ANALYSIS OF CUTANEOUS ADVERSE DRUG REACTIONS ON USING COMMONLY PRESCRIBED DRUGS AT A TERTIARY CARE HOSPITAL

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ABSTRACT

BACKGROUND

Drugs can cure, suppress or prevent a disease and are usually beneficial to humans. However, they can also produce undesirable or harmful effects, which are known as adverse drug reactions (ADR). Understanding the nature of ACDRs may help narrow down the search for the offending agent. The need for this study is for early diagnosis, to reduce the morbidity and mortality due to ACDR and to ensure safety of the patients.

MATERIALS AND METHODS

The present study was carried out at Bhaskar general hospital under ICMR project, Department of Dermatology where in 27 patients of ADR were enrolled to establish the aetiologic agent for a particular type of reaction, attention was paid to the drug history, temporal correlation with the drug, duration of rash, approximate incubation period, morphology of the eruption, associated mucosal or systemic involvement, improvement of lesion on withdrawal of drug and recurrence of lesion on rechallenge.

RESULTS

This study showed that the incidence of ACDRs were more in males 55.5% than in females 44.5%. Most of the Cutaneous ADRs were probable in type under causality assessment and moderate under severity assessment. The presentation of cutaneous ADR was in the form of rash, urticaria, fixed drug eruption. Drugs causing these included NSAIDS, Antiepileptic's and antimicrobials.

CONCLUSION

Effective strategy to prevent the occurrence of ADRs is always preferred. Some of the measures that may reduce the occurrence of cutaneous ADRs are listed below. Avoid polypharmacy. Prescribe drugs, which have been known to cause cutaneous ADRs, only if extremely necessary. Obtain history of skin reactions in the past. Educate the patients regarding common early symptoms of drug reactions (e.g. erythematous rash, oedema, urticaria, mucosal erosions, itching, burning of skin etc.) especially during start of a therapy.

KEYWORDS

Antimicrobials, Antipsychotic, Antiepileptic, Dermatology, Etiologic.

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BACKGROUND

Drugs can cure, suppress or prevent a disease and are usually beneficial to humans. However, they can also produce undesirable or harmful effects, which are known as adverse drug reactions (ADR).[1] It has been proved long ago that drug themselves can prove fatal; as the saying rightly goes "Drugs are Double Edged Weapons".

WHO defines an ADR as a "noxious, unintended or undesired effect of a drug, which occurs at dose used in humans for prophylaxis, diagnosis, therapy or modification of physiological functions".[2] Adverse drug reactions account for significant morbidity and mortality in health sector.

Skin is one of the major target organs for ADRs. Cutaneous adverse drug reactions (CADR) manifest as skin rashes and or eruptions. A CADRs is any undesirable change in the structure or function of the skin, its appendages or mucus membranes and it encompasses all adverse events related to drug eruption, regardless of aetiology.[3] The incidence of Cutaneous ADRs among patients in developed countries ranges from 1-3% whereas in developing countries such as India it is 2-5%.[4]

Complications of drug therapy are the most common type of adverse events in hospitalized patients. Many of the commonly used drugs have reaction rates more than one percent.[5] There is a wide spectrum of Adverse Cutaneous drug reactions (ACDR) ranging from transient maculopapular rash to fatal toxic epidermal necrolysis(TEN).[6] It was estimated 5-9% of all hospital cost are related to ADRs.[7]

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The wide and indiscriminate use of drugs has increased the incidence and the modes of presentations of cutaneous drug reactions.[8] Understanding the nature of ACDRs may help narrow down the search for the offending agent. The need for this study is for early diagnosis, to reduce the morbidity and mortality due to ACDR and to ensure safety of the patients.

Aims and Objectives

This study aimed to analyse clinicopharmacological characteristics and analysis of Cutaneous ADRs reported at tertiary care hospital.

