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A Prospective Study of Monitoring of the Adverse Drug Reactions in Paediatric Patients in Tertiary Care Hospital

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Abstract
Introduction: *Adverse drug reactions of drugs continue to remain as an important public health issue. Safety monitoring of medicines is the responsibility of all stakeholders of healthcare system since it continues to be an important cause of morbidity and mortality.In some countries adverse drug reactions are the one among the leading cause of mortality. The safety of patients and safe use of medicines are crucial for health policy development and the delivery of the best healthcare.*
Materials and methods:7*0 patients from the inpatient units of both males and females.The patients were selected based on inclusion and exclusion criteria. In the present study, the patients attended to the paediatric inpatient department with symptoms of ADRs. The study started with selection of the patients based on the inclusion criteria followed by the collection of all Adverse drug reactions in pediatric department by using patient data proforma.*
Results: *The results of the incidence of ADRs at GGH Kurnool, at AMC(ADR Monitering centre), Department of Pharmacology, Kurnool Medical College Kurnool are analysed after a study period of six months i.e from August 2018 to January 2019.All the ICSR(Individual Case Safety Report) (filled forms) are taken and studied. Atotal of 70 ADR forms are reported during the six months period of study.A total of 70 patients enrolled in the study are admitted as inpatiens in the Department of Pediatrics.*
Conclusion: *In the present study, the total number of ADRs reported were 70 for the period of August 2018 - January 2019. Incidence of ADRs is of 0.6%, Mortality was 0.2%. Among them higher percentage of ADRs arenoted with antimicrobials (43.2%) and with antiretrovirals (22.6%). Immune system is associatedwith most of the ADRs (29.89%). According to WHO- UMC scale of causality assessment majority of ADRs were possible 50.9%, Males (55.4%) are affected due to ADRs more than females, Type A (69.9%) reactions are commonly associated with ADRs.*
Key Words: *ADR, ICSR, UMC, WHO*

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I. Introduction

Adverse Drug Reaction (ADR)

It is defined as a response to a medicinal product that is noxious or potentially harmful and unintended, which occurs at doses normally used in human for prophylaxis, diagnosis or therapy of a disease (WHO report 498,1972).[1]

In India, epidemiological data of ADRs is limited to the incidence, risk factors and other clinical characteristics. Most of the Indian studies are based on the single centre, small sample and limited duration studies.[2]

Under-reporting, poor communication between health care professionals and patients regarding the potential harms of a prescribed drug, result in recording of less incidence of ADRs in India. It is difficult to extrapolate data from these studies to national level.

Considering these factors, a systematic review is required to estimate the ADR incidence based on Indian studies.

ADRs are the fourth leading cause of death[2]. ADRs may be responsible for the death of 15 out of 1000 patients admitted. Approximately 35% of hospitalized patients experience an ADR during their stay. They represent 5% to 10% of the hospital costs. Incidence of fatal ADRs is 0.23% to 0.4% in India. The average cost per patient who suffered from an ADR is INR 3,751/- in India.

ADRs risk increases with age (> 60), gender (females), number of prescribers (>2), prescription of multiple drugs (>5), duration of treatment (>1 month) & multiple diagnoses.

Age, for instance has a very critical impact on the occurrence of ADRs. Both very young and very old patients are more vulnerable to these reactions than other age groups. Alcohol intake also has a crucial impact on ADRs.[3]

Other factors are gender, race, pregnancy, breast feeding, kidney problems, liver function, drug dose and frequency and many other factors. Some of these factors can be changed like smoking or alcohol intake whereas others cannot be changed like age, presence of other diseases or genetic factors.[4]

Adverse reactions to analgesics (mainly non-steroidal anti-inflammatory drugs) and antibiotics constitute about half of all such reports in India[2]. This may be partly due to the fact that these are the most commonly used drugs in therapeutics[2]. Currently there are more than 4 million ADR cases reported at the ADR monitoring center- WHO-UMC (WHO Uppsala Monitoring Center), Sweden.[5]

II. Materials and Methods

Place Of Study: Paediatric Department, in patient unit of Government General Hospital, Kurnool.
Period Of Study: The study will be performed for 6 months from August 2018 to January 2019
Study Population: 70 patients from the inpatient units of both males and females.
Study Design: A Prospective Observational study
Sampling: The patients were selected based on inclusion and exclusion criteria. In the present study the patients presented to the paediatric inpatient department with symptoms of ADRs.
Patients Eligibility Criteria: The present prospective studywith subjects involved from paediatric inpatient department.
The subjects are selected based on inclusion and exclusion criteria.
Inclusion criteria

- Patients aged 0-12 years of either gender with suspectedADRs to pharmaceutical products were included in the study.
- Either gender is considered
- All the suspected ADRs that may be due to the medications, both prescribed and over the counter, taken by inpatients were ultimately noted and reported.

