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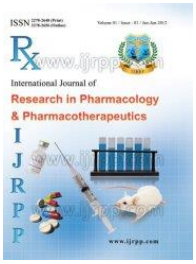

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A surveillance study of adverse drug reactions in a tertiary care teaching hospital in India

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ABSTRACT

Introduction

Medicines are the most common medical interventions, primarily used to relieve sufferings. But medicines themselves can prove fatal so it is rightly said that medicines are double edged weapons. Adverse reaction monitoring and reporting are very important in identifying the adverse reaction trends and ensuring drug safely.

Aims and objectives

To monitor and analyze the suspected adverse drug reactions reported at tertiary care teaching hospital, to characterize nature and predictability of ADRs and identify most common medicines causing ADRs

Material and methods

A retrospective observational study was conducted between January 2014 to June 2016. Suspected ADRs submitted to National pharmacovigilance center. Following parameters were studied, Age group-paediatric, adult, geriatric, Gender, Groupwise, systemwise classification of ADRs, Most common medicines causing ADRs, Causalty assessment of ADRs by using WHO-UMC causality assessment scale, Assessement of preventability criteria by Schumock and Thornton scale.

Results

During the study period a total 1099 ADRs reported were analyzed. Male experienced a significantly higher percentage of ADRs (55.86 %).Highest percentage of ADRs was found in adult age group 31-40 yrs. All ADRs were probable. There was no any certain ADR we could find out. Maximum number of ADRs were in the age group 31-40 years i.e 377(34.30%).Skin was the commonest organ showing highest no. of ADRs 41.87.Internal medicine was the commonest department 28.33% ADRs. Out of total antimicrobial agents causing ADRs, maximum number of ADRs were due to amoxicillin + clavulanic acid. Common symptoms due to ADRs of medicines were itching 174 (15.83%), skin rash 108 (9.82%).

Conclusion

There is urgent need of promotion of spontaneous reporting of ADRs. More awareness needs to be created to address these issues.

Keywords- *Adverse drug reactions, Pharmacovigilance, Causality assessment scale, Thornton and Schumock scale.*

INTRODUCTION

According to WHO, adverse drug reaction (ADR) is defined as "any response which is noxious and unintended, occurs at dosages normally used in humans for prophylaxis, diagnosis or therapy for disease or for the modification of physiological function" [1]. This includes allergies, idiosyncrasies, pharmacological and toxicological mechanisms and interactions between medicines and excludes adverse reactions due to drug overdose (poisoning) , drug abuse and therapeutic errors. Adverse drug reactions may arise as a result of immunological or non immunological mechanisms [2]. According to Rawlins and Thompsons classification, ADRs are defined as type A, type B, type C, type D, type E, type F, type G. Type A reaction is an over enhancement of the normal pharmacology of the medication, is predictable and related to dosage. Type B reaction is unrelated to normal pharmacology and is unpredictable. Type C reaction includes those associated with cumulative exposure to the drug and persists for longer period of time. Type D reactions consists of delayed reaction of carcinogenesis and teratogenesis. Type E includes End of treatment effects; Type F is Failure of therapy while Type G consists of Genetic reaction. [3, 4]

Adverse drug reactions are important clinical problems and a constant concern of public health system. The incidence of adverse drug reactions in Indian population ranging between 1.8%- 25.1% with 8% resulting in hospitalization [5]. Commonly prescribed medications like antimicrobial agents, analgesics and anti-inflammatory medicines, hypoglycemic medicines, diuretics, anticoagulants are responsible for 60-70% of ADRs [6].

To reduce these large percentage of ADRs and to minimize physical, mental and economical burden over patients because of ADRs, the establishment and assessment of causal relationship with drug and to initiate measures to treat the present ADRs has to be done earliest.