The objectives of analysis of cutaneous adverse drug reactions at a tertiary care hospital -

1. To study and evaluate incidence of ACDR at a tertiary care hospital to assess the impact of active surveillance on ADR reporting.
2. To improve the definition of various clinical patterns of patients with drug induced cutaneous side effects with systemic symptoms and their possible relationships with triggering medications.
3. To help in the identification of causal drug when the patients is taking several drugs

MATERIALS AND METHODS

The present study was carried out at Bhaskar General Hospital, Department of pharmacology, Adverse drug reaction monitoring Centre in association with department of dermatology where in 27 ACDR patients were enrolled**.** It was a prospective study conducted after the approval of the Institutional Ethics Committee and written Informed Consent Form was obtained from the patient during the study.

Reporting's were taken from Department of Dermatology. Patients were screened and recruited if they presented with visible skin lesion and suspected to be drug related. The importance and need for the study was explained to each patient. After obtaining the written informed consent the data was collected from patients, who were diagnosed with ACDR by the dermatologist. Reporting was done during the study period on daily basis according to 'CDSCO ADR Reporting Form'.

In every case a detailed history was taken, and thorough clinical examination was carried out. To establish the etiologic agent for a particular type of reaction, attention was paid to the drug history, temporal correlation with the drug, duration of rash, approximate incubation period, morphology of the eruption, associated mucosal or systemic involvement, improvement of lesion on withdrawal of drug and recurrence of lesion on rechallenge.

Inclusion Criteria

Subjects who are diagnosed with cutaneous ADRs by Department of Dermatology.

Exclusion Criteria

Subjects who complain of only symptoms without visible skin lesions, those who cannot recall the name of the suspect and medicines consumed, and those whose lesions turned out to be disease related on closer examination. A few subjects who reported to have taken indigenous (ayurvedic and homeopathic) medicines were excluded.

If more than one drug were thought to be responsible, the most likely offending agent was noted, and the impression was confirmed by subsidence of the rash on withdrawing drug.

Causality assessment was done by WHO-UMC Causality Assessment Scale which gives an overview of causality of CADR whether it is of certain, probable or possible type. Severity of CADRs was assessed by modified Hartwig and Siegel Scale. This scale of severity assessment classifies CADRs as mild, moderate or severe in nature.

All the proforma were manually checked and edited for completeness and consistency and were then coded for computer entry. After compilation of collected data, percentages obtained were tabulated.

RESULTS

A total of 27 cases of adverse drug reactions were identified during our study and these cases were analysed further.

Gender Distribution

ACDRs were common in males 15 cases (55.5%) than in females 12 cases (44.5%). The male: female ratio 1.25:1. Our study shows more male preponderance. (Fig. 1)

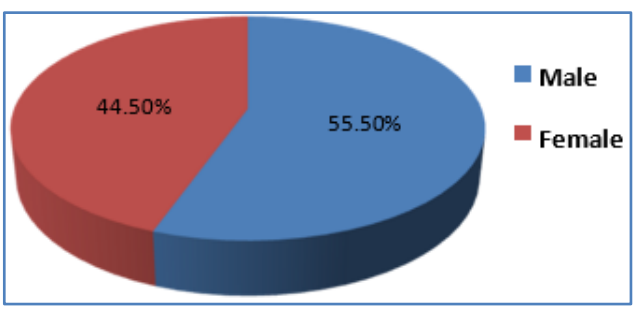

Figure 1. Gender Distribution of Subjects

Age Distribution

Patients of age group of 11 yrs. to 65 yrs. were included in study with a mean age of 38 yrs. Patients with age group of 11-20 yrs. were 3 (11.1%), with age group of 21-30 yrs. - 11(40.7%), with the age group of 31-40 yrs. - 6(22.2%), with the age group of 41-50 yrs. – 2 (7.4%), with age group of 51-60 yrs. – 3 (11.1%), with the age group of 61-70 yrs.-2 (7.4%)(Table 1).The highest percentage of ADRs were more in 21-30 yrs. age group followed by 31-40 yrs. of age group. (Fig. 2)

