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Research Article

CLINICAL PATTERN AND SEVERITY OF CUTANEOUS ADVERSE DRUG REACTIONS

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ABSTRACT

Objective: To analyze incidence, causative agents, severity and additional cost burden associated to cutaneous drug reactions amongst medicine inpatients.

Methods: A prospective spontaneous reporting study for the duration of twelve months in the Department of General Medicine and ICU of 850 bedded, tertiary care teaching hospital. Causality assessment of ADR was carried out using WHO scale, and assessment of severity was done using Hartwig Scale.

Results: Incidence of cADRs in medicine inpatients was found to be 2.3%. Higher rate of cADRs were observed in male population together with high proportion in adults in comparison to geriatric group. Antibiotics were the main causative agents followed by NSAIDs, antiepileptics. Most of the reactions were mild in nature and most of them were resolved completely. An additional financial burden of Rs.573.92 (10.62$) per patient was observed.

Conclusion: Lesser incidence of cADRs can be attributed to the fact that the study was confined to medicine inpatients. Most of the cADRs were preventable if detected early. Intensive monitoring of drug therapy would be beneficial in early detection of signals to prevent severity of these reactions and thus associated cost burden.

Keywords: Causality, Severity, Cutaneous Adverse Drug Reaction (cADRs).

INTRODUCTION

Cutaneous adverse drug reactions are defined as noxious, unintended, morphologic skin changes with or without systemic involvement that develop after local or systemic administration of drugs in dosage commonly used for prevention, diagnosis or treatment of disease or modification of physiologic function [1-3].

Majority of cutaneous ADRS are mild and self limiting, severe cutaneous adverse drug reaction (SCAR) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) are associated with significant morbidity and mortality [4]. Mortality rates for TEN, SJS, and DRESS were 28.6%, 2.2% and 5.9% respectively .In addition to mortality and morbidity risks, cutaneous ADRs also constitute a sizeable healthcare cost. In the United States, it is estimated that ADRs contribute to an additional US$ 1.56 to 4 billion in direct hospital costs per year, and it is estimated that 5%–9% of hospital costs in the United Kingdom are related to ADRs. Since quick and careful attention to the diagnosis and treatment of cutaneous ADRs is required, a standardized approach is necessary to establish a final decision of causality to result in a consistent, accurate and reproducible identification of ADRs [5].

In the US the incidence of fatal ADRs is 0.32% and they are estimated to be between fourth and sixth leading cause of death in inpatients [6]. Cutaneous ADRs are the most common, recognizable and reported form of ADR, presenting over 30% of all reported ADRs [7]. Adverse cutaneous reactions to drug are frequent, affecting 2 to 3% of all hospitalized patients. Only about 2% of these adverse cutaneous reactions are considered severe [8].

According to WHO database adverse reactions like rashes, pruritis, urticaria are reported respectively from 4.2%, 2.7% and 2.6% of patients receiving drugs. The incidence of adverse reactions increases with number of drugs [9].

Almost any medicine can induce skin reaction, certain drug classes such as NSAIDs, antibiotics and antiepileptics have drug eruption rates approaching 1-5% [10]. The hypersensitivity reaction in some patients may be due to over the counter medicine, herbal or homeopathic preparation, vaccine or contrast media or the pharmaceutical excipients [11].

Mechanism of such cutaneous responses to drugs can arise as a result of immunologic or non-immunologic mechanism that does not involve an immunologic process. The skin is among the organs most affected by adverse drug reactions. The list of conditions that can be triggered by medication includes nearly all dermatological diseases: Some examples are pigmentary changes related to accumulation in the dermis of amiodarone, antimalarial, minocycline, quinolones, and alteration of hair follicles by cytostatics and lipodystrophy associated with metabolic affects of anti-HIV medications.

Skin testing (patch testing and also prick and intradermal (IDT) testing), skin biopsy, laboratory test, microscopic tests with the suspected compound, has been reported to be helpful in determining the cause of a cADRs, and in studying the patho-physiological mechanisms involved in these reactions [12-13]. According to previous data, the results of drug skin tests mainly depend on the drug tested and the clinical features of the initial cADRs, but there are, at present, a few extensive studies that determine the sensitivity and specificity of these drug skin tests as a complementary tool for drug imputability in cADRs [14].

Incidence and severity of cADRs are higher in medicine inpatients, such a study was required to find the drugs inducing cADRs and added cost burden for treating it.

