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A Prospective Study of Cutaneous Adverse Drug Reactions in A Tertiary Care Hospital

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ABSTRACT

Objectives: To evaluate the incidence of Cutaneous Adverse Drug Reactions (CADRs) in a tertiary care hospital, its associated health impact and to establish a causal link between the drug and reaction.
Methods: A Prospective and observational study was conducted over a period of 1 year (1,Dec2010 to 30, Nov 2011) in patients presenting with cutaneous manifestations after drug intake, attending Department of Dermatology, Rajiv Gandhi Government General Hospital. Causality assessment of ADR was done according to WHO scale and data analysed statistically.
Results: 210 CADRs were recorded. Among them,118 (58%) were males and 92(44%) females. The age group 21-40 yrs showed the maximum number of cases(n=84,40%). The drugs commonly responsible were anti-bacterials(39%) followed by Anti-epileptics(14%) and NSAIDS(12%). Over the Counter drugs accounted for 17%.The presentation of CADRs were as follows: urticaria-26%(n=56), maculopapular rash -24% (n=51),Toxic Epidermal Necrolysis - 6%(n=13).The time lag between drug intake and onset of reaction was between 2 and 5 days in 35%.WHO scale showed 2% as certain; 69% probable and 29% possible. 33% (n=69) required hospital admissions of which 3% required Intensive Care. CADRs outcome showed improvement in 95%(n=200) and 2%(n=4) expired.
Conclusion: Cutaneous reactions are the common manifestations of ADRs. Causality link between drug and the reaction was established.33% required hospital admissions.

Keywords: *Adverse Drug Reactions,Skineruption,cutaneous adverse drug reaction, casuality.*

INTRODUCTION

Man had been using medicines to treat his illness dating back to the pre-historic times. Nowadays, medicines have become the inevitable elements in day to day modern life and they have made tremendous contributions for the wellbeing of the mankind, but we are also facing the darker side in the form of adverse drug reactions. Adverse Drug Reaction (ADR) is defined by WHO, "As a response which is noxious and unintended and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function."

Drugs can be remarkably beneficial and improve quality of life by reducing symptoms and at the same time by producing a sense of well-being. However, most of the drugs we use produce adverse effects, even if used properly. As innovation in medicine increases and new drugs are developed, there is potential for an increasing number of ADRs.

As the drugs that are widely used act by altering one or more aspects of cellular and molecular function, most drugs have the risk of producing reactions that may not be desirable all the time. Hence, the ultimate goal of pharmacotherapy cannot be to prescribe a risk-free regimen, but to ensure that the risks are kept as low as possible (Golan, 2007). Hence, proper data about the adverse effects helps physicians to prescribe drugs, balancing the benefits and hazards. 10-15% of patients receiving medications experience ADRs. The incidence of serious ADRs is 6.7 percent (Lazarou et al., 1998).ADRs account

for 5 to 9 % of hospital costs (Moore et al., 1998). ADRs have been recognised as a major public health issue, as they account for a significant percentage of hospital admissions and impose an economic burden on society. Proving that a specific drug is responsible for an adverse reaction in a patient may be extremely difficult because of multiple drug exposures and the underlying diseases. Increasing costs of health care and increased awareness of patients towards the untoward effects of drugs and the rise in the cases of litigation against hospitals and health care providers have made doctors aware of the need for monitoring adverse drug reactions. This emphasises the need for an efficient Pharmacovigilance system, which is a science of assessing and monitoring ADRs (WHO Collaborating Centre for International Drug Monitoring, 2007)

Cutaneous Adverse Drug Reactions (CADRs) are one of the most common types of adverse reaction tothedrug.The incidence of CADRs in hospitalised patients is about 2–3% (*Medical Clinics of North America*, 2010). The skin is involved in 20% of all ADRsin the form of clinical findings or subjective symptoms on skin, mucosae, or the adnex structures. Any dermatologic condition that appears within 2 weeks of starting a medication should include a drug induced eruption in the differential diagnosis (Habif, 2009). In some cases, cutaneous eruptions are recognised during drug development, whereas in other cases, they are very rare and can be noted only in the post marketing period of the drug. The reactions are predictable in some instances, but in the others the reactions are idiosyncratic, and were only noted only after a large experience with the agent.