Exclusion criteria

- Medicines of alternative system like Ayurveda, Homeopathy, Unaniwere excluded
- Drug addicts, all mentally retarded people.
- Over dosage and excess consumption.
- Unconscious patients and patients unable to respond to verbal questions were also excluded from study.

Study Protocol: All the patients with adverse drug reactions are assessed by using WHO-UMC CAUSALITY assessment scale and HARTWIG scale of severity assessment.

Method Of Study: The study begin with selection of the patients based on the inclusion criteria followed by the collection of all Adverse drug reactions in pediatric department by using patient data proforma.

III. Results

The results of the incidence of ADRs at GGH Kurnool, at AMC(ADR Monitoring Centre), department of Pharmacology, Kurnool Medical College, Kurnool are analysed after a study period of six months i.e from August 2018 to January 2019.

Patient characteristics: All the ICSR (filled forms) are taken and studied. Atotal of 70 ADR forms are reported during the six months period of study.
A total of 70 patients enrolled in the study are admitted as inpatients in the Department of pediatrics.

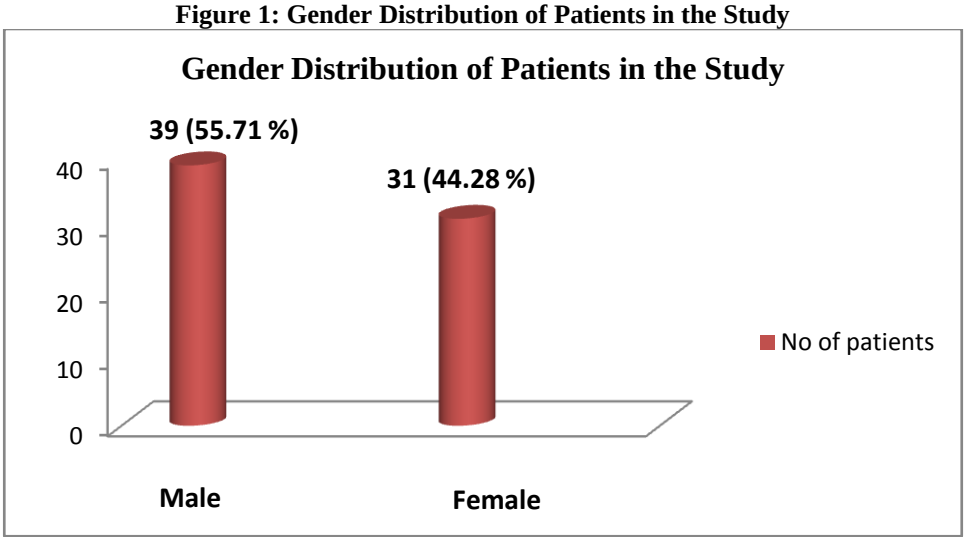
Gender Distribution of Patients in the Study

A total of 70 patients are admitted as inpatients in the department, the percentage distribution of study population showed that 39(55.71%) males and 31(44.28%) females are affected, which are represented in table:

Table 1: Gender Distribution of Patients in the Study

Gender	No of patients	%
Male	39	55.71%
Female	31	44.28%
Total	70	99.99%

Figure 1: Gender Distribution of Patients in the Study



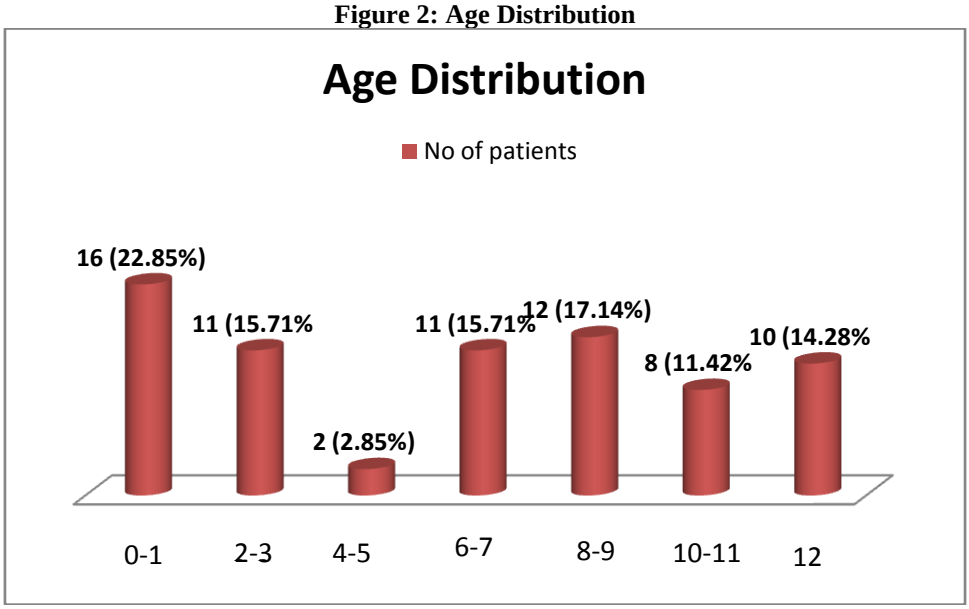
AGE DISTRIBUTION:

Total distribution of patients with age group shows that majority of patients were found in the age group of years followed by 0-1 years 16 (22.85%), 2-3 years 11(15.71%), 4-5 years 2 (2.85%), 6-7years 11(15.71%) , 8-9 years 12 (17.14%), 10-11 years 8 (11.42%), 12 years 10 (14.28%) were represented in table

Table 2: Age Distribution

Age frequency	No of patients	Percentage (%)
0-1	16	22.85%
2-3	11	15.71%
4-5	2	2.85%
6-7	11	15.71%
8-9	12	17.14%
10-11	8	11.42%
12	10	14.28%

Figure 2: Age Distribution



DISTRIBUTION OF PATIENTS ACCORDING TO AGE AND GENDER:

Total distribution of patients age group based on gender shows that the majority of patients among males and females were found in the age group of 12 years - males 39(55.71%), females 31(44.28%) which are represented in table:

Table 3: AGE DISTRIBUTION IN MALES

Age frequency	No of patients	Percentage (%)
0-1	10	14.28%
2-3	6	8.57%
4-5	2	2.85%
6-7	5	7.14%
8-9	6	8.57%
10-11	4	5.71%
12	6	8.57%

