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Prevalence and causality assessment of cutaneous adverse drug reactions

[1] Syeda Mehmooda Batool Bushra, [2] Safa Riyaz, [3] Salma Tasneem, [4] Rumana Hameed, [5] Syeda Rana Nikhat,

[6] Dr. NM Prasad Naik

[1-4] Department of Pharmacy Practice, MESCO College of Pharmacy Osmania University, Hyderabad, Telangana, India
[5] Department of Pharmacology, MESCO College of Pharmacy, Hyderabad, Telangana, India
[6] Department of Dermatalogy, Osmania General Hospital, Hyderabad, Telangana, India

Abstract
Background: Cutaneous Adverse drug reactions (CADRs) are among the most frequent Adverse Drug Events (ADEs). Considering their impact on patient's lives and relatively high incidence, identifying the risks and monitoring of CADRs is of great clinical significance to prevent patient from unwanted exposure to drug toxicity.
Objective: To determine the prevalence of different types of CADR's and there causal relationship with the offending drug.
Material &methods: A prospective, observational and non-invasive study was carried out in department of Dermatology at a Tertiary care hospital for duration of 6 months. Patients with 18 years or higher with visible skin lesions suspected to be drug related were included. Assessment was carried out by WHO, Naranjo's and Hart wig's classification graded on a 3-point scale. Descriptive statistics were used to examine the normality of data and describe the analysis.
Results: Among 90 cases analyzed 34cases (37.8%) were males and 56 (62.2%) were females. Maximum patients belonged to the age group of 21-30 years (34.4%). The most common CADR observed was steroid induced acne (38.6%) and most common group of offending drugs were topical corticosteroids (38.8%). According to WHO and Naranjo's scale most of the observed cases were classify as probable (97.8%) and as per the Hart wig's classification, 56 cases (62.2%) were moderate in severity. One case (1.1%) was fatal leading to death
Conclusions: A wide range of clinical spectrum of CADRs was observed. Out of which steroid induced acne was the most common Cutaneous ADRs seen. Topical corticosteroids were the most common offending agent with highest prevalence in females. Most of the cases were of probable and moderate in severity. Fatal case was observed with Toxic epidermal necrolysis leading to death. Further identification and reporting of CADRs is essential in promoting drug safety and better patient care, among health care professionals and patients.

Keywords: cutaneous adverse drug reactions, WHO scale, naranjo's scale

1. Introduction

Adverse drug events (ADEs) are among the major challenges in modern medicine. Adverse drug reaction (ADR) has been defined in so many ways. WHO defines ADR as any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, therapy of disease, or for the modification of physiological function [1]. A Cutaneous adverse reaction caused by a drug is any undesirable change in the structure or function of the skin, its appendages or mucous membranes, and it encompass all adverse events related to drug eruption, regardless of the etiology [2].

In India epidemiological studies estimated that ADRs are fourth to sixth leading cause of death [3]. Cutaneous Adverse drug reactions (CADRs) are among the most frequent ADEs, approximately 2.9%-5.6% of the hospital admissions are due to ADR and 35% of the hospitalized patients experience at least one ADR during their stay in the hospital [4].

There are various clinical patterns that cause Cutaneous ADRs. Different studies show different prevalence of reactions. Fixed drug eruption (FDE) recoded about 24% of all ADRs, following Urticaria and Macupapular rash about 12.2% in hospitalized patient. Erythema multiform accounted for about 4.9% of the population with CADRs. Small incidence was seen with Steven Johnson Syndrome (SJS) and Toxic epidermal Necrolysis (TEN) about 2%. Most of the mortality cases are seen with Toxic Epidermal Necrolysis (TEN) about 25- 30 % than Steven Johnson Syndrome with a mortality rate of 5-10%. Allergic reactions were also seen in most of the patients who are allergic to drugs accounting for 5%. About 10% mortality is seen of DRESS. However there is lack of comprehensive data amongst outpatient. The inadequacy of data could be due to diagnostic dilemmas and lack of awareness of report [3]. The incidence of Adverse Cutaneous reactions to drugs is higher in women than in men and increased incidence of adverse drug reaction [5].

