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To Study and Evaluate the Incidence of Cutaneous Adverse Drug Reaction (CADRS) in the Patients Attending Dermatology Department of A Tertiary Care Teaching Hospital

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ABSTRACT
Adverse cutaneous drug reactions (CADRs) are commonly reported type of ADRs and are caused by a wide varieties of drugs. The clinical patterns of adverse cutaneous drug reactions and the drug responsible for them is changing every years due to the emergence of newer molecules and changing trends in the use of drugs.
Our objective was to evaluate the clinical pattern of CADRs and their causative drugs in the tertiary health care.
It was cross sectional observational study of 1 year duration. There wre 52 patients with adverse cutaneous drug reaction were recruited. The majority of CADRs was in the age group of 18-35 years (63.46%). The male to female ratio was 0.79:1.
Fixed drug eruption (FDE) was the most common adverse cutaneous drug reaction (34.61%) followed by maculopapular rash (23.07%), acneform eruption (11.53%), SJS/TEN (11.53%), erythema multiforme (7.69%), urticaria (7.69%) and the most common cause was NSAIDs followed by antimicrobial agents.
Knowledge of these drug eruptions, the causative drugs are essential for the clinicians and implementing the ADRs reporting and monitoring system, one can promote drug safety and better patients care, among health care professionals.
Key words: *Cutaneous adverse drug reaction, Adverse drug reaction, causative agents.*

INTRODUCTION

According to WHO, an adverse drug reaction (ADRs) is defined as "a response to a drug that is noxious and unintended and occurs at doses, used in man for prophylaxis, diagnosis or therapy of a disease or for modification of physiological functions [1]. Cutaneous ADRs are the most common ADRs and have become very common in present time [2]. They are thought to occur up to 3% of medical in patients.

ADRs are claimed to be the fourth leading cause of death highest than pulmonary disease, AIDS, accidents and automobiles death.

The growing number of newly approved drugs coupled with the complex treatment modalities have contributed to an increased risk of ADRs.

Pharmacovigilance is usable in educating doctors about ADRs and in the authorized regulation of drug use. Its main motive is to reduce the risk of drug related loss to the patients.

Cutaneous adverse drug reaction (CADRs) is a frequent and challenging clinical issue in our daily practice in dermatology. They involve complex and incompletely understood pathophysiology mechanism and manifest under different clinical patterns varying from mild to severe life-threatening CADRs [3].

CADRs can mimic skin diseases which are not usually drug induced, like licken planus, psoriasis, lupus erythematosus or phemphigus vulgaris. The time course of the different CADRs is also very variable. They occur within minutes, hours, days, weeks or even months after drug administration and may last a few hours to weeks, months or years. Moreover virtually any drug can induce a CADRs, each drug can induce several clinical patterns of CADRs and there is no universal test to confirm drug hypersensitivity.

MATERIAL AND METHODS

This study was carried out in the patients attending the department of dermatology TMMC & RC, Moradabad, UP, India from March 2015 to feb.2016 (1year).

This was prospective, cross-sectional and observative study of patients (n=52) who attended the dermatology department of TMMC & RC, Moradabad, U.P, India.

This study gets ethical approval from medical research and ethics committee at the Theerthanker Mahaveer medical college and research centre (TMMC & RC).

Written informed consent from the patients/legal guardians was obtained prior to conduct study. Demographic data such as patients initials, age, gender, occupation were recorded and Provisional diagnosis, also.

The diagnosis of CADRs was based on examination done by consultant dermatologist.

The patient who consume medicine other than allopathic medications (like Ayurvedic / Homeopathic etc.) and who are not able to recall the name of suspected medicine consumed (improper drug history) were excluded from the study. Detailed history of the patients including present illness and past or concurrent systemic illness were also taken.

The criteria for the diagnosis of ACDRs were as follows [4].