Figure 3: Age Distribution In Males

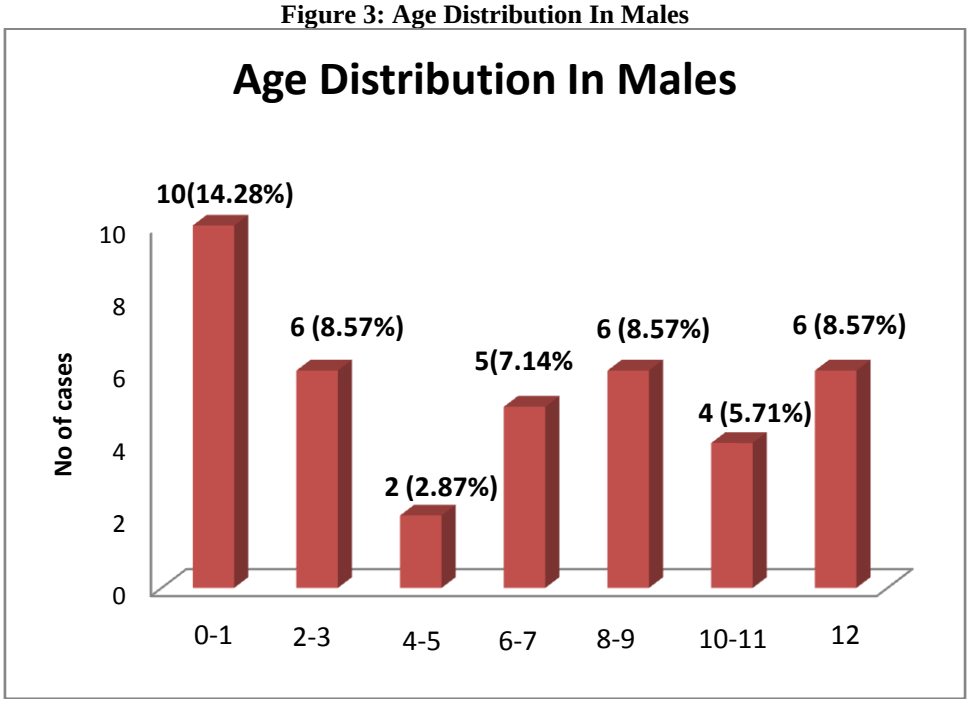


Table 4: Age Distribution In Females

Age frequency	No of patients	Percentage (%)
0-1	6	8.57%
2-3	5	7.14%
4-5	0	0%
6-7	6	8.57%
8-9	6	8.57%
10-11	4	5.71%
12	4	5.71%

Figure 4: Age Distribution In Females

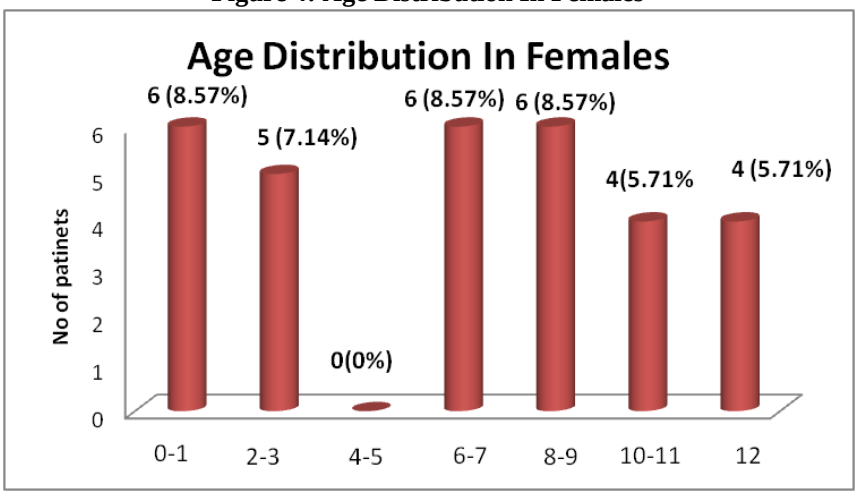


Table 5: Percentage Of Incidence Of ADRs Based On Drug Class

Drug system	Class	No of AE	Percentage	Total	N%
Autocoids	NSAID	6	8.60%	7	10.0%
	Antihistaminic	1	1.42%		
RS	Antiasthamatic	2	2.85%	2	2.85%
CNS	Antidepressant	3	4.28%	11	15.62%
	Antiepileptic	5	7.14%		
	Antipsychotic	-	-		
	Opioid	3	4.28%		
Blood	Vitamins &Minerals	3	4.28%	3	4.28%
GIT	Antiulcer	3	4.28%	3	4.28%
Antimicrobial	Antibiotic	34	48.6%	44	62.86%
	Antitb	1	1.42%		
	ART	-	-		
	Antimalarial	1	1.42%		
	Antifungal	1	1.42%		
	Antiviral	7	10.0%		