Almost any medicine can induce skin reaction, certain drug classes such as NSAIDs, Antibiotics (eg. Penicillin, Sulfonamide) and Antiepileptics (eg. Phenytoin) have drug eruption rates approaching 1-5% in previous reports. According to WHO database adverse reactions like rashes, pruritis, and urticaria are reported respectively from 4.2%, 2.7% and 2.6% of patients receiving drugs [3].

Adverse drug reactions (ADRs) are a major cause of morbidity, hospital admission, and even death. Hence it is

essential to recognize ADRs and to establish a causal relationship between the drug and the adverse event. It is desirable that ADRs should be objectively assessed and presented. Majority of CADRs are diagnosed clinically. These reactions may differ with different classes of drugs. Generating data is essential to understand the pattern of CADRs of different classes and generating information regarding offending drugs[3]. Recognition of the offending drug enables early withdrawal and improved outcomes. This will help the doctors to ensure safe drug usage and be aware of offending drugs thereby reducing morbidity and mortality. Observational studies are tools to know the pattern of reactions and causative drugs [7].

2. Objectives

The objective of this study was to observe the types of Drug induced Cutaneous Adverse drug reactions (CADRs) in the patients attending the Dermatology Department, Prevalence of Cutaneous Adverse drug reaction at Tertiary Care Hospital, to determine causal relationship with final outcome of CADRs and to recognize the offending drug, to determine the severity index of the adverse reactions, prevent CADRs and minimize hospitalization, to achieve a better treatment outcome and improve productivity and health.

3. Materials and Methods

It was a prospective, observational, non-invasive study carried out at Out Patient and Inpatient Department of Dermatology at Osmania General Hospital, Hyderabad over a period of six months (January 2015-June 2015).

Inclusion criteria

- Patients of either sex as inpatients and outpatients attending Dermatology Department.
- Patients more than 18 years of age.
- All patients attending Dermatology department, presented with visible skin lesions suspected to be drug related included in the study.

Exclusion Criteria

- Patients less than 18 years of age.
- Patients without visible skin lesions.
- Patients who could not recall the name of the suspect medicines consumed.
- If lesions turned out to be disease related (e.g., viral exanthemas, rash of rickettsial infections, and collagen vascular disease,) on closer examination.
- Patients who reported to have consumed indigenous (ayurvedic and homeopathic) medicines were also excluded.
- Patients unable to respond to verbal questions.

Demographic data like patient name, age, sex, brief description of the suspected ADR, Information about the suspected drug were recorded in the case collection form. Causality of ADRs was evaluated by WHO-UMC assessment scale [7] and Naranjo's scale [8] of which Unlikely, Conditional or Unassessible cases were excluded. The final diagnosis of CADR was based on history of drug exposure, clinical findings and under supervison of consultant Dermatologist. Severity of ADRs was evaluated by Hartwig and Siegel's classification graded on a 3-point scale [9].

4. Results

During the study period, a total of 95 cases of suspected Cutaneous ADRs were recorded from January 2015 to June 2015, out of which 5 cases were excluded because the offending drug was not identified or the data was insufficient to make any analysis. The remaining 90 cases were analyzed, among which one case was fatal leading to death. Maximum patients belonged to the age group of 21-30(34.4%),followed by 18-20 age group (22.2%),31-40 age group (20%), 41-50(13.3%), >50 age group(10%). Table 1 and Figure 1(a) shows details of age distribution pattern of CADRs encountered during the study. 34 cases (37.8%) were males and 56 cases (62.2%) were females showing female predominance. Table 1 and Figure 1(b) shows sex distribution patterns seen during the study.

