAIDs as a cause for CADRs in 18% of the patients.[12]

Of the various cutaneous manifestations of drug reactions, maculopapular rash was seen most commonly in 42.8% of the patients, followed by FDE in 20.8% and urticaria in 12.08% of the patients in the present study. Maximum incidence of maculopapular rash was seen in cases of antimicrobial use, followed by NSAID use. This is in concordance with the results of other studies.[15,16] Anticonvulsants as the most common cause of maculopapular rash were reported by Sharma *et al*. The present study also documented the most common CADR following antiepileptic use as maculopapular rash. FDE was most commonly due to cotrimoxazole use and similar results have been reported in other studies.[5,12,17] Only one case of FDE was seen due to tetracycline use, in a patient who had used fixed drug combination of tetracycline and ibuprofen. This also could not be definitely associated with use of tetracycline. Similar observations have been made in other studies.[18,19] Cutaneous manifestations of ADRs have been remarkably similar for most drugs and have been seen to be consistently associated with them.

In conclusion, ADRs are potentially avoidable causes for seeking medical care. They increase the burden of work and can be fatal at times adding to the common person's negative perception of allopathy. With the number of drugs being marketed increasing every year, it is of paramount importance to have an in-depth understanding of their possible adverse reactions and this is possible only when the physician is trained adequately and is actively looking for any ADRs. A robust mechanism for reporting of ADRs is required while the clinician is to be always on the lookout for ADRs. So, anticipating, preventing, recognizing and responding to ADRs should be the prime concern of the clinicians so as to minimize the incidence of ADRs.

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