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Research Article

Analysis of Cutaneous Adverse Drug Reactions at a Tertiary Care Hospital – a Prospective Study

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Abstract

Purpose: *To analyze the clinical, pharmacological and economical aspects of the cutaneous adverse drug reactions (ADRs) reported at Civil Hospital, Ahmedabad, India.*
Methods*: A prospective observational study over a period of one and half years (November 2006 to April 2008) was undertaken. Semi-spontaneous reporting along with a review of case record forms were used. The reports were analyzed for clinical pattern, causal drug groups, causality (WHO-UMC criteria), severity (*Hartwig and Siegel scale*) and preventability (modified* Schumock and Thornton *criteria). The cost of ADRs was calculated on the basis of hospital expenditure per patient and the amount spent by patients themselves.*
Results: *Out of 143 reports, chemotherapeutic agents (39 %) were the most commonly suspected drugs followed by unknown medicines (29 %). Most of the ADRs were designated as possible or probable (69 %) and moderately severe (96.5 %) in nature. However, 14 – 16 % were definitely preventable. Cost incurred by the hospital was Indian national rupees (INR) 374,255, i.e.,USD 8241. While average cost incurred by outpatients was INR 99 (USD 2.18) and that of hospitalized patients was INR 264 (USD 5.81).*
Conclusion: *A large number of cutaneous ADRs are due to unknown medicines. This calls for strict drug control mechanisms, patient education regarding self-medication and maintenance of prescription records. The cost associated with ADRs is high. ADR monitoring is essential to reduce patient suffering as well as to achieve the substantial savings in health care cost.*

Keywords: *Cutaneous adverse drug reactions, Cost of ADRs, Preventability, Patient education*

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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). They account for about 5 % of all hospital admissions in UK [1]. Skin is one of the major target organs for ADRs. Cutaneous adverse drug reactions manifest as skin rashes and/or eruptions. The incidence of cutaneous ADRs among inpatients in developed countries ranges from 1 - 3% whereas in developing countries such as India it is 2-5 % [2]. It was estimated that 5 to 9 % of all hospital costs are related to ADRs [3]. Thus, ADRs are a significant economic burden, in addition to a frequent cause for the cessation of otherwise effective drug therapy in patients [4].

This study aimed to analyze the clinico-pharmacological characteristics and cost analysis of cutaneous ADRs reported at Civil Hospital, Ahmedabad, India, a tertiary care teaching hospital.

PATIENTS AND METHODS

A prospective observational study was conducted over a period of one and half year (November 2006 to April 2008) at a tertiary care teaching hospital in western India with a bed capacity of 2040 and average occupancy rate of 61 %. The institutional ethics committee approved the study protocol. The study site was the Department of Dermatology. The dermatology outpatient department (OPD) operates daily from 9 am to 5 pm and there is a designated ward for serious patients requiring hospitalization. The investigators visited the outpatient clinic daily as well as the in-patient ward of the department from 9.00 am to 12.00 noon. A semi-spontaneous reporting method was used to document the ADRs. All the patients with clinically suspected cutaneous ADRs either attending the OPD or admitted in the ward, and willing to participate in study were included.

The suspected ADRs were assessed by the consultant dermatologist and the relevant details were filled up in a case record form (CRF) after structured interview of the patient. The hospitalized patients were followed up daily until discharge. The outpatients were not followed up. The data obtained were analysed for clinical presentation of ADRs and causal drug groups. Causality assessment was carried out using WHO-UMC scale [5]. The severity of ADRs was categorized as mild, moderate and severe using Hartwig and Siegel scale [6]. Preventability of the ADRs was evaluated using the criteria of Schumock and Thornton, as modified by Lau et al [7]. Cost of ADRs was calculated as the expenses incurred by the hospital and the amount spent on transportation, medicines and loss of daily wages by the patients. Average hospital expenditure per patient per day is INR 1445 (USD 31.86). The data collected were compared with other similar studies using *Chi* square test. $P < 0.05$ was considered as statistically significant.

RESULTS

A total of 143 ADRs reported during the study period that met with the inclusion/exclusion criteria were included. Out of these, thirty-seven were hospitalized and 106 were OPD cases. A detailed analysis of these reports is given as follows.