The most common pattern of Cutaneous ADR observed was Steroid induced acne (38.6%). The second common CADRs was seen is fixed drug eruption (FDE) (13.3%) followed by Erythematous rash (11.1%), Toxic Epidermal Necrosis (TEN) and Urticaria recording (7.5%). Among which one was fatal experienced from TEN. Steven Johnson Syndrome recorded (4.4%). About (3.3%) of Vasculitis and Erythema was observed (2.2%) were seen with Erythroderma, Photosensitivity reaction and Drug rash eosinophilic systemic syndrome (DRESS). Alopecia, Exfoliative Dermatitis, Infectious eczema dermatitis, and Acanthosis like- nigricans were identified in only about (1.1%).Table 2 and Figure 2 show details of the Clinical patterns of CADRs encountered during our study

The most common group of offending drugs responsible for Cutaneous ADRs were Topical corticosteroids (38.8%), among which Betamethasone recorded the highest incidence of CADRs followed by Antibiotics with (24.8%), among which Ciprofloxacin was the common offending drug seen followed by Metronidazole, Tetracycline, Amoxicillin, 1 case was seen with each of Cotrimoxazole, Ceftriaxone and Dapsone. Use of tetracycline in one patient was fatal leading to death. Use of Anti-epileptic drugs was seen in (15.4%), where phenytoin recorded the highest number of ADRs. NSAIDs were seen in (10%), (3.3%) with Anti-tubercular drugs, Oral and Parentral corticosteroids with (3.3%). Rare cases about (1.1%) were seen with, Antifungal (Fluconazole), Opioid Analgesic (Tramadol), Angiotensin converting enzyme inhibitors (ACEI) (Captopril), and Non-nucleoside reverse transcriptase inhibitor (NNRTI) (Efavirenz). Table 3 and Figure 3 shows detail results of therapeutic drugs classes implicated in CADRs encountered in this study

Causality Assessment

90 cases of CADRs were analyzed. According to Naranjo's Scale, most cases were of probable (97.8%) and (2.2%) showed a definite score. According to WHO Scale (2.2%) scored certain, remaining all (97.8%) were of probable. Unlikely, conditional, unclassifiable were excluded from the study Table 4 and Figure 4 show details of causality assessment of CADRs based on Naranjo's and WHO scale

Severity Index

Severity of CADRs was assessed as per the Hartwig's classification graded on a 3-point scale. The results of assessment of the severity index revealed that most of the cases were moderate in severity accounting for (62.2%), followed by mild with (26.7%) and (10%) were identified as severe.One case (1.1%) was fatal leading to death. Table 5 and Figure 5 show the details of severity assessment of CADRs encountered during the study period.

Table 1: Age and sex distribution of CADRs

Age group	Males	%	Females	%	Total	%
18-20	6	17.64%	14	25%	20	22.2%
21-30	9	26.48%	22	39.28%	31	34.4%
31-40	9	26.48%	9	16.07%	18	20%
41-50	5	14.7%	7	12.5%	12	13.3%
>50	5	14.7%	4	7.15%	9	10%
Total	34	38%	56	62%	90	100%

Table 2: Clinical patterns of CADRs

Clinical type	Frequency	Percentage
Steroid induced acne	34	38.6%
Fixed Drug Eruption (FDE)	12	13.3%
Erythematous rash	10	11.1%
Toxic Epidermal Necrolysis(TEN)	7	7.5%
Urticaria	7	7.5%
Steven Johnson syndrome	4	4.4%
Vasculitis	3	3.3%
Erythema multiforme	3	3.3%
Erythodema	2	2.2%
Drug Rash Eosinophilic Systemic Syndrome(DRESS)	2	2.2%
Photosensitivity reaction	2	2.2%
Eczema dermatitis	1	1.1%
Exfoliative dermatitis	1	1.1%
Alopecia	1	1.1%
Acanthosis like nigrans	1	1.1%

Table 3: Drugs responsible for CADRs

Drug name	Individual group	No. of cases	Total no. of cases	Percentages
Topical corticosteroids	Betamethasone	24	35	38.3%
	Mometasone	10		
	Clobetasol	1		
Antibiotics	Ciprofloxacin	7	22	24.8%
	Metronidazole	6		
	Tetracycline	4		
	Amoxicillin	2		
	Cotrimoxazole	1		
	Ceftriaxone	1		
	Dapsone	1		
Antiepileptics	Carbamazepine	2	14	15.4%
	Phenytoin	12		
NSAIDS	Diclofenac sodium	4	9	10%
	Naproxen	2		
	Aspirin	2		
	Ibuprofen	1		
Antitubercular	Isoniazid	1	3	3.3%
	Rifampicin	2		
Oral corticosteroids	Prednisolone (oral)	2	3	3.3%
	Hydrocortisone (IV)	1		
Opioid Analgesic	Tramadol	1	1	1.1%
Antifungal drugs	Fluconazole	1	1	1.1%
Angiotensin converting enzyme inhibitor (ACEI)	Captopril	1	1	1.1%
Non-nucleoside reverse transcriptase inhibitor (NNRI)	Efavirenz	1	1	1.1%

