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PATTERN OF CUTANEOUS ADVERSE DRUG REACTIONS IN TERTIARY CARE TEACHING HOSPITAL IN KUMAON REGION

Pharmacology

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ABSTRACT

Cutaneous adverse drug reactions (CADRs) are minor and self limiting, sometimes even severe and life threatening. They are common and the prevalence of it ranges from 2 to 5% of the inpatient in Indian hospital setting. This was a retrospective study conducted at the tertiary care centre at Dr.Sushila Tiwari Government Medical College Hospital & Haldwani Nainital from May 2016 to April 2017 with the purpose of analysing the cutaneous adverse drug reactions so as to gain insight into the pattern of reactions and identify suspected drugs. A total of 123 patients were recruited, out of which 34.95% were males and 65.04% were females. Most common cutaneous ADR was maculopapular rash (35.2%) whereas antimicrobials (46.5%) were the most common drugs causing CADRs. WHO causality scale assessed that 51.13 % of reactions fell under possible and 48.48 % under probable causality.

KEYWORDS

CADRs, WHO, ADRs.

INTRODUCTION:

Safe use of drugs is the major responsibility of clinicians and heath care professionals so as to minimise suffering and health care cost. Drugs are very often related with the risk of adverse effects, no matter how safe and efficacious they are. The world health organization (WHO) defines an adverse drug reaction (ADR) as any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for diagnosis, prophylaxis or therapy.[1] Drug reaction may occur to any prescribed drug, over the counter medications and herbal concoctions. ADRs place a considerable burden on the society. Results of a meta-analysis revealed that serious ADRs account 6% of hospitalized admissions in USA.[2]

Cutaneous adverse drug reactions (CADRs) are responsible for majority of ADRs in hospitalized patients; prevalence of it may range from 2 to 5 % of the inpatient in Indian hospital setting.[3] There is wide variation of cutaneous reactions ranging from maculopapular rash to severe toxic epidermal necrolysis. Although majority of cutaneous reactions are minor reactions and are self limiting, sometimes severe and life threatening situations arises. The pattern of cutaneous adverse drug reactions and responsible drugs, changes every year with the introduction of newer drugs and evolving prescription practices.

Considering the importance of monitoring of ADRs for improving public health, Pharmacovigilance Programme of India (PvPI) was started in 2010.[4] Under this programme, ADRs monitoring centre have been started in many medical institutions and hospitals all over the country. 50% of approved drugs have been associated with some type of adverse effects that have only been seen after its marketing.[5][6] Pharmacovigilance has involved an excellent system for monitoring, with the objective of understanding the various characteristics of ADRs like severity, expectedness, risk factors, seriousness, association and their frequency. Therefore, the present study was carried out with the purpose of analysing the cutaneous adverse drug reactions so as to identify the suspected drugs and gain insight into the pattern of reaction and as to minimise the suffering and cost.

MATERIAL AND METHODS:

Study Area: This study was conducted at tertiary care centre at Dr Sushila Tiwari Government medical college Haldwani, Nainital. Approval of the Institutional Ethical committee was obtained for the study.

Study Period and Study Population: The Data was collected using suspected ADRs reporting forms during the period of one year (May 2016 to April 2017) from various departments to the ADR monitoring centre attached to department of Pharmacology under the Pharmacovigilance Programme of India (PvPI).

Study Design: It was a retrospective study conducted using ADR reporting form obtained from various departments, who had prescribed different drugs during the study period. The demographic details of patients were recorded. Details of medication along with chief complaints, drug history and other relevant history were also noted. Details about occurrence, nature and severity of ADRs, dechallange and rechallange information were also recorded. Relevant laboratory investigations were also noted. Patients of both sexes with all ages with different indications, developing at least one ADR during treatment were included in the study.

Study tool: Suspected ADR reporting form designed by National coordination centre, Indian Pharmacopoeia Commission was used to collect the relevant data. All reported ADRs were assessed for causality using WHO causality scale[7] and for severity using Hartwig and Siegel scale[8]. The WHO causality assessment scale determines the causal relationship of a suspected drug to the ADR in question and categorize into "Certain", "Probable", "Possible", "Unlikely", "Conditional/ Unclassified" and "Unassessable/ Unclassifiable". The Data collected was analyzed using Microsoft excel sheet; frequency and percentage were determined for each variable.

RESULT:

Total of 123 patients were included in our study, of which 43 (34.95%) males and 80 (65.04%) females experienced CADRs (Table 1). Most common age group experiencing cutaneous ADRs was 20 to 29 years (Table 1).

Table 1. Demographic distribution.

