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Original Research Article

CUTANEOUS MANIFESTATIONS OF THE ADVERSE DRUG REACTIONS REPORTED BY ADVERSE DRUG MONITORING CENTRE OF ANIIMS, PORT BLAIR

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Abstract

Cutaneous drug reactions are one of the commonest adverse events related to drug use, which lead to discontinuation of treatment as well as loss of follow-up, elevated treatment cost and a contributor to morbidity and mortality with the effect on the social interaction of the patient. Therefore this study was done with the aim to look into the pattern of ADR's and also which are the common offending drugs as well as their causality, and severity.

Materials & Method: All adverse drug reactions (ADRs) forms from the different clinical department of ANIIMS, Port Blair were used for patient information from August 2015 to December 2016 forms with cutaneous drug reactions were analyzed only and assessed for causality, and severity.

Observations: Out of 336 adverse drug reaction forms, 240 (71.4%) were having ADR's as cutaneous manifestations. In the present study, out of 240, 150(62.5%) patients were male and 90 (37.5%) were female patients. Skin rashes was the most common presenting ADR as 130 (54.1%) patients had skin rashes in the form of macules, papules or even depigmented rashes, followed by urticaria in 56(23.3%) patients,), Itching & Pruritus in 39(16.2%) patients followed miscellaneous ones in 15(6%) of the patients. Most common drug classes which caused these cutaneous manifestations included antimicrobial agents, anti-inflammatory, and steroidal agents. Naranjo's scale was used as a tool to establish the causality. The observations showed that 220(91.6%) ADRs fall in the category of probable as per the scale, 12 (5.0%) were classified as possible; 5 (2.0%) as doubtful and 3 (1.25%) were surely related to the drug.

Conclusions: The present study shows cutaneous drug reactions are a common presentation amongst the reported ADR's of ANIIMS, Portblair. Further, there is a need of intensive monitoring for ADRs in each and every setup as most of them are preventable. Also, it is the need of the hour to ensure the safety of the patient.

Keywords: CADR's, Skin rashes, Adverse drug reaction, Naranjo's causality assessment scale.

Introduction

As per the WHO Definition, an ADR is defined as any response to a drug which is noxious, unintended and which occur at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases, or for the modification of physiological function or state.[1] Adverse drug reactions (ADRs) are an important cause of morbidity, hospitalization, increased health expenditure and even death.[2] ADR reporting leads to an increased general vigilance and may influence the recommendations for drug use through regulatory authorities.[3] No drug is free from the adverse effects. Treatment is the part of the healthcare system, and drugs are given as a part of treatment. Safety of the patients should be taken care of by the health care professionals while prescribing a drug and therefore they should be aware of adverse effects of drugs. Clinically important ADRs are diverse but cutaneous drug reactions are most common among the various adverse reactions attributed to the drugs.[2] Cutaneous drug reactions are defined as any undesirable change in the structure or function of skin, its appendages or mucous membranes, encompassing all adverse events related to drug eruption regardless of etiology.[3] Of the various adverse reactions to drugs, cutaneous drug reactions account for 10-30% of all the reported ADRs.[4,5] Cutaneous drug reactions are also a contributory factor to approximately 3% of all disabling injuries during hospitalization.[6] Various medical colleges in India have been assigned the designation of ADR Monitoring Centers (AMCs) by Pharmacovigilance program of India (PvPI) under the supervision of CDSCO, which play a vital role in collection and follow-up of ADR reports. These hospital-based AMCs aim to identify and quantify the risks associated with the use of drugs. Thus, Pharmacovigilance plays a vital role in establishing the safety profile of marketed drugs.[7] Cutaneous drug reactions have a wide variety of presentation of which ranges from a transient maculopapular rash to severe Stevens-Johnson syndrome (SJS). Hence, there must be continuous efforts to look into this aspect of ADR's with an enhanced focus so that patient's quality of life should be least affected.

Materials & Methods

The present study was an observational and analytical study conducted over a period of 15 months from August 2015 to December 2016 at Andaman & Nicobar Islands Institute of Medical Sciences, Port Blair, designated as an ADR monitoring Centre, by PvPI, after obtaining the approval from institutional Ethics committee. In this study, a total of 336 suspected ADR forms filled from August 2015 to December 2016 were enrolled and forms with Cutaneous drug reactions were analyzed and assessed. A total of 240 (71.4%) ADR's were having cutaneous manifestations. Individual causality assessments were undertaken using the Naranjo's causality assessment scale which classifies drug reactions into definite, probable, possible and doubtful ADR.[8] The severity of the reaction was assessed using ADR Severity Assessment Scale (Modified Hartwig and Siegel) which classifies ADR into mild, moderate and severe.[9] Data was expressed in percentage using Microsoft Excel Software and accordingly, results were obtained.