MATERIALS AND METHODS

Data Collection

A prospective spontaneous reporting study approved by the Institutional Ethics Committee (IEC) was conducted over a period of twelve months from October 2011 to September 2012. The study was coordinated by Pharm D students. Patients of either sex above 18 years of age who developed a cADRs admitted in medicine ward and medical ICU were included in the study. Patients experienced cADRs before taking drugs, patients treated on Outpatient department (OPD) basis and patients with drug abuse were excluded from the study.

WHO definition of a cADRs was adopted. Spontaneous reporting system was the method followed for monitoring cADRs. Medical staff, medical post graduates, nursing staff and patients were educated and encouraged to report cADRs by creating awareness

through brief presentations and conducting clinical meetings. cADRs notification forms were kept in the nursing stations of medicine wards and the ICU. PharmD students played a crucial role in monitoring through daily participation in ward rounds and encouraging the physicians to report. Any reaction noted by the student was brought into the notice of the physician, who if convinced enough of the drug cause of reaction filled the notification form. Informed consent was taken from the patient for suspected ADRs before documentation. The demographic details of the patient were collected along with the current concern and drug therapy details in a systematically designed patient profile form. All relevant data including the drugs patient received prior to the onset of reaction, respective dose, and route of administration with frequency, date of onset of reaction and the patient's allergic status were noted. In addition to this patient's medication history and other co-morbidities were identified to assess causality relationship between the suspected drug and reaction. Patients were interviewed and the medication order and records were reviewed on daily basis throughout the stay of patient in the hospital.

Causality assessment of ADRs was carried out using WHO scale[15] which categorizes the causality relationship into certain, probable, possible, unassessable/unclassifiable, unlikely and conditional/unclassified. Severity of ADRs was graded as per scale developed by Hartwig et al [16] as mild, moderate and severe. The most common class of drugs causing ADRs were identified and documented. Cost incurred for the patients to treat cADRs was calculated.

RESULTS

A total of 94 suspected cADRs in 74 patients were reported and evaluated from 4086 patients (47 males, 37 females) (Figure 1) during the study period. The overall incidence was 2.3%. Male experienced a significantly higher incidence of cADRs than female (Figure 2). The overall incidence of ADRs found to be higher with adult patients (62%) than geriatrics (38%) (Figure 3). This trend was observed in both cADRs related admissions and cADRs occurring during the hospital stay.

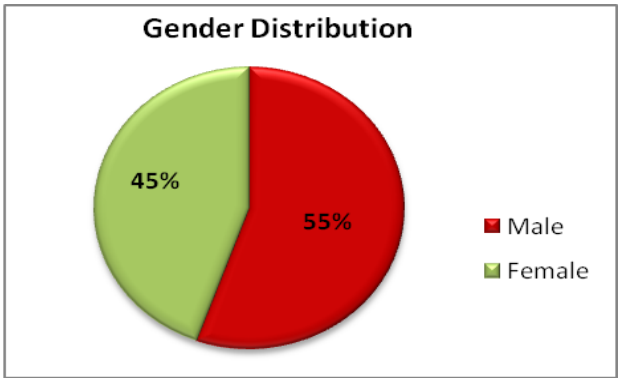

Fig. 1: Gender distribution of subjects

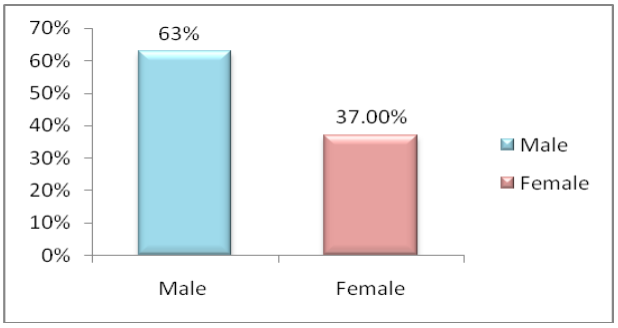

Fig. 2: Distribution of cADR's Vs Gender

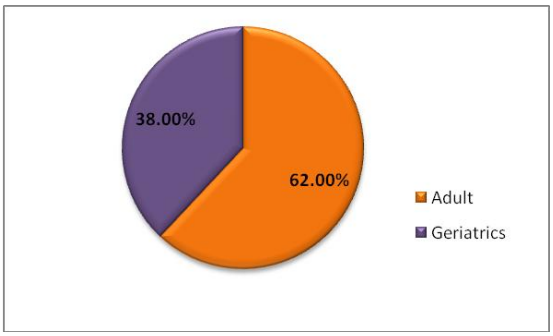

Fig. 3: Distribution of cADR's Vs Age

The most common causative agents were antibiotics (48.9%), NSAIDS (27.6%), antiepileptic (10%), antimicrobials (04%), and antimalarials (2.1%) (Table.1). Rashes on upper and lower limbs (31.9%) was the most cADRs found in study followed by Erythmatous & purpuric rash (14.8%), Maculopapular rash/eruptions (12.7%), Rashes all over body (10.6%), Erythmatous rash (8.5%), Urticaria (8.5%) and S J Syndrome (4.2%) (Table 2).