Age (Yrs.)	No. of Cases	Percentage
11-20 yrs.	3	11.1%
21-30 yrs.	11	40.7%
31-40 yrs.	6	22.2%
41-50 yrs.	2	7.4%
51-60 yrs.	3	11.1%
61-70 yrs.	2	7.4%

Table 1. Age Distribution

Clinical Type	Frequency	Percentage
Rash	11	40.7%
Urticaria	4	14.8%
Fixed Drug Eruption	4	14.8%
Maculopapular rash	3	11.1%
Urticaria angioedema	2	7.4%
Bullous Eruption	1	3.7%
Erythematous Pustules	1	3.7%
Ulceration on Lips	1	3.7%

Table 2. Clinical Pattern

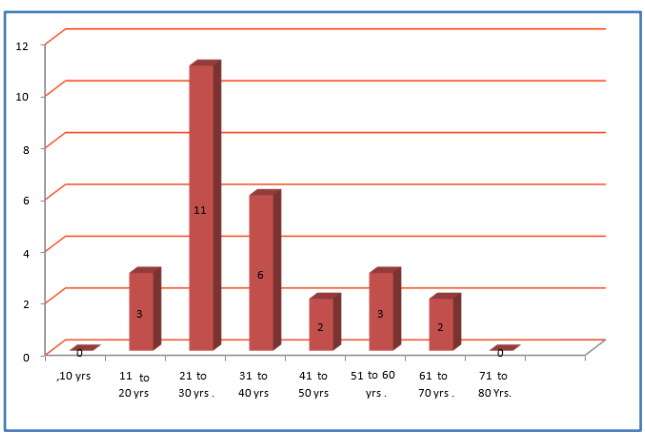

Figure 2. Distribution of Patients

Clinical Type of CADRs

The highest reaction pattern observed was rash (40.7%) followed by urticarial and fixed drug eruption (14.8% each) and then by maculopapular rash (11.1%). Urticarial angioedema (7.4%), bullous eruption, erythematous pustules, ulceration on lips were less common (3.7% each) (table 2).

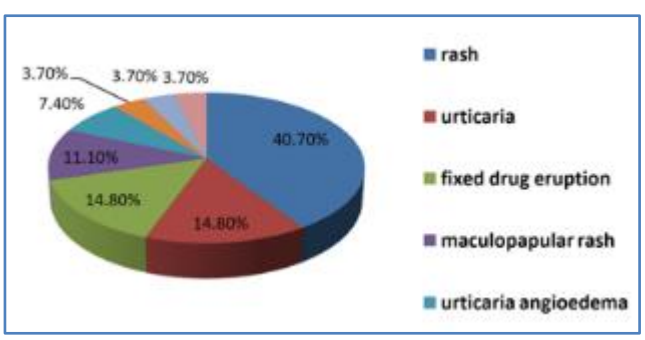

Figure 3. Clinical Adverse Drug Reaction System Pattern

Drugs Involved

The major drug group responsible were NSAIDs, which accounted for 10 cases (37%) of CADRs, followed by antimicrobials, antiepileptic's (table 3)

Drugs involved	Frequency	Percentage
NSAIDs	10	37%
Antimicrobials	6	22.2%
Antiepileptic	4	14.8%
Vaccine	1	3.7%
Antipsychotic	1	3.7%
Antacid	1	3.7%
Hormone	1	3.7%
Multivitamin	1	3.7%
Inj. Iron-sucrose	1	3.7%
Antileprosy	1	3.7%