In India, large number of pharmaceutical preparations- branded and generic are available and there is a common practice of over the counter different systems of health care traditions and lack of awareness on rational drug use are expected to produce a high level of drug-induced illness [7]. There is a paucity of ADR data in Indian context so here the role of pharmacovigilance comes. Pharmacovigilance is a science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine related problem [8]. So it is worthwhile to detect, assess and characterize the pattern of ADRs in outpatient departments of tertiary care hospitals.

MATERIAL AND METHODS

A longitudinal, retrospective, observational, study was conducted in patients attending outpatient department from January 2014 to march 2016. All suspected ADRs of patients in the hospital were referred by health care professionals and the diagnosis was made by concern doctors. The data was recorded as per spontaneous ADR reporting system [9]. The recorded data was filled in the ADR form obtained from pharmacovigilance program of India (2011) and Central Drug Standard Control Organization (CDSCO) website.

Patient's gender, type of ADR, history of diseases, starting date of ADR, suspected drug causing ADR, primary source of ADR, concomitant medicines given, reporting person's initials (doctor, nurse, resident, physician, pharmacist) etc. were noted. The data was analyzed and causality assessment was done according to WHO – UMC causality assessment scale [10], severity assessment was done by Hartwig-Siegal severity scale and preventability assessment was done by modified Thornton and Schumock scale. Respective physician of the institution helped in the process and data was analyzed by using simple proportions method.

RESULTS

During the study period a total 1099 ADRs reported were analyzed.

Fig. 1- Gender-wise distribution of ADRs

Male experienced a significantly higher percentage of ADRs (55.86 %) than females (44.13 %). Male to female ratio according to occurrence of ADRs was 1.26.

Fig. 2- Age-wise distribution of ADRs

Highest percentage of ADRs was found in adult age group 31-40 yrs i.e 377 (34.30%), more than 15 years of age (99%) and only 1% ADRs in age group less than 15 years. According to WHO-UMC causality assessment scale, all ADRs were probable.

There was no any certain ADR that could be found out.

Fig. 3-System-wise distribution of ADRs among OPD patients

Skin was the commonest organ showing highest no. of ADR 41.87%, second highest is Gastrointestinal tract system 34.31%, Central nervous system ADRs were 13.55%, other miscellaneous ADRs were 12.59 including respiratory, cardiovascular system, renal, haematological and musculoskeletal system.

Fig. 4-Department-wise frequency of ADRs among study patients

Internal medicine was the commonest department 28.33% ADRs, second commonest department was ART 20.05% % and rest of the department were skin 19.96%, TB chest 10.02%, Psychiatry 7.35%

Fig. 5 -Common group of medicines causing ADRs

Drug-wise distribution of ADRs was antimicrobials 22.24%, analgesic 19.91%, ART 12.92%, anti-TB 9.74%, antipsychotic medicines 8.05%, antidiabetic medicines 7.83%, antiepileptic medicines 7.20%, antihypertensive medicines 5.93%, calcium 4.46% and folic acid 4.23%.

Fig. 6 -Antimicrobials causing ADR

In the present study, out of total antimicrobial agents causing ADRs (195), maximum number of ADRs were due to amoxicillin+clavulanic acid i.e 48 (24.61%), followed by amoxicillin 44 (22.56%), ciprofloxacin 26 (13.33%), cotrimoxazole 21 (10.76%).

Fig. 7- Most common medicines causing ADRs

Most common medicines causing ADRs were efavirenz 85, diclofenac sodium 61, amoxicillin+clavulanic acid 59 and rifampicin 44.

Table 1-Symptom-wise classification of ADRs

In this study, common symptoms due to ADRs of medicines were itching 174 (15.83%), skin rash 108 (9.82%), gastritis 104 (9.46 %), headache 72 (6.55%) and vomiting 68 (6.18%).

Fig. 8- Hartwig-Siegal severity scale

72.70% were mild reactions, 26.93% were moderate reactions and 0.36% were severe ones. There were three serious ADRs, two Stevens Johnson syndrome due to Nevirapine and Carbamazepine and third anaphylactic reaction due to injection Ceftriaxone.