Table 1: Drugs inducing cADRs

Agents	No. of cADRs	%
Antibiotics	46	48.9
NSAIDS	26	27.6
Antiepileptics	10	10.6
Antimicrobials	04	4.2
Antimalarials	02	2.1
Steroids	02	2.1
Proteolytic enzyme	02	2.1
Vit. B12	02	2.1
Total	**94**	**100.0**

Table 2: Types of cADRs

Clinical Type	No. of cADRs	%
Rashes/itching on upper/lower limbs	30	31.91
Erythmatous & purpuric rash	14	14.89
Maculopapular rash/eruptions	12	12.76
Rashes all over body	10	10.6
Erythmatous rash	8	8.51
Urticaria	8	8.51
S J Syndrome	4	4.25
Erythmatous multiforme	4	4.25
Rashes all over body + severe itching	4	4.25
Total	**94**	**100.0**

Causality assessment of suspected ADRs shows out of 94 reported CADRs 14 (14.89%) were assessed to be "Possible", 80 (85.10%) as "Probable" (Figure 4) Reported reactions were found to be "Mild" (48, 51.06%) followed by "Moderate" (22, 23.4%) and "Severe" (24, 25.5%) (Figure 5).

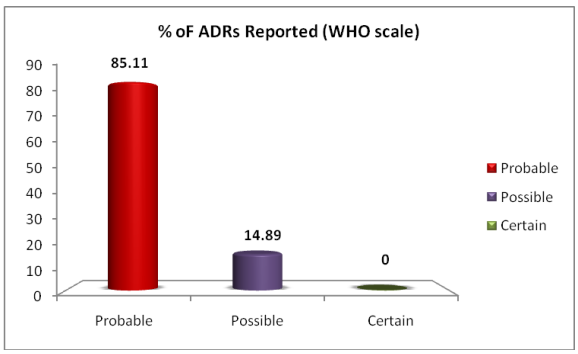

Fig. 4: Causality Assessment of cADRs

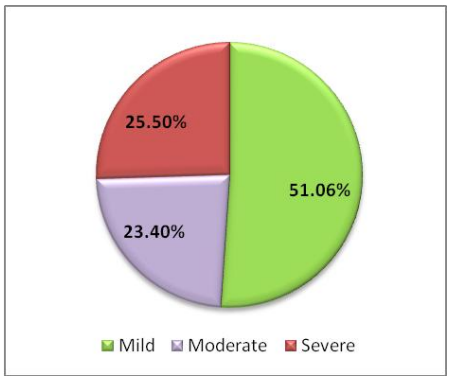

Fig. 5: Severity Assessment of cADRs

The total cost incurred on 94 treating cADRs in 74 patients was Rs 42,470.09 (785.54$) with a mean of Rs.573.92 (10.62$) per patient (Table 3).

Table 3: Cost incurred in treating cADRs

No. of cADRs in patients	No. of patients incurred cost	Total cost incurred in INR (US $)	Average cost per patient in INR (US $)
94	74	42,470.09 (785.54$)	Rs.573.92 (10.62$)

Spectrum putative drugs and their associated clinical reaction pattern is given in Table 4. In majority of ADRs (59.44%) "Complete recovery" was achieved, 18.88% ADRs were found to be "recovering" and 11.19% ADRs were of "unknown" outcomes in which the outcomes could not be assessed as the patients sought voluntary discharge from the hospital. Life threatening reactions were reported in three patients (2.10%) who were recovered later.