VARIABLES	NUMBER (n =123)	PERCENTAGE (%)
GENDER		
Male	43	34.95
Female	80	65.04
AGE IN YEARS		
0 -9	10	8.13
10-19	11	8.99
20-29	28	22.76
30-39	20	16.26
40-49	15	12.19
50-59	12	9.75
60-69	20	16.26
70 and above	07	5.69

Most common cutaneous ADR was maculopapular rash (35.2%) followed by urticaria (31.9%) and alopecia (22.3%) (Table 2). 51.13 % of reaction falls under possible, 48.48 % under probable and 0.37% under certain causality (Table 2).

Table 2. Pattern and Causality of Cutaneous Adverse Drug Reactions.

PATTERN OF ADRS	WHO CAUSALITY SCALE				
	Possible	Probable	Certain	Total (n=264)	%
Maculopapular Rashes	40	53	-	93	35.2
Hyperpigmentation of skin	-	2	-	2	0.8
Urticaria	40	44	-	84	31.9
Alopecia	36	22	1	59	22.3
Angioedema	14	5	-	19	7.0
Oral ulcers	3	-	-	3	1.1
Fixed Drug eruptions	3	1	-	4	1.5
Bilateral blisters on legs	-	1	-	1	0.4
Contact dermatitis	-	1	-	1	0.4
Pigmentation of Nails	-	1	-	1	0.4
SJS	1	-	-	1	0.4
Total (%)	135 (51.1)	128 (48.5)	1(0.4)	264	100

Most common class of drugs causing cutaneous ADRs was antimicrobial (46.5%) followed by anticancer (22.3%) and non-steroidal anti-inflammatory drugs (18.18%) (Table 3, Figure 1). WHO criteria indicated 40.64% of reactions were serious, out of which 37.39% of reactions required intervention whereas 59.34 % were non-serious.

Table 3 Commonly incriminated drugs causing cutaneous adverse drug reactions

GROUP (%)	CUTANEOUS ADR (n=264)	DRUGS (NO OF PATIENTS)
Anticancer (22.3)	Alopecia	Cisplatin(10), Cyclophosphamide(7), Carboplatin(4), Docetaxcel(3), Doxorubicin(10), Etosposide(4), 5- Fluorouracil(11), Paclitaxcel(6), Methotrexate(1), Bleomycin(1), Leucovorin(1), Zoledronic Acid(1)
	Angioedema	Paclitaxcel(1)
	Nail Pigmentation	Paclitaxcel(1)
	Oral ulcer	Methotrexate(1)
NSAIDS (18.2)	Maculopapular Rash	Paracetamol(10), Ibuprofen(2), Diclofenac(2), Aceclofenac(3), Ecosprin(1), Etoricoxib(1)
	Urticaria	Diclofenac(4), Paracetamol(7), Aceclofenac(2), Etoricoxib(1), Ecosprin(1), Ibuprofen(2), Thiocolchicoside(1)
	Contact dermatitis	Diclofenac(1)
	Oral ulcers	Paracetamol(2)
	Fixed drug eruption	Paracetamol(1)
	Angioedema	PCM(2), Aceclofenac(2), Flupirtine(2), Thiocolchicoside(1)
Antimicrobial (46.5)	Maculopapular Rash	Ceftriaxone(1), Metronidazole(1), Amoxicillin(2), Ciprofloxacin(3), Cefixime(2), Cefotaxime(1), Doxycylline(1), Amphotericin(1), Azithromycin(1) ,Gentamycin(1), Linezolid(1), Amikacin(1), Starnidazole(1), Clindamycin(1), Rifampicin(11), Isoniazid(11), Ethambutol(8), Pyrazinamide(10)
	Fixed drug eruption	Doxycylline(1), Ceftriaxone(1), Azithromycin(1)
	Urticaria	Azithromycin(1), Amoxicillin(2), Amphoterecin(1), Metronidazole(3),Ceftriaxone(1), Doxycycline(1), Ciprofloxacin(1), Cotirmoxazole(1), Cefixime(1), Isoniazid(11), Rifampicin(10), Pyrazinamide(11), Ethambutol(11), Levofloxacin(1)
	Angioedema	Rifampicin(1), Isoniazid(1), Ethambutol(2)
	SJS	Rifampicin(1)
	Blisters	Ceftriaxone(1)
Antiepileptic (5.3)	Urticaria Maculopapular rash	Phenytoin(2), Oxcarbazipine(1) Phenytoin(5), Valproic acid(2), Oxcarbazipine(1)
	Angioedema	Pregabalin(2), Oxcarbazipine(1)
Antiretroviral (3)	Urticaria Maculopapular rash Angioedema	Tenofovir/Lamivudine/Efavirenz(4) Tenofovir/Lamivudine/Efavirenz(2), Abacavir(1) Tenofovir/Lamivudine/Efavirenz(1)
Antirheumatic (0.75)	Skin Hyperpigmentation	Hydroxychloroquine(2)
Corticosteroids (1.13)	Maculopapular Rash	Methylprednisolone (1)
	Angioedema	Prednisolone(2)
Opioids (1.13)	Urticaria	Tramadol(1), Drotaverine(1)
	Maculopapular rash	Drotaverine(1)
Vaccine (0.37)	Maculopapular rash	Measles vaccine(1)
Hormones (0.75)	Urticaria Maculopapular rash	Progesterone(1) Progesterone(1)
Others (1.5)	Angioedema	Pyridoxine(1), Iron sucrose(1)
	Urticaria	Pantoprazole(1)
	Maculopapular rash	Ondansetron(1)