1. The time interval between the introduction of the drug and the onset of a reaction should be within a specific time Maculopapular rash<7 days, Urticaria 7-21days, Steven Johnson Syndrome / Toxic Epidermal Necrosis (SJS/TEN) and Erythema Multiforme 1-3weeks, Drug hypersensitivity syndrome 2-6weeks, Photodermatitis up to 1 year, Exfoliative dermatitis 1-6weeks, Fixed drug eruption (FDE) 30min-16hours.
2. Improvement is the condition of the patient after dechallenge / withdrawal of the suspected drug.
3. Drug rechallenge producing similar reaction again.

To establish the etiologic agents for ACDRs, attention was paid to the drug history, temporal correlation with the drug, duration of the rash, pattern of lesion, improvement of lesion on withdrawal of drug & recurrence of lesion on rechallenge if possible. Rechallenge was not undertaken in any of our cases because of the possible associated risks. If more than one drug was thought to be responsible, the most likely offending agent was noted and the impression was confirmed by subsidence of the reaction with time or on withdrawing the drug. Finally data was recorded in CDSCO form [5] and was compiled and analysed.

According to the WHO causality definition ADRs were categorized as certain, probable, possible and unlikely.

RESULT

In our study 52 patients were included after applying inclusion and exclusion criteria. The mean age of the patients developing cutaneous adverse drug reaction (CADRs) was 39.36+16.77 (range 2-70years). A majority of patients were in the age group of 21-40years. Males accounted for 44.23% (23) of cutaneous adverse drug reaction and females accounted for 55.76% (29). The male and female ratio was 0.79:1. Age and gender wise distribution of patients reporting with CADRs is summarized in [Table-1].

Fixed drug eruption (FDE) is the most common cutaneous adverse drug reaction accounting for 34.61% (18) followed by maculopapular rash; 23.07% (12), acneform eruption; 11.53% (6), SJS/TEN; 11.53% (6), erythema multiforme; 7.69% (4), Urticaria; 7.69 (4) and less common pattern are hyperpigmentation.

The most common drugs responsible for CADR in prospective study were metronidazole, paracetamol and levofloxacin for fixed drug eruption, while diclofenac and levofloxacin for maculopapular rash. Antimicrobial 46.15%(24) other NSAID 38.46%(20) and steroid were responsible for other various CADRs [Table-2].

According to WHO causality assessment 13 were certain (25%), 30 were probable (57.69%) and 10 were possible (9.23%) in nature. On severity assessment by modified Hartwig and Siegel`s scale, out 52 CADRs 8 (15.38%) were mild 42 (80.70%) were moderate and 2 (3.84%) were severe.

TABLE-1 Age and sex wise distribution of patients who developed CADRs in prospective study.

Age group (in years)	Male	Female	Total	Percentage
1-17	05	06	11	21.15
18-35	15	18	33	63.46
36-53	03	05	08	15.38
54-71	00	00	00	00
total	23	29	52	100

TABLE-2: Drug responsible for CADRs in prospective study (n=52).

Sr. No.	Type of reaction	No. of patients	Drug`s (group) responsible
1	Fixed drug eruption	18	Antimicrobial (10)
			NSAIDs (8)
2	Maculopapular rash	12	NSAIDs (6)
			Antimicrobials (4)
			Antiepileptic (2)
3	Acneform eruption	06	Steroid (4)
			Antimicrobial (2)
4	SJS/TEN syndrome	06	NSAIDs (4)
			Antimicrobial (2)
5	Erythema multiforme	4	Antimicrobial (2)
			NSAIDs (2)
6	Urticaria	4	NSAIDs (2)
			Antibiotic (1)
			Anaesthetics (1)
7	Hyperpigmentation	2	Antileprotics (1)
			NSAIDs (1)

TABLE-3: Drug responsible for Cutaneous adverse drug reactions.