Inclusion Criteria

1. Any Adverse drug reactions manifesting as Cutaneous symptoms in the patients.

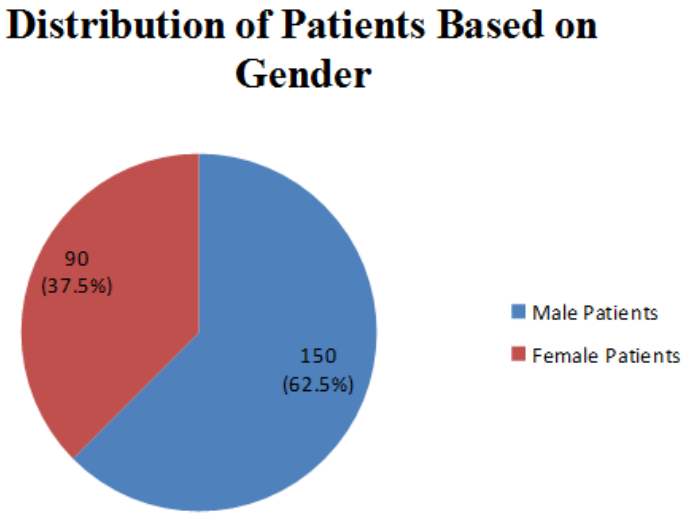
Exclusion Criteria

2. Incomplete ADR Forms or the forms in which causality was not established
3. When the detailed history of the event and medications was not available.
4. Pregnant & Lactating Females

Observations

In the present study, out of 240, 150 (62.5%) patients were male and 90 (37.5%) were female patients with a male: female ratio of 1.66:1. (Figure1)

Figure 1



Most cases in the present study were in the age group of 21-40 years as 116(48.4%) patients were in this age group followed by 41-60 years age group with 80(33.4%) patients, followed by <20 years age group with 27(11.2%) patients, and least affected patients were in the age group of > 60 years age group with 17 (7.0%) patients. (TABLE1)

Table 1: Distribution of Patients Based on Age Group

S.No	Age Group	No. of Patients	Percentage
1	<20 Years	27	11.2%
2	21-40 Years	116	48.4%
3	41-60 Years	80	33.4%
4	>60 Years	17	7.0%
TOTAL		**240**	**100%**

In this study, most common offending drugs were antimicrobial agents which caused CADR's in 136(56.6%) patients, followed by Nonsteroidal anti-inflammatory drugs (NSAIDs) causing adverse drug reactions with cutaneous manifestations in 78(32.5%) patients. Miscellaneous drugs causing ADR's in 26 (10.9%) patients and include drugs like Anti-epileptics in 5 (2.0%) patients, Oral contraceptive pills in 5 (2.0%) patients, Minoxidil 5% topical solution in 3 (1.25%) patients, Chloroquine in 3(1.25%) patients, Isotretinoin tablet in 2(0.9%) patients, Amlodipine in 2(0.9%) patients, corticosteroids in 2(0.9%) patients. Fixed drug combination causing cutaneous manifestations included Ciprofloxacin Tinidazole combination in 4(1.7%) patients. (Table 2)

Table 2: Distribution of Patients Based on Drugs Causing Cutaneous Adverse Drug Reactions

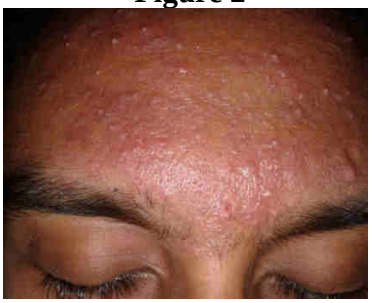
S.No	Drugs Causing CADR	No. of Patients	Percentage
1	**Antimicrobial Agents**	**136**	**56.6%**
	Metronidazole	48	20%
	Fluoroquinolones	32	13.3%
	Tetracyclines	26	10.8%
	Amoxicillin	22	9.2%
	Cotrimoxazole	08	3.3%
2	**NSAIDS**	**78**	**32.5%**
	Ibuprofen	36	15%
	Aspirin	27	11.2%
	Diclofenac	15	6.3%
3	Miscellaneous Drugs	**26**	**10.9%**
	i) Anti-epileptics	5	2.0%
	ii) Oral contraceptive pills	5	2.0%
	iii) Ciprofloxacin -Tinidazole	4	1.7%
	iii) Minoxidil 5% topical solution	3	1.25%
	iv) Chloroquine	3	1.25%
	v) Isotretinoin	2	0.9%
	vi) Amlodipine	2	0.9%
	vii) Corticosteroids	2	0.9%