Table 2- Modified Thornton and Schumock preventability scale

51.95% reactions were not preventable whereas 40.85% reactions were possibly preventable.

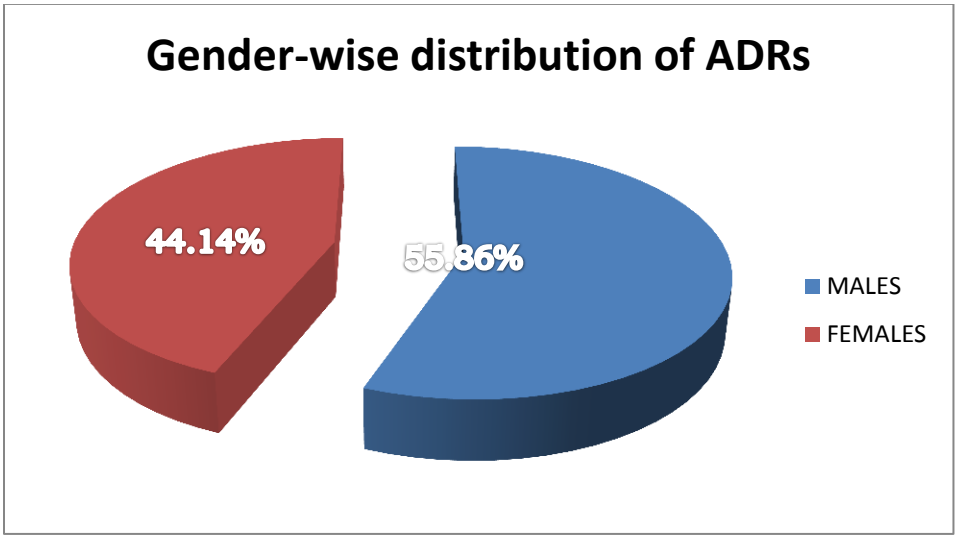

Fig. 1- Gender-wise distribution of ADRs

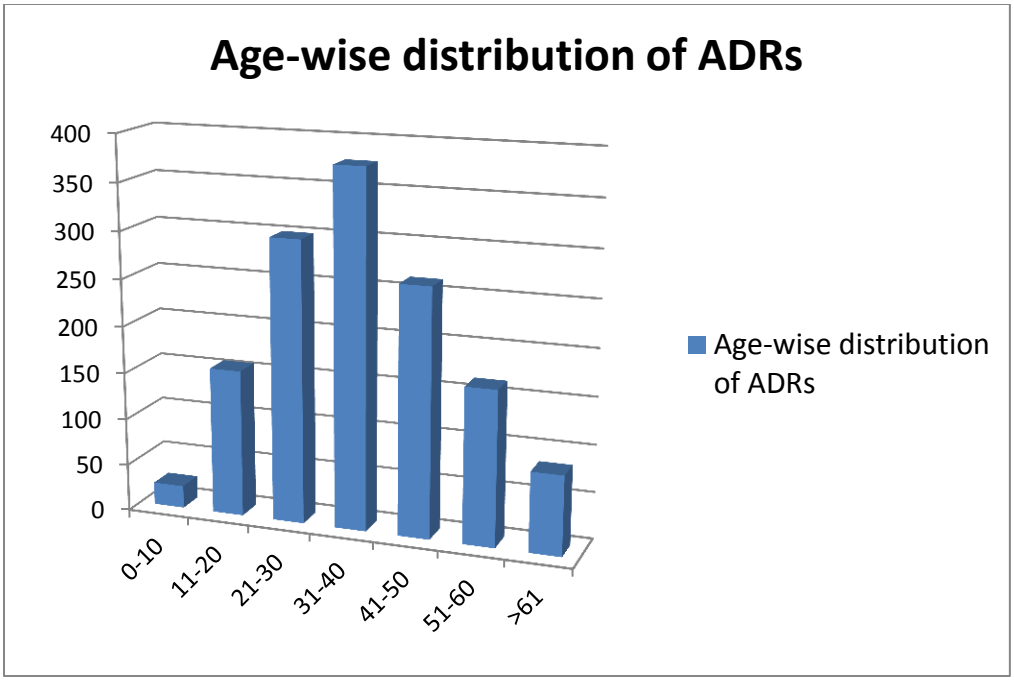

Fig. 2-Age-wise distribution of ADRs

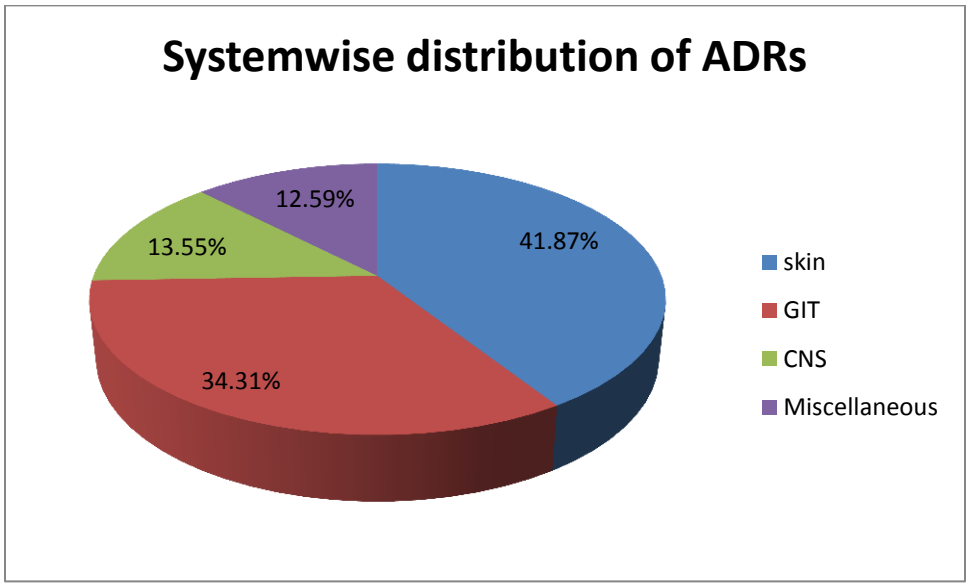

Fig. 3-System-wise distribution of ADRs

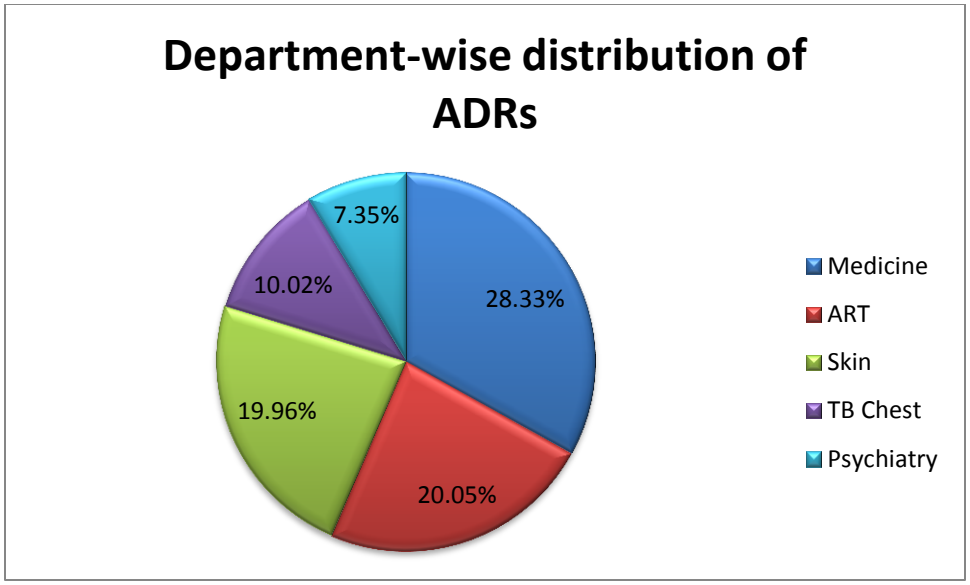

Fig. 4-Department-wise frequency of ADRs

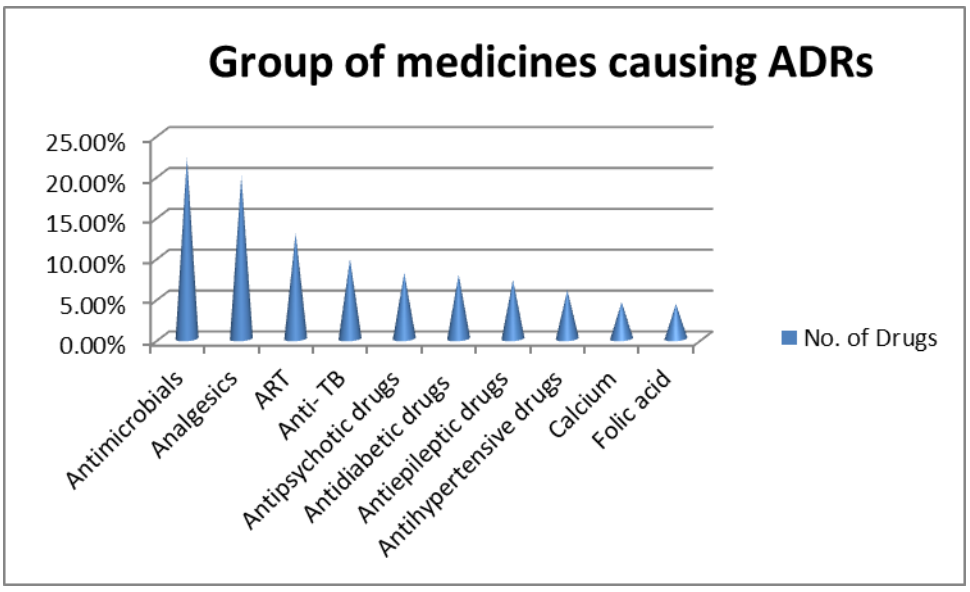