1. Clinical profile

One-third of the patients were within the age range of 16 to 30 years (33.5 %) and man to woman ratio was 1.3:1. Most of the ADRs (71.3 %) developed within a week of drug administration. A total of 172 drugs suspected to be the cause of the reported cutaneous ADRs are shown in Figure 1.

Antimicrobials were the most commonly suspected drugs followed by unknown medicines, non-steroidal anti-inflammatory drugs (NSAIDs) and antiepileptics. In fifty

cases, the nature of suspected drug was not known because patients had them without label and prescription. Among antimicrobials, the most common drugs were co-trimoxazole (15 %) and fluroquinolones (15 %) while phenytoin (67 %) and carbamazepine (20 %) were the commonest antiepileptics. A large number of clinical presentations were observed including fixed drug eruptions (FDEs), maculopapular rashes, urticaria, Steven Johnson syndrome (S.J.syndrome) angioedema, erythema multiforme etc. FDEs (27.3 %) were the commonest presentation followed by maculopapular rashes (24.5 %). A significant number (10.5 %) of patients developed S.J.syndrome. Phenytoin (33 %) and nevirapine (27 %) were responsible for more than 50 % cases of S.J.syndrome.

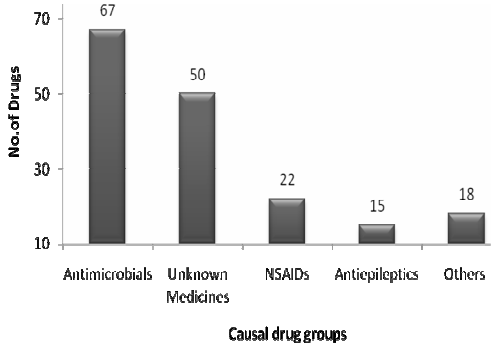

Fig 1: Causal drug groups for cutaneous ADRs

2. Causality assessment of ADRs

In 63 ADRs (41.6%), the response to dechallenge was satisfactory (as the event abated or started abating after stoppage of drug). In the rest of the patients, however, either it was not attempted (due to therapeutic reasons) or could not be assessed (lack of follow-up). An accidental rechallenge occurred in three cases leading to recurrence and 3 patients died of S. J. syndrome. The WHO-UMC scale was used for causality assessment. “Possible” (46 %) was the most common causal category followed by probable (23 %). In 42 (29 %) of the cases, it was rated as unassessable because the nature of drug was unknown.

3. Preventability

A majority of the ADRs were not preventable (57 and 79% of total and serious ADRs, respectively). However, as Figs 2 and 3 indicate, 14% of total and 16% of serious ADRs were preventable.

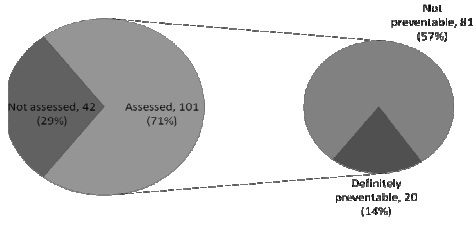

Fig 2: Preventability of all ADRs

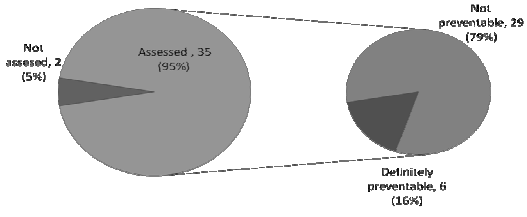

Fig 3: Preventability of serious ADRs

Preventability could not be assessed in 42 ADR reports, as the medication names were not available.

4. Severity assessment (Hartwing scale)

Most of the ADRs were moderately severe (138/143 or 96.5 %) while three cases were severe in nature, though preventable.

5. Cost of ADRs

Average stay of patients with cutaneous ADRs in our study was 7 days (95 %CI, 5.4, 8.7; range 2 to 28 days). Hence, the average cost incurred by the hospital for patients with cutaneous ADRs was INR 10,115 (USD 223). The cost of ADR to patient was calculated for both out- and in-patients. For each outpatient, it was INR 99, i.e, USD 2.18 (95 %CI, 80.6, 117.4; range INR 15 - 503), while for hospitalized patients, it was INR 264 (USD 5.82) (95 %CI, 204.4, 323.6; range INR 35 -

878). Some of the hospitalized patients purchased the medicines from private pharmacy outlets whenever the drugs were not available in the hospital pharmacy.