In this study the most common Cutaneous ADR was skin rashes accounting for 130 (54.2%) patients in the form of Macules, Papules, Maculopapular rash, depigmented patches, followed by Urticaria in 56(23.5%) patients,), Itching & Pruritus in 39(16.3%) patients followed miscellaneous ones in 15(6%) of the patients including Photosensitivity, Bullous lesions, erythema multiforme, lichenoid eruption. (Table 3)

Table 3: Distribution of Patients Based on Types of Cutaneous Reaction

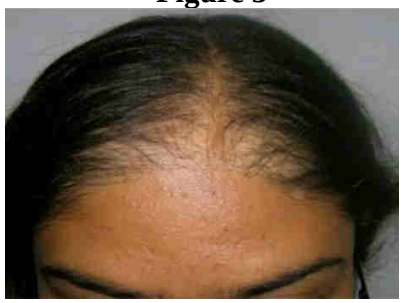
S.No	Type of Cutaneous Reaction	No. of patients	Percentage
1	**Skin Rashes**(Macular rash-59, Papularrash-22, Both Maculopapular rashes- 35, Depigmented Patches-14)	**130**	**54.2%**
2	**Urticaria**	**56**	**23.5%**
3	**Itching & Pruritus**	**39**	**16.3%**
4	**Miscellaneous**	**15**	**6.0%**
	Photosensitivity	04	1.6%
	Bullous Lesions	04	1.6%
	Erythema Multiforme	03	1.2%
	Lichenoid Eruptions	02	0.8%
	Acneiform Eruptions(FIG 2)	01	0.4%
	Alopecia (FIG 3)	01	0.4%

Figure 2



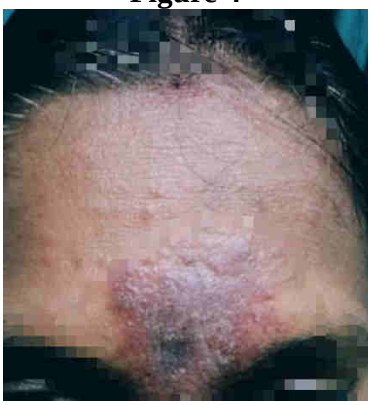
Acneiform Eruptions with use of Topical Minoxidil 5% solution in a Male Patient

Figure 3



Frontal Bald Patch in a Female Patient with use of Isotretinoin

Figure 4



Cutaneous Lesion with use of Topical Diclofenac Gel

Discussion

Adverse Drug Reaction most commonly manifests as Cutaneous symptoms & signs.[10] There is a wide range of Cutaneous ADR's which can be from mild maculopapular rashes to severe Toxic Epidermal Necrolysis by the use of different classes of drugs. Others can be pruritis, morbilliform rashes, erythema multiforme, exfoliative dermatitis and much more. Some severe CADRs may even be fatal and also result in serious morbidity.[11] Usually, these drug-induced skin eruptions are erythematous, morbilliform or maculopapular in nature.[12]

In the present study, a total of 240 CADRs were reported. The number may be less due to reasons like the exclusion of incomplete, and doubtful causality ADR forms. Most of the minor ones which do not require hospitalization have been excluded from the study, another reason might be Under-reporting of ADR's by Healthcare professionals and patients as well.

In the present study, there is slight Male preponderance as the male: female ratio was 1.66:1 which has been seen in some other studies.[13,14] In this study, most common offending Drug for CADR was Antimicrobials accounting for 136 (56.6%) patients. Similar results have been obtained

in other studies where antimicrobials were responsible for 56.9% and 55.88% of Cutaneous ADR's.[15,16]

In this study, most common form of CADR was skin rash in 56.6% of patients which included macular, followed by a maculopapular rash. Other studies also support this finding, as the maximum incidence of maculopapular rash was seen by antimicrobial use, followed by NSAIDs. This is also in concordance with the results of other studies.[17,18]

Conclusion

ADRs are preventable to some extent. ADRs are known to increase the burden of overall treatment cost and can be fatal which harms the doctor-patient relationship and patient's trust on his doctor. Newer molecules are added every year some of which are potential drugs, it is of utmost importance for healthcare professionals to understand the possible adverse reactions and training of the healthcare professionals will decrease the CADR's to some extent. Spontaneous reporting of ADR's should be strengthened and measure should be taken to promote the reporting of ADR's by clinicians as this step will be in patient's interest.

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Conflicts of Interest – None Declared

Abbreviations

ADR- Adverse Drug Reaction

AMC- Adverse Drug Reaction Monitoring Centre

ANIIMS – Andaman & Nicobar Islands Institute of Medical Sciences

CADR – Cutaneous Adverse Drug Reaction

PvPI – Pharmacovigilance Programme of India

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