Fig. 5 -Common group of medicines causing ADRs

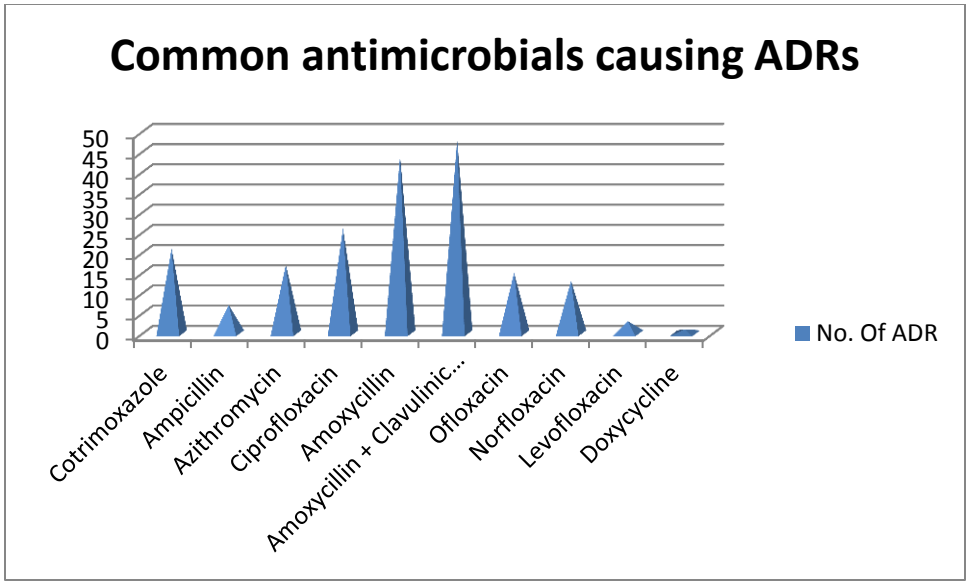

Fig. 6 –Common antimicrobials causing ADRs

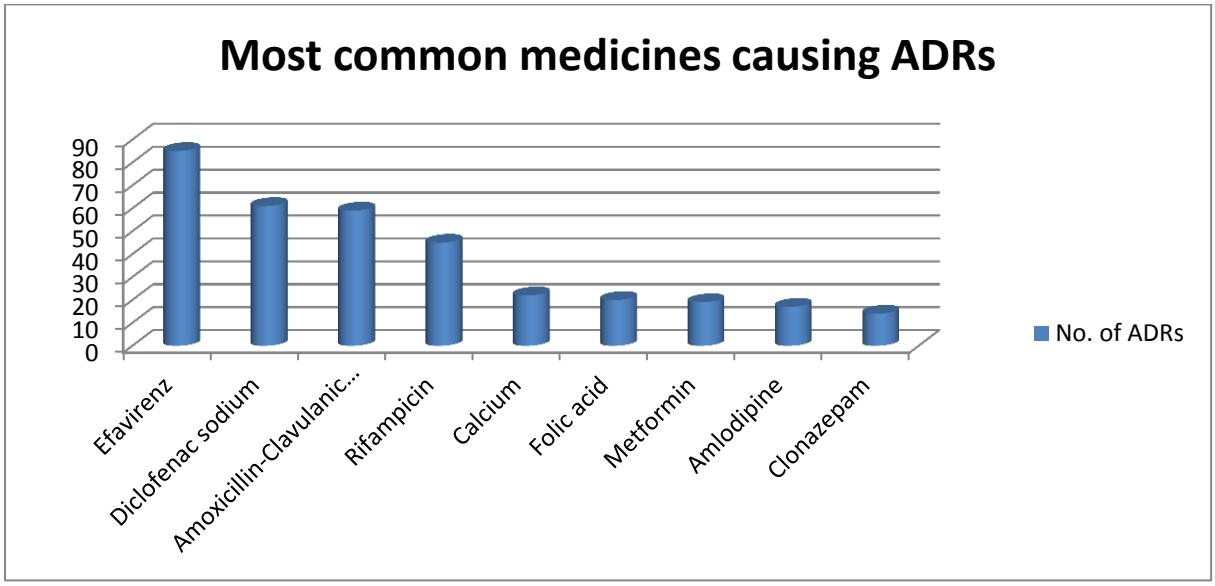

Fig. 7- Most common medicines causing ADRs

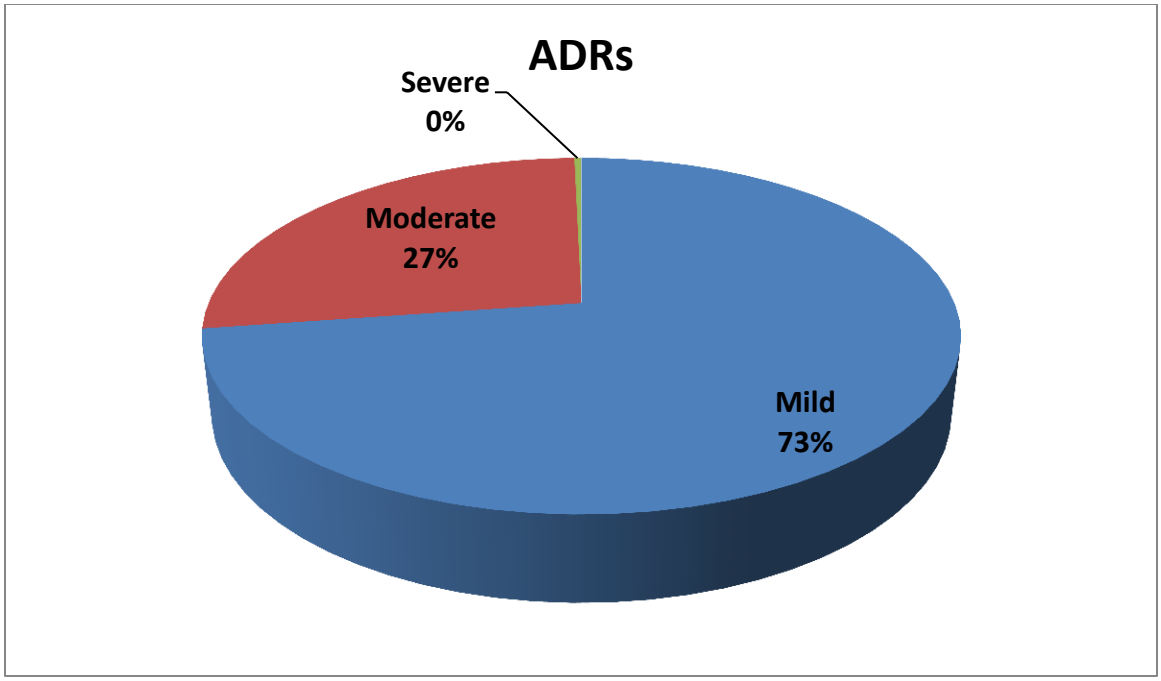

Fig. 8- Hartwig-Siegel severity assessment scale

Table 1-Symptom-wise classification of ADRs

Sr. no.	Symptom	No. of ADRs	Percentage of ADRs (%)
1.	Itching	174	15.83
2.	Skin rash	108	9.82
3.	Gastritis	104	9.46
4.	Headache	72	6.55
5.	Vomiting	68	6.18
6.	Nausea	43	3.91
7.	Anemia	43	3.91
8.	Constipation	43	3.91