Drug	No. of patients	Percentage
Antimicrobial	17	32.69%
NSAIDs	26	50%
Antiepileptic	4	7.69%
Steroids	3	5.76%
Other	2	3.84%
Total	52	100%

DISCUSSION

In our study Cutaneous adverse drug reaction (CADRs) with higher incidence in adult age group between 21-40years (63.46%) CADRs and in previous studies higher CADRs reported of 21-35years [6-7]. There were 29 (55.76%) females and 23 (44.23%) males in our studies. Female cases were already reported in many studies, [8,9,10]. In our study conducted for a duration of 12 months,

(March 2015-february2016) showed a total 52 cases.

CADRs was most commonly observe with NSAIDs drugs (50%) in our study. NSAIDs was the main age group of drugs (42.6%) to cause various types of drug induced reaction in previous study, supporting our study [6].

In our study sulphonamide, fluroquinolones and penicillins were the main antibiotic to cause CADRs. Similar to this previous studies reported that sulphonamides, penicillins and quinolones were found to be the major cause of CADRs [6].

In our study SJS (3 case), and FDE (2case) with cotrimoxazole and EM (2 case) with sulphadiazine. Three (3) patients on ofloxacin developed maculopapular reaction in our study. 2 patients on furazolidone produce FDE in our study which may be due to structural similarity to sulphonamides. Sulphonamide have been noticed to develop EM, exofoliative dermatitis and SJS supporting our study [11,12,13,14].

Among fluroquinolones ciprofloxacin produced SJS (2 cases) and ofloxacin EM (1 case) and ofloxacin maculopapular reaction (3 cases) in our study. Doxycycline produce hyperpigmentation.

Photosensitivity, hypersensitivity reactions, erythema multiforme, fixed drug eruption and several skin reaction have been reported with fluroquinolones by several authors [15,16,17]. Mostly CADRs were found in newer drug like cephalosporines and fluroquinolones when compared to the reports of previous studies with older antibiotics [7].

In other studies, incidence of CADRs with NSAIDs were 21%, 35%, 30% and 38% respectively [7,8,11]. The most common reaction were purposa macula papular eruption and FDE and common drug were ibuprofen and acetaminophen [7,18,11,19]. In our study incidence of cutaneous ADRs with NSAIDs were (n=32.69) which occurred with Nimesulide (3 cases) and diclofenac sodium (2 cases). Drug involved in CADRs were antiepileptics and the incidence was n=7.69% in our study. In other studies the incidence was reported as 23.8% and 25% respectively [7,8] which was higher than our study. We observed maculopapular rash (1 case) with phenytoin sodium in our study. Similarly, several studies had show that SJS, FDE and DHS(drug hypersensitivity syndrome) were the main CADRs seen with phenytoin sodium[20,17,7]. We got ADRs only with phenytoin sodium, where as other studies reported ADRs with phenytoin as well as with carbamazepine [7,17,14]

In our study according to Naranjo`s causality scale, 03 ADRs (n=5.76%) were definite, 38 ADRs (n=73.07%) were probable and 11 ADRs (n=21.15%) were possible. The study of Guwahati by Lihite et al showed higher cases of probable ADRs similar to the our study.

CONCLUSION

It was concluded from our study that dermatological adverse drug reaction was a common occurrence and awareness for them is essential for diagnosis and prevention. The dermatological ADRs varied in their appearance, duration, causality, severity, and preventability. NSAIDs and Antimicrobial agents were the most common implicated drug class. NSAIDs group diclofenac, aceclofenac and nimesulide were most commonly responsible drug for produce CADRs. Antimicrobial group such as fluroquinolones & ciprofloxacin were the most common drugs for produce cutaneous adverse drug reaction. Depending upon nature of ADRs, actions against suspected drug along with symptomatic treatment were given whenever found significant.Most of ADRs gets unreported due to lack of interest in ADRs monitoring and reporting at hospital settings. By present piece of work, pharmacist contributed patients safety and rational use of drug by assessing, reporting and treating ADRs. Causality assessment also resulted in high score of probable category. The healthcare system should promote the spontaneous reporting of dermatological adverse drug reaction to pharmacovigilance centres for ensuring drug safety. ADRs study will provide useful information of adverse cutaneous drug reaction

from central India to the existing information of CADRs available rest of India

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