Almost any medicine can induce skin reactions ranging from common eruptions like urticaria to rare life threatening conditions like Toxic Epidermal Necrolysis.Drug eruption rates in certain drug groups such as antibiotic, antiepileptics and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)approaches 1 to 5% (Bigby, 2001). Although the majority of cutaneous reactions are mild and self-limiting, severe reactions such as Stevens-Johnson syndrome(SJS),Toxic Epidermal Necrolysis (TEN), and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) have been reported to occur in one out of every 1,000 hospitalised patients and are associated with significant mortality and morbidity(Roujeau & Stern, 1994). Recognition of severe cutaneous drug eruptions is difficult because they often occur in complicated clinical scenarios that may include exposure to multiple drugs. Once a reaction had occurred, it is important to prevent such similar future reactions in the patient due to the same drug or a cross-reacting medication. Physicians must always maintain a high degree of suspicion regarding the possibility of drug-induced disorders.

Although such cutaneous reactions are common, complete data on their incidence, severity, and health impact are not available. So this study was undertaken to find out the incidence of Cutaneous Adverse Drug reactions and to establish a causal link between drug and reaction in a tertiary care hospital.

OBJECTIVES

To evaluate the occurrence of Cutaneous Adverse Drug Reactions and to assess its associated health impact. To establish a causal link between the drug and reaction using WHO-UMC Causality Assessment Scale.

MATERIALS AND METHODS

The study was conducted in the Department of Dermatology, Rajiv Gandhi Government General Hospital in collaboration with the Institute of Pharmacology, Madras Medical College, Chennai.The study was started after obtaining approval from the Institutional Ethics Committee, Madras Medical College.Patients attending the out-patient Department of Dermatology were explained about the study purpose in their local language. Informed consent was obtained from those participants who were willing to participate in the study.

All patients presenting to the Dermatology department with cutaneous manifestations after drug intake and those referred from other departments were included in the study. The CADR diagnosis was made by the dermatologist. Causality assessment of the ADR was done using the WHO-UMC Causaulity assessment scale,by establishing the temporal association of drug use with ADR,response following stoppage (de-challenge) and re-challenge(if possible).All reactions were classified into distinct morphological patterns, and all patients received adequate treatment.

Study Methodology

Single-centre, Prospective, Observational study

Study Duration:12 months

Study Centre: Out-patient and in-patient Department of Dermatology, Rajiv Gandhi Government General Hospital, Chennai.

Inclusion criteria:

All age groups
Sex: both male and female

History of skin lesion following intake of medications – both over the counter and prescribed.
Both in-patients and out-patients

Exclusion Criteria:
Cases without definite history of drug intake prior to reaction.
Over prescribing, over dosage, and excess consumption
Patients taking more than ten prescription drugs
Drug addicts

Recruitment:
Patients diagnosed with drug eruptions and treated as out-patients or admitted to the medical wards were recruited in the study.

Evaluation:
The four main questions to be answered regarding a drug eruption are,
1) Is it a drug reaction?
2) Is it a severe eruption or the onset of a form that may become severe?
3) Which drugs are suspected, and which drugs should be withdrawn?
4) What is recommended for future use of drugs?

The framework for evaluating a patient with CADR is,

Detailed history
The following were evaluated,

- General medical history.
- Drug exposure (start date, dose, duration of use)
- Time interval between the initiation of therapy and the onset of reaction
- Previous history of adverse drug reactions or history of allergy
- Re-exposure to the same drug, if any
- Improvement of the lesion after decreasing the dose or after withdrawing the offending drug
- Personal history of skin disease
- Family history of hypersensitivity syndromes
- Other diseases or injuries that cause the same type of eruption
- Occupational or environmental exposure to other substances that may be the etiologic agents

Clinical diagnosis of the reaction –by morphological pattern.
The first step in evaluating a patient with a potential drug reaction is to diagnose the eruption by morphological pattern. In diagnosing whether the patient's current eruption could be related to a specific medication, two basic questions should be asked, which of the patient's medications cause this pattern of reaction? And how commonly does this medication cause this reaction pattern?.

Analysis of drug exposure:
Prescription drugs, Non-prescription medications, Herbal or any other therapies. Previous experience of the patient with the same or related drug?
Has the suspected medication been reported to cause the given reaction which the patient is experiencing? If so, how commonly? The patient should be asked if he/she had a previous reaction to the same or related medications, as the current eruption may be a cross-reaction from previous exposure.

Alternative etiologic candidates:
Other drug and non-drug causes for the patient's eruption.

Timing of events:
When did the eruption appear relative to the administration of the suspected medication? A detailed history from the patient and a careful review of the patient record are used to establish the chronologic sequence of all the drug therapy.

Evidence of overdose if any:
Certain reactions are related to the rate of administration or the cumulative dose.

Response to discontinuation of the drug (De-challenge):
Does the eruption resolve on de-challenge?
Re-challenge if possible:

If the offending drug reproduces the reaction on re-administration? This is strong evidence for the medication to have caused the reaction. Re-challenge is not possible if the reaction is severe.