Table 3. Drugs Involved

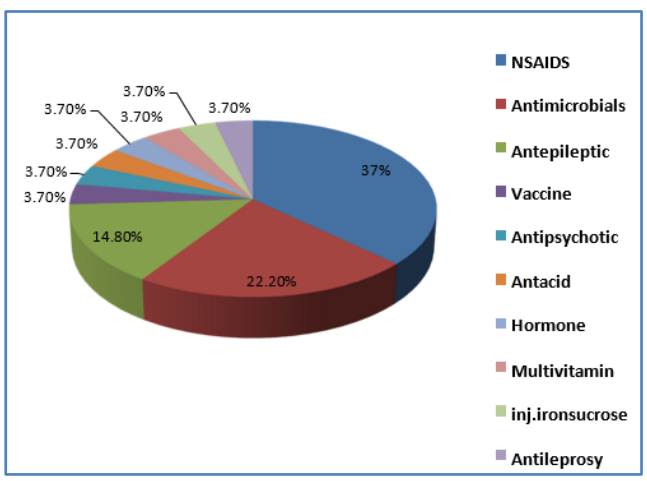

Figure 4. Drug Use Pattern

Clinical type and Drugs Involved

A single type of CADR was caused by different group of drugs in different individuals.

Similarly, a single drug was responsible for different types of reactions in different individuals. In this way heterogeneity was observed (table 4)

Among the 11 cases of Rash, 5 cases were due to NSAIDS (45.4%), 2 cases were due to antimicrobials (18.1%), 2 cases were due to antiepileptic (18.1%), 1 case was due to antipsychotic (9%), and 1 case was due to antacid (9%). Among 4 cases of Urticarial, 1 case was due to NSAIDS (25%), 1 case was due to hormone (25%), and 1 case was due to iron sucrose inj. (25%), 1 case was due to tetanus toxoid (25%). Among 4 cases of Fixed drug eruption, 3 cases were due to NSAIDS (75%), 1 case was due to antimicrobial (25%). Among 3 cases of Maculopapular Rash, 1 case was due to antimicrobial (33.3%), 1 case was due to antiepileptic (33.3%), 1 case was due to multivitamin (33.3%). Among 2 cases of urticarial angioedema, 1 cases was caused by NSAIDS (50%), 1 case was caused by antimicrobial (50%). 1 case of Bullous eruption was caused by NSAIDS. 1 case of Ulceration on lips was caused by antiepileptic. 1 case of erythematous pustule was caused by antileprosy drug.

Clinical Type of ACDR	Drugs Implicated	No. of Cases
Rash[9]	Paracetamol	5
	Phenytoin	2
	Metronidazole	1
	Risperidone	1
	Omeprazole(inj.)	1
	Ofloxacin	1
Urticaria[4]	Inj. Iron sucrose	1
	Inj. tetanus toxoid	1
	Paracetamol	1
	Hormone (Thyronorm)	1
Fixed Drug Eruption[4]	Paracetamol	2
	Diclofenac	1
	Amoxicillin	1
Maculopapular Rash[3]	Amoxicillin	1
	Multivitamin	1
	Carbamazepine	1
Urticaria Angioedema[2]	Diclofenac	1
	Ciprofloxacin	1
Bullous Eruption[1]	Paracetamol	1
Ulceration on Lips[1]	Phenytoin	1
Erythematous Pustules[1]	Thalidomide	1

Table 4. Clinical Type with Drugs Involved

Among NSAIDS the most offending drug was paracetamol (80%), followed by Diclofenac (20%)