Table 4: Causality assessment of CADRs (WHO and Naranjo's Scale)

Type of reaction	Who Scale		Naranjo Scale			
	No. of cases	Percentage	No. of cases	Score		%
Definite	2	2.2%	2	+10		2.2%
Probable	88	97.8%	88	No of cases	Score	97.8%
				40	+6	
				44	+7	
				4	+8	
Possible	0	0%	0	0		0%

Table 5: Severity index of CADRs (Hartwig's Severity Assessment Scale)

Severity index	No. of cases	Percentage
Mild	24	26.7%
Moderate	56	62.2%
Severe	9	10%
Fatal	1	1.1%

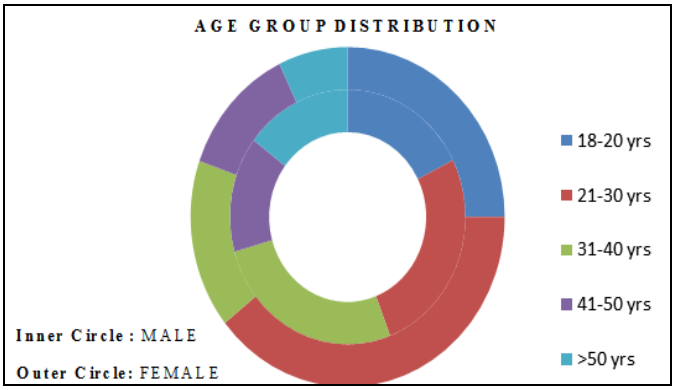

Fig 1(a): Age distribution of CADRs

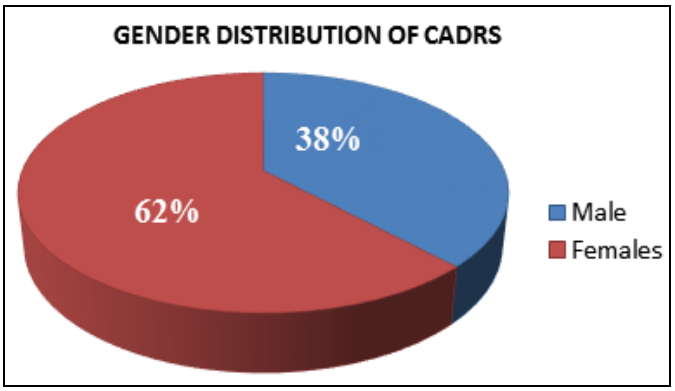

Fig 1(b): Gender distribution of CADRs

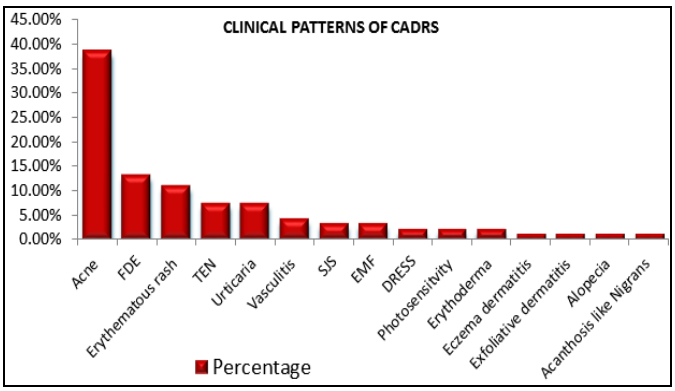

Fig 2: Clinical patterns of CADRs

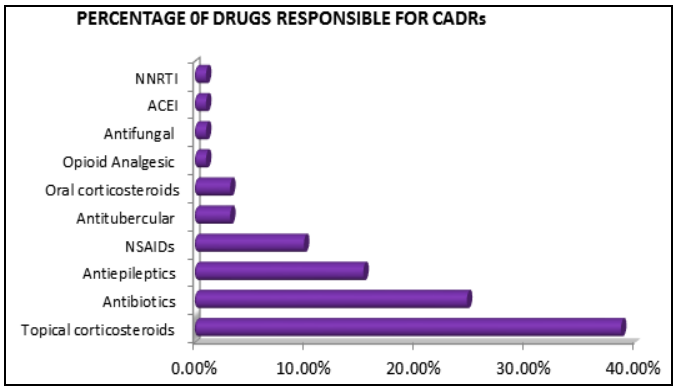

Fig 3: Drugs responsible for CADRs

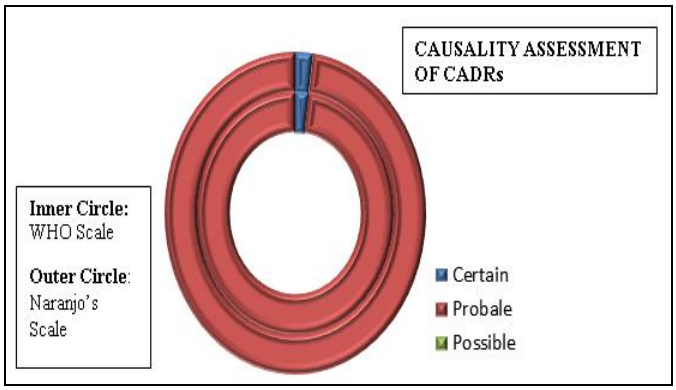

Fig 4: Causality assessment of CADRs (WHO and Naranjo's Scale)

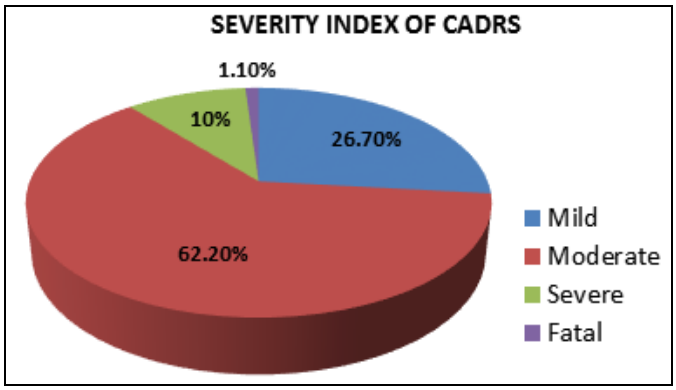

Fig 5: Severity index of CADRs (Hartwig's severity assessment scale)

5. Discussion

A Prospective, Observational and non-invasive study was carried out for a period of 6 months recording 95 cases, out of which 5 cases were excluded because the offending

drug was not identified or the data was insufficient to make any analysis. The remaining 90 cases were analyzed, among which one case was fatal leading to death. Of the 90 cases, 34(37.8%) were males and 56 (62.2%) were females contributing to female preponderance, which was similar to that of studies reported in the literature by Ruchika Nandha, *et al* (2011) [10], V Sudershan *et al* (2011) [11], Saraswoti neupane and Surya Raj