Table 4: Spectrum putative drugs and their associated clinical reaction pattern

	Rashes/itching on upper/lower limbs	Erythmatous and purpuric rash	Maculopapular rash/eruptions	Rashes all over body	Erythmatous rash	Urticaria	S J S	Erythmatous multiforme	Rashes with severe itching
Antibiotics									
Cotrimaxazole									
Piperacillin	3	3	1	1			1	1	
Tazobactum	1	2	2					1	
Ciprofloxacin	1								
Cephalexin	1								
Levofloxacin	1								
Ceftriaxone									
Lornoxicam									
Metronidazole									
Ciprofloxacin									
Clarithromycin									
Amoxicillin + Clavulanate potassium									
Antiepileptic									
Phenytoin			2				1		2
NSAIDS									
Nimesulide					1				
Ibuprofen	4				2	3			
Diclofenac	3								
Paracetamol									
Antimalarial									
Artesunate			1						
Corticosteroid									
Dexamethasone	1								
Anti-asthmatic									
Salbutamol						1			

DISCUSSION

It is difficult to diagnose cADR, and a challenging clinical problem in hospital patients. It is still difficult to assess temporal relationship to the suspected drug for causality assessment in an acute setting, where the patient is usually on multiple medications, some of which may be essential and life-saving [17]. The frequency of cADRs in a particular population is influenced by the drug utilization habit, the reaction rates of favorite drugs and pharmacogenetic traits of the population studied. Most epidemiological studies analyzed the

occurrence of cADRs in inpatients and revealed a wide variation in the prevalence rate which ranged from 0.36% to 12.2% [18-23]. Kim and Lee[24] and Bang et al.[25] reported that 2.7% and 3.8% of patients visited hospitals because of cutaneous ADRs, respectively, and Shin et al.[26] reported that 8.9% of inpatients had cutaneous ADRs. Hahm[27] reported that 2.6% of inpatients with dermatology consultations were diagnosed with cutaneous ADRs. The lower rate of cADRs seen in our setting (2.3%) was probably due to inclusion of general medicine and ICU inpatients only. According to the report by Kim et al.[28], the incidence of cutaneous ADRs was 1.32% in the 1970s, 1.33% in the 1980s, and 1.78% in 1990s; the gradual increase in the incidence of ADRs has been attributed to diversification, abuse, and misuse of drugs. However, the incidence and type of cutaneous ADRs evaluated by dermatologist in 2000's has not been reported. As the incidence of ADRs is increasing, people perceive ADRs with greater concern. Proper monitoring systems and causality assessment are required to prevent the severe cutaneous ADRs which cause death, threaten lives, affect fetuses, and lead to permanent disability [29-30]. Since cutaneous ADRs are the most common; it is highly desirable for dermatologist to actively participate in the process of detection and management of these cADRs.

Different scales/algorithms are used for assessment of ADRs which includes Naranjo algorithm, WHO scale, French algorithm, RUCAM algorithm, and Hartwig scale. The Naranjo algorithm, which was established in 1981, is the most widely used assessment tool and consists of ten simple questions [31]. While we have used WHO Scale for assessing causality of cADRs occurring inpatients which is another widely used algorithm for causality assessment.

Comparing the incidence of cADRs by gender, we found our inference to be conflicting with some studies reporting a female preponderance [20,23,32] and was in line with studies male preponderance [19,21,33]. This study showed male preponderance with male female ratio of 1:0.5.

Mean age of 38.7 years is in line with to Asian studies which reported younger patients more compared to geriatric studies from Europe and US [18-21, 23, 33]. Our study showed younger group (62%) had significantly higher rate of cADRs compared with the geriatric group (38%).

Literature suggests maculopapular eruptions as the most frequent reaction pattern [34] while according to our study rashes and itching is the most common cADRs reported while maculopapular eruptions are third highest reactions seen on patients. Our study confirmed some data already known about cADRs: antibiotics (34.1%) are responsible for major portion of cADRs, followed by NSAIDS/antipyretics (27.0%), CNS depressants (12.1%), anticancer drugs (7.1%) [5] similar to conclusion of Lee *et al*[17] ,antibiotics (50.5%) as most common offender for cADRs followed by anticonvulsants (11.3%) allopurinol (8.2%) ,NSAIDs (7.2%), chemotherapeutic agents (7.2%). This pattern is similar to our pattern i.e., antibiotics (48.9%), NSAIDS (27.6%), antiepileptic (10%), antimicrobials (04%), and antimalarials (2.1%). Possible reason behind antibiotics sharing major portion of cADRs could be its wide use in medicine and ICU patients than antiepileptics, NSAIDS, anticancerous drugs in hospital setting.

CONCLUSION

cADRs are integral part of drug therapy since the study was restricted to medicine inpatients; lesser incidence of cADRs was observed in this study. Most of them were preventable if detected early. Detailed medical history would play a vital role to avoid preventable ADRs assessing underlying risk factors. Also intensive monitoring of drug therapy has to be strictly followed for getting early signals to prevent incidence and thus cost burden.

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