9.	Mouth ulceration	41	3.73
10.	Diarrhea	33	3
11.	Drug eruption	33	3
12.	Disorientation	32	2.91
13.	Joint pain	24	2.18
14.	Acne	21	1.91
15.	Gynaecomastia	16	1.45
16.	Pain in abdomen	16	1.45
17.	Metallic taste	15	1.36
18.	Dry mouth	12	1.09
19.	Angioedema	8	0.72
20.	Giddiness	8	0.72
21.	Weight gain	2	0.18
22.	Anaphylactic shock	2	0.18
23.	Steven Johnson syndrome	2	0.18

Table 2- Modified Thornton and Schumock preventability scale

Age-group	Definitely preventable (%)	Possibly preventable (%)	Not

			Preventable (%)
Paediatric (uptil 12years)	0	10 (0.9)	18 (1.63)
Adult (13-60 years)	76 (6.91)	399 (36.3)	498 (45.31)
Geriatric (>60years)	3 (0.27)	40 (3.63)	55 (5)
Gender			
Male	50 (4.54)	261 (23.74)	158 (14.37)
Female	29 (2.63)	188 (17.1)	413 (37.57)

DISCUSSION

In the present study, total of 1099 ADRs were documented from a tertiary teaching care hospital of Central India. In this study, males experienced a significantly higher percentage of ADRs than females, a finding consistent to Shamna et al [11]. Most of the patients in our study were in the age group 31-40 years whereas Harsha et al study most of the patients were in 41-60 yrs [5] Distribution of ADRs according to WHO-UMC causality assessment scale [10] showed all ADRs were probable and none as a certain. Maximum ADRs were due to antimicrobial agents (AMAs) a finding consistent with other studies [12]. This shows the importance of physician's awareness to AMAs related ADRs in daily life. Since the ADR manifestation may be similar with the disease course and increase the unnecessary investigations and results in undue delay to proper and rational treatment.