Sharma (2012) [12], Akram Ahmed *et al* (2012) [13], Mahmood Farshchian *et al* (2015) [14]. Unlike in study of Shalini Chawla *et al* (2011) [15] and Tejas K Patel, Sejal H Thakkar, DC Sharma- Review (2015) [16] which showed male preponderance.

In our study, highest percentage of CADRs was recorded in the age group of 21- 30 showing (34.4%) which is in accordance with studies reported by Shalini Chawla *et al* (2011) [17] where the mean age of patients who experienced CADRs was 32, and V Sudershan *et al* (2011) [18] reported with higher incidence in adult age group between 21-30 years. Adverse drug reactions reported in our study showed maximum incidence with the application of Topical corticosteroids (38.8%), followed by Antibiotics (24.8%), among which Ciprofloxacin was the common offending drug. (15.4%) were seen in patients who administered Anti-epileptic drugs where phenytoin recorded the highest number of ADRs. NSAID was about (10%). Antitubercular, Oral and Parenteral corticosteroids were the offending agent recording (3.3%). Rare cases (1.1%) were seen in patients taken Antifungal agents, Opioid Analgesic, Angiotensin converting enzyme inhibitors (ACEI), and Non-nucleoside reverse transcriptase inhibitor (NNRTI). Studies carried out by Bharani Kalpana R, *et al* (2014) [19] have reported that oral Antimicrobials, Injectable Antimicrobials, NSAID's and Topical Steroids (Betnovate) were the leading cause of ADRs. All the other literature articles showed the highest offending drug to be Antimicrobials accounting for nearly 50% of the cases, followed by NSAIDs, Antiepileptics.