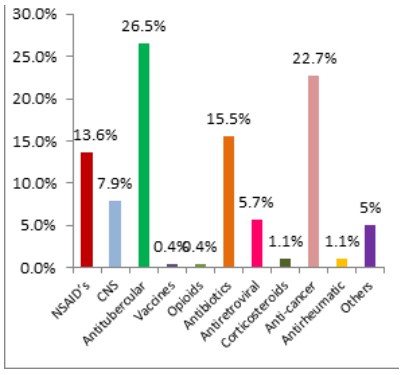

Figure 1. Commonly incriminated drugs causing CADRs.

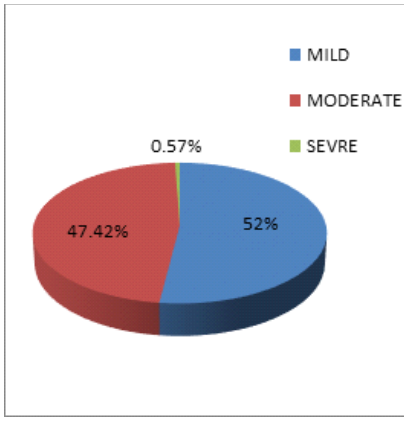

Figure 2. Severity Assessment using Hartwig and Siegel scale

Severity of 52% ADRs were Mild, 47.42% cases were moderate 0.57 cases were severe according to modified Hartwig and Siegel severity assessment scale(Figure 2).

DISCUSSION:

The present study evaluated the pattern of cutaneous adverse drug reactions, its association with offending drugs; and its causality and severity. Out of 123 ADRs form evaluated, 80 (65.04%) were females and 43(34.65%) were males. This was in agreement with the study conducted by Ruchika et al[9] who showed female preponderance, whereas Nivethitha T et al[1] and Saritha et al showed male preponderance.[10] The increased risk of ADRs in females may be due to the difference in their hormonal, pharmacokinetic and immunological profile. Majority of the patients with the cutaneous reactions were young in the age group of 20 to 29 years similar to the reports of Hemant K Garg et al, Jelvehgari et al and Solensky K Garg et al.[11,12,13,14] The probable reason for this observation could be due to an increase exposure of antimicrobials in this age group which increases the risk of drug eruptions.[11][14] In contrast to this, Al-Raaie F et al found elderly and adult patients to be most commonly affected.[15]

A wide spectrum of clinical presentation was observed in the study. The most commonest was maculopapular rash (35.2%) followed by urticaria (31.9%), alopecia (22.3%), angioedema (7%). Above finding were similar to the findings reported by Sandeep Mahapatra et al and Hemant K Garg et al.[3,11] High incidence of SJS reported by Sandeep Mahpatra et al[3] which was contrary to our study.

Antimicrobials including antitubercular drugs were most commonly suspected followed by anticancer, NSAIDs and antiretroviral drugs. This was in agreement with most of the studies done in middle east and India.[11,15,16] This may be due to wider use of antimicrobials and NSAIDs by patients reporting to outpatient and inpatient department. Anticancer drugs causing ADRs were also significant because of cancer institute also reporting to our ADR centre. Most common drugs causing cutaneous ADRs were antimicrobial (46.5%) followed by anticancer (22.3%) and NSAIDs (18.18%). Most of the ADRs caused were either mild (52%) or moderate (47.42%) where as only 0.57% were severe. Assessing the severity of ADR is an essential component in pharmacovigilance which may require active intervention and discontinuation of suspected drug. Occurrence of CADRs is influenced by several factors, patients with previous history of drug reactions are more likely to develop CADRs. Atopy could be one of the reason for development of cutaneous adverse drug reaction.[15] Ethinicity and drug usage pattern can also have a marked influence.

CONCLUSION:

The occurrence of cutaneous ADR was wide ranging from maculopapular rash to severe toxic epidermal necrolysis. Antimicrobial were the most common class of drugs causing CADRs. Therefore, use of drugs causing serious ADRs and newly approved drugs should be closely monitored to find out unknown ADRs, so as to reduce morbidity and mortality.

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