NSAIDS	No. of Cases	Percentage
Tylenol	8	80%
Diclofenac	2	20%

Table 5

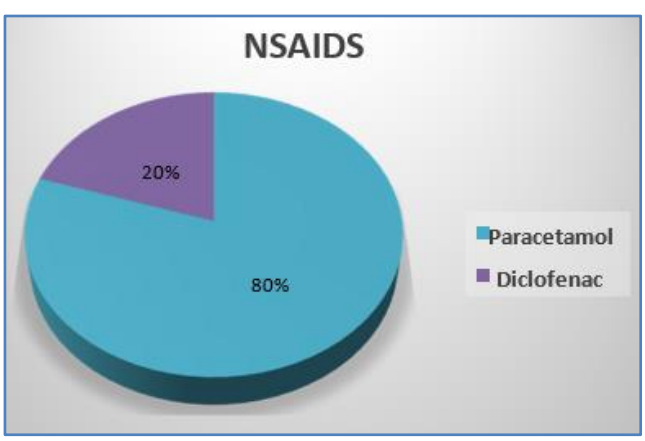

Figure 5. NSAIDS

Among antimicrobials the most offending drugs were amoxicillin (33.3%), ofloxacin (33.3%), followed by ciprofloxacin (16.6%) and metronidazole (16.6%). (Table 6).

Antimicrobials	No. of Cases	Percentage
Amoxicillin	2	33.3%
Ofloxacin	2	33.3%
Ciprofloxacin	1	16.6%
Metronidazole	1	16.6%

Table 6. Antimicrobials

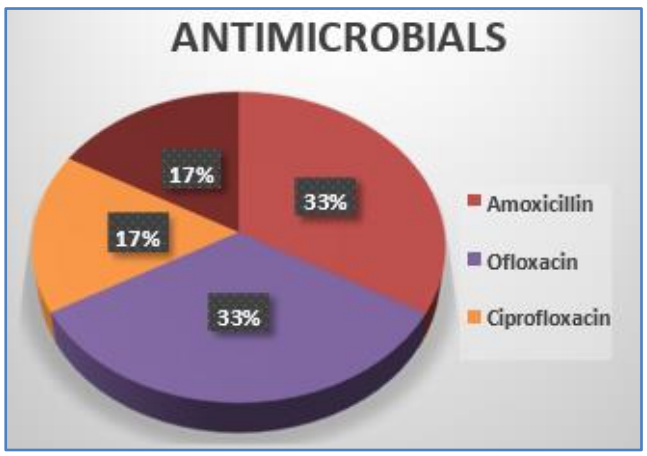

Figure 6. Antimicrobials

Causality Assessment

Causality assessment was done using WHO-UMC Causality Assessment Scale which shows highest no of cases come under the scale of probability 25 cases (92.5%), certain 1 case (3.7%), possible 1 case (3.7%)(table 7)

Assessment	Type	No. of Cases	Percentage
Causality	Certain	1	3.7%
	Probable	25	92.5%
	Possible	1	3.7%

Table 7. Causality Assessment

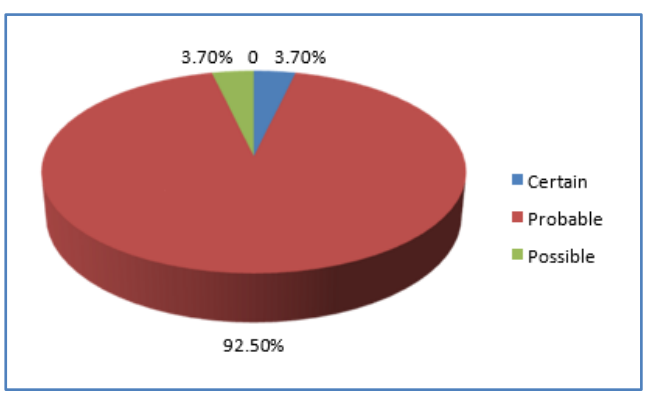

Figure 7. Causality Assessment

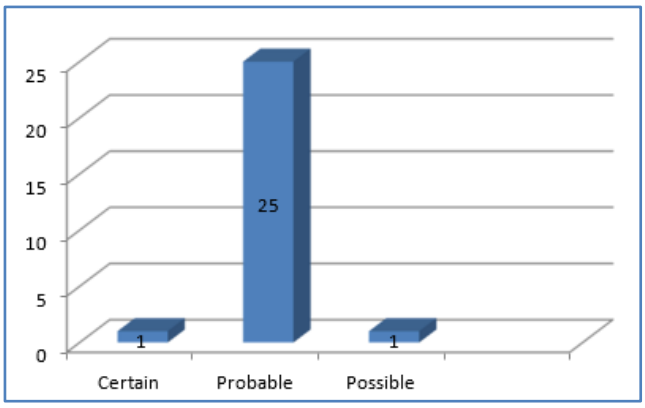

Figure 8. Causality Assessment

Severity Assessment

Severity assessment was done using the Hartwig severity scale. Maximum no of cases fall under moderate (55.5%), followed by mild (37%) and severe (7.4%)(table 7)