DISCUSSION

This prospective study carried out over a period of eighteen months at a tertiary care centre showed that cutaneous ADRs developed within seven days (71.3%) to one month (16.1%) of the drug administration. This emphasizes the need to observe patients closely in the initial period of treatment. Several such studies have been carried out in India and elsewhere [8-13]. Antimicrobials were the commonest offending agents (67, 4 %) followed by unknown (unidentified) medicines, NSAIDs and antiepileptics. Pudukadan *et al* [9] and Puvailai *et al* [10] have also found antimicrobials frequent causal drugs for cutaneous ADRs. This is not surprising since antimicrobials are a common item in most prescriptions written in India and elsewhere [14]. .

Surprisingly, unknown or unidentified medicines constituted the second most common offending group, causing 40 non-serious and 2 serious cutaneous ADRs. The nature of these drugs remained unknown because either the patients brought the drugs in loose, unidentified packs or had consumed them as self-medication. A large number of cutaneous ADRs with over the counter (OTCs) or unknown drugs call for stricter drug control measures, patient education regarding self-medication and maintenance of patient or prescription records.

In the present study, cutaneous ADRs presented commonly as fixed drug eruptions (FDEs) - 27.3%, maculopapular rashes (24.5%) and urticaria (15.4%). Our observations were similar to those of Pudukadan et al [9] (see Table 1).

Noel et al [15] and Fiszenson-Albala *et al* [13] reported a significantly ($p < 0.05$) lower proportion of FDEs. The probable explanation for this difference may be because of genetic, ethnic or environmental factors which need an in depth analysis of these studies or the prescribing pattern of antimicrobials. In our study, cotrimoxazole was commonly prescribed while penicillin was frequently prescribed in other studies. We also observed that 11 % of cutaneous ADRs were SJ syndrome and three of the patients died. The higher occurrence of SJ syndrome in our study may be because we are a tertiary care hospital, and seriously sick patients are referred to us from within the state and also from neighboring areas.

Most of the ADRs in our study were designated as possible or probable in WHO-UMC scale (69 %). However, 29 % of the ADRs were unassessable due to the unknown nature of the drug.

A majority of ADRs were categorized as moderately severe while three cases were severe in nature. Assessing the severity of ADRs is an essential component in pharmac-

Table 1: Comparison of cutaneous ADRs (present study) with other similar studies

Clinical presentation	Our study (%, n=143)	Ghosh *et al* (Manipal, south India (%, n=53	Pudukadan *et al* (south India) (%, n=90)	Puvailai *et al* (Bangkok, Thailand) (%, n=132)	Fiszenson-Albala *et al* (France) (%, n=48)
Maculopapular rash	25	21	12	60*	57*
Fixed drug eruptions	27	4*	31	9*	0 *
S. J. syndrome	11	2*	19	5	2*

** Statistically different ($p < 0.05$) compared to our study*

ovigilance studies as an ADR may require intervention including the stoppage of the suspected drug(s) and even hospitalization in severe cases. We also found that 14 % of total and 16 % of serious ADRs could have been prevented, resulting in considerable resource saving and avoidance of patient suffering. The past history in all these cases was suggestive of ADRs. A proper evaluation and history-taking would have prevented these ADRs. This could also have been brought to the notice of the prescribers to prevent recurrence in future.

Cost of ADRs incurred by the hospital for 37 hospitalized patients was INR 374,255 (USD 8241). In our study, average hospital expenditure per patient was INR 10,115. A similar study done at Mumbai showed a cost of INR 6197 (USD 150) per patient in the hospital [16]. The difference may be attributed to drug prices, wages, food and telephone bills, and type of patients included in the study. Higher average cost incurred by hospitalized patients was partly due to the purchase of medicines from private pharmacy as sometimes drugs are not available in the hospital pharmacy (where drugs are generally cheaper)and also as a result of loss of daily wages.

Limitations of study

Due to lack of follow-up and inadequate record-keeping, the total number of patients treated at Dermatology OPD could not be ascertained and hence the incidence rates cannot be computed from the collected data. Moreover, ADRs of recently introduced drugs could also not be generated.

CONCLUSION

The present study demonstrates that a large number of cutaneous ADRs can be prevented. ADR monitoring can reduce patient suffering and cost of treatment. Patients' awareness regarding OTC drugs and self-medication should also be strengthened.

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