Causality assessment using WHO-UMC Causality Assessment Scale.
The reactions were classified as Certain, Possible, Probable, Unlikely, Unclassified or Unclassifiable according to the WHO-UMC Causality Assessment Criteria.

The decision to continue or discontinue the suspicious medicine depends on the severity of the reaction, the severity nature of the primary disease, the degree of suspicion of causality, and the feasibility of an alternative safer treatment. In severe drug reactions, elimination of all possible suspect drugs or unnecessary medications was attempted.

Analysis Of Results:
The results will be analysed under the following headings:

- Total Drug Reactions for the period - out patient and in patient
- Male –Female ratio
- Age group commonly affected
- Groups of drugs commonly associated with ADR
- The common skin reaction caused by drugs
- Duration of lesion
- Time duration betweenintake of the drug and the onset of reaction
- Causality assessment

Statistical Analysis:
Descriptive statistics was used to analyse the data and results were expressed in percentages.

RESULTS
A total of 210 patients were reported with CADRs in the study period. 56% of them were males, and female constituted about 44%. The male-to-female ratio was 1.27: 1.

The maximum number of CADRs was observed in the age groups -- 21-40 years (40%) and 40-60 years (29%). The most common offending drugs were the anti-bacterials, which constituted about 39%, followed by anti-epileptics (14%) and NSAIDS (12%).

Most of the drugs were administered by the the oral route, which accounted for about 63%, followed by the intravenous route, which accounted for about 32%. Urticaria was the most common pattern, followed by the maculopapular rash. Severe CADRs, such as SJS/TEN, accounted for about 6%.

Most of the reactions, about 35%, occurred within 2 to 5 days of drug intake.29% of the reactions occurred within 6 hours of intake of the offending medication.

TABLE: 1 Time interval between the initiation of drug therapy and the onset of reaction

TIME INTERVAL BETWEEN DRUG INTAKE AND ONSET OF REACTION	NUMBER OF PATIENTS	PERCENTAGE %
<6 hrs	60	29%
6hrs-1day	20	10%
2-5days	73	35%
6-15days	22	10%
16-25days	7	3%
>25 days	8	13%
TOTAL	210	100%

75% of the patients showed positive de-challenge and in 25% of patients, de-challenge was not done. Re-challenge was done only in about 2% of patients.

The more number of patients fall under the category Probable,145 patients (69%), followed by the category Possible, 61 patients (29%).Only 2% of the patients belong to 'Certain' category.Totally 69 (33%) of them required admission to the hospital, of which 3% were admitted in the Intensive Care Unit. Among the210 patients, 200 (95%) recovered completely.4 patients (2%) died from severe CADRs.The outcome was unknown in about 3% of the patients.

DISCUSSION

The drug, which is capable of producing a therapeutic effect, can also produce unwanted side effects. The consequences of Adverse Drug Reactions on society are immense. Drug reaction syndromes are often challenging, but they are a manageable problem.

Adverse drug reactions are an inevitable risk factor associated with the use of modern medicines. However, careful attention can minimise the risk of developing ADRs in many patients. They constitute 0.3% to 7% of all the hospital admissions and the 4th to 6th leading cause of death among the hospitalised patients (Lazarou et al., 1998).

Because of the steady and rapid increase of newer drugs entering the market, adverse drug reaction monitoring is of prime importance. Our country has a higher population with many drug consumers, and also, the pre-clinical and clinical data are not sufficient to establish the safety of a drug. This scenario necessitates reporting any untoward drug reaction to assess its safety. ADRs pose a challenge for the doctor-patient relationship.

Information about ADRs is always incomplete when the drug is first introduced into the market. Premarketing exposure of the drug is usually to a limited number of subjects. Therefore, the probability of identifying rare ADRs is very low. The details about adverse reactions may be known only after long exposure to the drug in a large number of patients.
Skin rashes are among the most common reactions to drugs. A cutaneous adverse drug reaction should be suspected in any patient who develops an eruption during treatment. The reaction may be due to any drug the patient had been exposed to recently, including prescribed drugs and over-the-counter medicines, homoeopathic or herbal preparations.

Certain groups of patients appear to be at a higher risk of cutaneous adverse drug reactions. There is a high incidence of hypersensitivity reactions in patients with altered immune status. Knowing the potential risk of dermatologic reactions associated with drugs may help clinicians in choosing the most appropriate therapy. It also helps in deciding which drug might be removed first in case of drug eruption in a patient taking multiple medications.
Drug reaction syndromes are often challenging but are easily manageable. A systematic stepwise approach can help to solve these complicated clinical scenarios. All alternatives in the differential diagnosis need to be considered. A wide spectrum of cutaneous manifestations can be produced by different classes of drugs. These drug reactions were less commonly reported.