The common clinical pattern of Cutaneous ADR observed in our study was Steroid induced acne recording about (38.6%). The second common CADR was seen is Fixed drug eruption (FDE) with about (13.3%) followed by Erythematous rash that showed (11.1%), Toxic Epidermal Necrosis (TEN) and Urticaria recording (7.5%).in which 1 was fatal with TEN wherein similar mortality with TEN was seen in the study of Saraswoti neupane and Surya Raj Sharma (2012) [12] Steven Johnson Syndrome were identified in (4.4%). About (3.3%) of Vasculitis and Erythema was observed, (2.2%) were seen with Erythoderma, Photosensitivity reaction and Drug rash eosinophilic systemic syndrome (DRESS). Rare cases about (1.1%) was seen in Alopecia, Exfoliative Dermatitis, Infectious eczema dermatitis, and Acanthosis like nigranicans. Unlike in other studies Fixed drug eruption was the highest recorded clinical pattern of ADR by Saraswoti neupane and Surya Raj Sharma (2012) [12]. Some studies have observed urticaria and exanthematous rash as offending agents by Karamsad Suthar J.V1 and Desai S.V (2011) [20] recording both about 31.42%, whereas studies by Balpande K.G.,et.al (2013) [6] recorded (32.75%) and (26.72%) respectively. Acute urticaria was the most common clinical presentation (59.2%) in the study by Mahmood Farshchian *et al* (2015) [14].

According to Causality assessment as per the Naranjo's scale, (2.2%) scored definite, Remaining all about (97.8%) scored probable and as per the WHO scale (2.2%) scored certain, rest all (97.8%) were of probable. Unlikely, conditional, unclassifiable were excluded from the study. Most of the studies showed the same assessment data giving high incidence of probable cases about (55.89%) reported by Meena Shrivastava *et al* (2011) [21], and about (90.62%) as reported by Palanisamy S, Arul Kumaran KSG, Rajasekaran A (2009) [22] and about (78.26%) reported by Himangshu Mahato *et al* (2014) [23].

The results of assessment of the severity index revealed most cases with moderate about (62.2%), followed by mild about (26.6%). (10%) were identified as severe. One case (1.1%) was fatal leading to death. which was similarly seen in the study by Saraswoti neupane and Surya Raj Sharma (2012) [12] In our study all the cases were Type B (Bizarre type) which was similiarly seen in the study by Karamsad Suthar J. and Desai S.V (2011) [20] where 100% ACDRs were Type B (Bizarre immunological allergic drug reaction).

6. Conclusion

Clinical patterns and the drugs causing ADR are remarkably similar to those observed in other studies except for minor variations. A wide clinical spectrum of cutaneous ADRs ranging from Steroid induced acne to Fixed Drug Eruption (FDE), Erythematous rashes, serious Toxic Epidermal Necrosis (TEN), Urticaria, Steven Johnson Syndrome (SJS) and Drug Rash Eosinophilic Systemic Syndrome (DRESS) was observed. Out of which Steroid induced acne was the most common cutaneous ADRs seen. Topical corticosteroids were the most common and among which Betamethasone was offending agent causing Cutaneous ADRs. The study demonstrated the causal relationship that was established using WHO and Naranjo's algorithm. It was evaluated that majority of the cases assessed were "probable", with few cases of "certain". The analysis revealed the severity of Cutaneous ADR showing majority of the cases as moderate followed by mild and severe. Fatal case was seen with TEN leading to death. These variations may be explained by the differences in drug usage patterns and short duration of the study.

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