Assessment	Category	No. of ADRs	Percentage
Severity	Mild	10	37%
	Moderate	15	55.5%
	Severe	2	7.4%

Table 7. Severity Assessment

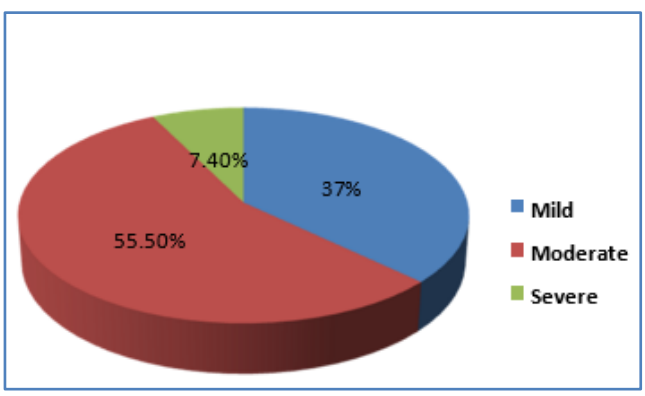

Figure 9. Severity Assessment

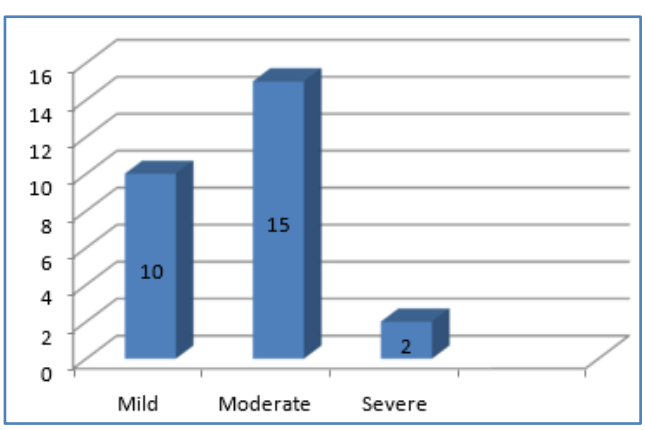

Figure 10. Severity Assessment

DISCUSSION

This present study showed that the incidence of ACDRs were more in males 55.5% than in females 44.5%, with the male: female ratio 1.25:1. Our study showed male preponderance which was similar to the other studies carried out by Priya Prathap et al., Sharma VK et al., Shah SP et al.[10,11,12] Moreover, others' studies like Chatterjee S et al., Sudarshan et al., Nandha R et al. showed female preponderance.

In this study, the frequency of CADRs were maximum in patients with age group of 21-30 yrs. (40.7%) followed by 31-40 yrs. (22.2%),11-20 yrs. (11.1%),51-60 yrs. (11.1%).Thus this study has documented a higher prevalence of drug reactions in the age group of 21-30 yrs. which was similar to the studies carried out by Reena Verma et al.[13] Whereas studies conducted by Sharma VK et al., Padukadan D et al.[11,14] showed the higher prevalence of CADRs in the age group of 20-40 yrs. and studies done by Leap et al., Hafner JW JR. et al. reported that the most common age group affected cutaneous reactions was above 40 yrs.[15,16]