Among the various systems affected by ADRs, skin is the most common system showing 41.87% ADR cases as it is the biggest organ in the body and GIT is the next system to affect in 34.31% ADR cases as majority of medicines are given via oral route and CNS in 13.55% of ADR cases as few medicines cross blood brain barrier. This finding is similar to Indian studies [11, 13]

Among the various departments reporting ADRs medicine is the most common department (28.33% ADRs) [11]; next departments to report ADRs were ART (20.05%), Skin (19.96%) and TB chest (10.02%). All these department are allied to medicine and the treatment line is based on the medications only so these departments report maximum number of ADRs than surgical departments where surgery is the main treatment. Departments like ART, skin and TB includes chronic infectious conditions which require use of combination of medicines for prolonged duration. Increase in number of drugs per prescription increases chances of drug interaction and leads to causation of adverse drug reaction increasing the morbidity and mortality and cost of drug treatment. The attributable financial burden of drug-related morbidity and mortality is around Rs. 690 (US $15) per adverse drug reaction [14]. In this study, most common group of medicines causing ADRs were AMAs, analgesics, ARTs, anti-tuberculosis, anti-psychotic, anti-diabetics, anti-epileptic and anti-hypertensives. Amoxicillin-clavulanic acid (45%) was most common antimicrobial used followed by amoxicillin (42%). Majority of patients treated in hospitals received at least one antibiotic and a significant proportion of them either receive two or more which leads to increased chances of ADR's in patients[15].According to modified Hartwig and Siegel severity scale, 72.70% were mild reactions majority consisted that of itching, diarrhea, metallic taste, 26.93% were moderate reactions like drug eruptions, some cases of pain in abdomen and angioedema. 0.36% were severe reactions included immediate hospitalization and prompt treatment.

A severe adverse drug reaction is "any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening[16]". Two cases were of Steven Johnsons syndrome due to nevirapin and carbamazepine and a case was of anaphylactic shock due to injection ceftriaxone. Shamma et al showed 8% of severe reactions whereas it was 5% for Yerramalli et al [17]. According to modified Thornton and Schumock preventability assessment scale, 64.28% reactions were not preventable in paediatric age group as oppose to Salas De Las R et al. whereas 98.7% were not preventable in children [18]. Non-preventable reactions may be non predictable and may occur after a single dose, caused by immunological abnormality (drug allergy), inherited genetic abnormalities (idiosyncrasy). Measures to decrease the severity of

the non-preventable adverse drug reactions are use of proper resuscitative measures and apt supportive measures and quick identification of ADR that is by taking appropriate drug history, studying patient's case records, selecting alternative drug with different chemical structure and symptomatic treatment of the patients. Sensitivity tests must be performed while using penicillins, ester-linked local anesthetics, various anti-seras like ATS, ADS, ASV and iodine containing radio-contrast media. In our study, 45.40% reactions were possibly preventable whereas Tiwari P quoted 5% reactions in this category [19]. These can be minimized routinely monitoring the patients and by early diagnosis and by best possible drugs with different group. Patients should be kept under strict surveillance when prescribed with notorious medicines like oral anticoagulants, oral hypoglycemics and drugs with narrow therapeutic index and medicines affecting the vital functions.

CONCLUSION

Majors that help to minimize the adverse drug reactions are proper and essential laboratory monitoring, genetic testing (G6PD deficiency, HLA-human leucocyte antigen testing), patient education for any untoward or any undesired symptom or reaction so that they actively report at the earliest, early recognition and reporting of ADR. Dying from disease is sometimes acceptable but dying from drug is never acceptable so culture should be cultivated to report adverse drug reactions. Awareness regarding reporting of adverse drug reactions among all health-care professionals, patients and their relatives is of utmost importance. In the era of modern medicine, patient should be treated with optimal use of medicines as medicines are very hands of Gods if they are used prudently.

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