In this Prospective study conducted in a tertiary care hospital, there was a slight male preponderance (M: F = 1.27:1) which was same as the study conducted by Sharma et al ((Sharma et al., 2001).

Majority of patients were in the age group 21 - 40 years, which correlated with the study conducted by Sharma et al (Sharma et al., 2001). Another study conducted by Solensky R et al observed that adults aged 21 - 40 years were at increased risk of drug eruptions caused by antibiotics, probably due to increased exposure of this age group to antibiotics (Solensky & Mendelson, 2001). However, other studies conducted by Wolkenstein P(Wolkenstein & Revuz, 2000) and Revuz J(Revuz, 2001) noted that the elderly were more commonly affected. Similarly, Kauppinen's study (Kauppinen & Stubb, 1984) also revealed that the largest number of cases was seen in the 6th decade. This could be related to the difference in the health care-seeking behaviour.

In the present study, antibiotics accounted for the largest group (39%), followed by antiepileptics (14%) and NSAIDs (12%). This was similar to the studies conducted by Puvailai et al (Puvailai & Choonhakarn, 1998) and Pudukadan et al (Pudukadan & Thappa, 2004) who also found that antimicrobials are the most frequent causative agents of cutaneous ADRs. This is because the antimicrobials were commonly prescribed.

Multiple medical problems increase the risk of developing an adverse drug eruption (Revuz, 2001) .The occurrence of ADRs is influenced by many factors, such as prolonged hospital stay and polypharmacy (Weiss et al., 2002).

About 17% (n=36) of drugs causing CADRs were over-the-counter drugs. Thus there is need for strict drug control measures, maintenance of prescription details and patient education about the consequences of self-medication.
Adverse cutaneous drug reactions vary in their morphological pattern and distribution. Recognition and description of the skin lesions are essential in establishing the correct diagnosis. The exact morphology needs to be recognised. Of the various

types of CADRs seen in this study, urticaria (26%) was the most common morphological pattern, followed by maculopapular rash (24%). Other studies conducted by Sharma et al (Sharma et al., 2001), Kauppinen (Kauppinen & Stubb, 1984), Sullivan et al(Sullivan & Shear, 2002) have noted the maculopapular eruption to be the most common morphological pattern.

In this study, most cutaneous ADRs developed within 2 to 5 days of drug administration (n=73, 35%).This explains the need for observing patients closely in the initial period of treatment.

De-challenge was performed in about 75% of the patients, and they showed improvement after the drug withdrawal. Re-challenge was performed in only about 4 (2%) patients. It was attempted only in less severe cases, in 3 cases of antibiotic-induced urticaria and 1 case of drug-induced lupus caused by Isoniazid.

Most of the CADRs (69%) fall under the category 'Probable' of the WHO Causality Assessment Scale which was similar to a study by Shah et al(17). As we enrolled cases only with a definite history of drug intake before the eruption, the categories 'Unlikely', 'Unclassified' and 'Unclassifiable' were not encountered.
Only 2% of the patients belonged to the 'Certain' category. This is because only about 2% of patients had a a positive re-challenge.

33% (n=69) of patients with CADRs required hospital admissions, of which 3% required treatment in the Intensive Care Unit, which was similar to another study conducted by Lee H Y et al in Singapore (Lee et al., 2010).

About 95% of patients recovered, and about 4 patients died from severe CADRs.
3 of the 4 patients died because of Toxic Epidermal Necrolysis, and 1 patient died because of the progression of maculopapular rash to Toxic Epidermal Necrolysis. This indicates the need for promptly withdrawing the offending drug and initiating proper treatment as soon as possible.

A sound knowledge about the drug eruptions may help the clinician in better management of the patients. All drugs must be regarded as being potentially hazardous and the risk due to drug reactions must be weighed against the expected therapeutic benefit for each patient. Patients can also be made aware to inform the clinician about the possible reaction that occurs to him.

CONCLUSION

From our study we report that,210 patients had been reported with CADRs during the study period.33% of CADRs required hospital admissions, among which 3% required admission in Intensive Care Unit.2% of patients died from severe CADRs. Causal link between drug and the reaction was established.

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AUTHORS' CONTRIBUTIONS

All the authors contributed equally in experimental work and manuscript preparation.

CONFLICTS OF INTEREST

The authors declared there are no conflicts of interest.

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