In the present study, the most suspected ADR were rashes in 11 cases (40.7%) followed by urticaria is in 4 cases (14.8%), fixed drug eruption is in 4 cases (14.8%), maculopapular rashes is in 3 cases (11.1%), urticarial angioedema is in 2 cases (7.4%) followed by bullous eruption, ulceration on lips, erythematous pustules are in 1 case each (3.7%). Highly occurring ADR in present study was rashes, which is similar to results obtained in other studies like Dimple Gohel et al., Ghosh S et al.[17,18] However some other studies from India reported Fixed Drug Eruption to be the most common type of ACDR Pudukadan D et al.[14]

In our study, cutaneous adverse drug reactions were most commonly observed with NSAIDS (37%), followed by antimicrobials (22.2%) and antiepileptics (14.8%). Few studies have reported that NSAIDS were the main group of drugs to cause different types of skin reactions, thus supporting our study Bai CK et al., Sharma VK et al.,[19,11] Other studies show that the most offending drugs were antimicrobials Chatterjee et al.[4]

Among the 11 cases of Rash, 5 cases were due to NSAIDS (45.4%), 2 cases were due to antimicrobials (18.1%), 2 cases were due to antiepileptics(18.1%), 1 case was due to antipsychotic (9%), and 1 case was due to antacid (9%).Among 4 cases of Urticaria, 1 case was due to NSAIDS (25%), 1 case was due to hormone (25%), and 1 case was due to iron sucrose inj. (25%), 1 case was due to tetanus toxoid (25%).Among 4 cases of Fixed drug eruption, 3 cases were due to NSAIDS (75%), 1 case was due to antimicrobial (25%). Among 3 cases of Maculopapular Rash, 1 case was due to antimicrobial (33.3%),1 case was due to antiepileptic (33.3%),1 case was due to multivitamin (33.3%). Among 2 cases of Urticaria angioedema, 1 case was caused by NSAIDS (50%),1 case was caused by antimicrobial (50%). 1 case of Bullous eruption was caused by NSAIDS. 1 case of Ulceration on lips was caused by antiepileptic. 1 case of erythematous pustule was caused by antileprosy drug.

Among NSAIDS the most offending drug I was paracetamol (80%), followed by diclofenac (20%). In the present study, paracetamol was highly suspected drug. The same finding also found in study conducted by Ghosh S et

al, among antimicrobials the most offending drugs are amoxicillin (33.3%), ofloxacin (33.3%), followed by ciprofloxacin (16.6%) and metronidazole (16.6%).

In the present study, causality assessment was done by WHO-UMC causality assessment scale. Most of the ADRs were designated as probable (92.5%), followed by certain (3.7%), possible (3.7%). The causality assessment of reported ADRs by WHO-UMC scale revealed that the majority of the reported ADRs were probable, which is in accordance with the Chatterjee S et al., Acharya T et al.[4,20]

In the present study, severity assessment was done by modified Hartwig and Siegel's scale. Most of the cases designated as moderate (55.5%), followed by mild (37%)and severe (7.4%). A majority of ADRs were categorized as moderate and similar findings are reported in the other studies Jai Krishna et al., Acharya T et al., Shah SP et al., Ghosh S et al.[21,20,12,18]

CONCLUSION

Our present study showed male preponderance, with more no. of cases in the age group of 21-30 yrs. The most common reaction was rash. The most common offending drugs were NSAIDS followed by antimicrobials. Most of the cases fall under the category of causality type of probable and most of the cases are of moderate under severity assessment.

Studies are needed on cutaneous ADRs to promote drug safety and a better health care.

To establish measures that may reduce the occurrence of cutaneous ADRs are listed below.

Avoid polypharmacy. Prescribe drugs, which have been known to cause cutaneous ADRs, only if extremely necessary. Obtain history of skin reactions in the past. Educate the patients regarding common early symptoms of drug reactions (e.g. erythematous rash, oedema, urticaria, mucosal erosions, itching, burning of skin etc.) especially during start of a therapy.

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