Figure 5: Percentage of incidence of ADRs based on drug class

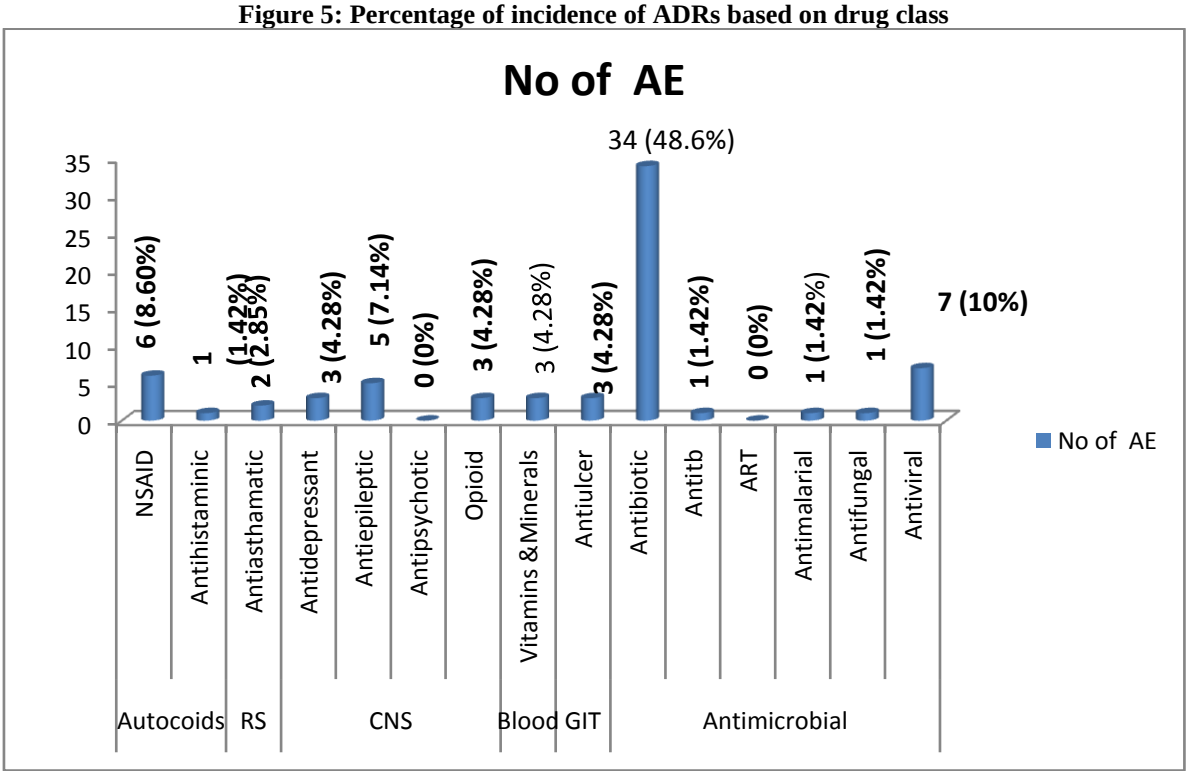


Table 6: System wise ADRs caused by individual drugs

ADR SYSTEM WISE	ADR	DRUGS	N	N%	TOTAL AE%BASED ON SYSTEM OF INVOVLEMENT
CNS	Ataxia	Phenytoin	1	1.42	9(12.85)
	Fatigue	Sodium valproate	1	1.42	
	Loss of cognitive function	Phenytoin	1	1.42	
	Dystonia	Haloperidol	1	1.42	
	Headache	Metronidazole	1	1.42	
	Nausea	Metronidazole	1	1.42	
	dizziness	ceftriaxone	1	1.42	
	Sleeplessness	Lamivudine+zudovudine	1	1.42	
	Tremors	Phenytoin	1	1.42	
CVS	Facial edema	Amikacin+combiflam	2	2.85	3(4.28)
	hypotension	salbutamol	1	1.42	
Endocrine	Weight loss	Zidovudine, lamivudine, nevirapine	1	1.42	

EYE	Blurred vision	Artesunate	1	1.42	
	Eyelid swelling	Combiflame	1	1.42	4(5.68%)
	Irritation of eyes &redness	Ciprofloxacin	1	1.42	
	Yellow discoloration	ATT Drug	1	1.42	
GIT	Stomach pain	TLE +erythromycin	2	2.84	34(48.28%)
	Abdominal pain	Ceftriaxone	1	1.42	
		Metronidazole	1	1.42	
	constipation	Pantoprazole	1	1.42	
		Phenytoin	1	1.42	
		Metronidazole	1	1.42	
	diarrhea	Zinc	1	1.42	
		TLE	1	1.42	
		Amoxicillin	1	1.42	
	Ulceration of lips	Aceclofenac	1	1.42	
	Erosion of lips	Phenobarbital	1	1.42	
	Upper lip swelling	Combiflame	1	1.42	
	Vomiting	Ceftriaxone	7	10.0	
		Zinc	1	1.42	
		Ofloxacin	1	1.42	
		Metronidazole	3	4.28	
		Paracetamol	1	1.42	
		Salbutamol	1	1.42	
		Amoxiclav	1	1.42	
		Potassium chloride	1	1.42	
		Sodium valproate	1	1.42	
		Amikacin	1	1.42	
		Methylphenidate	1	1.42	
		Pantoprazole +paracetamol	1	1.42	
	Oral candidiasis	Ceftriaxone	1	1.42	
	Gastritis	Diclofenac	1	1.42	
Immune System	Anaphylaxis	Vit-k	1	1.42	27(38.5%)
	Bullous eruption	Diclofenac	1	1.42	
	Exfoliative dermatitis	Abacavir +lamivudine	2	2.85	
		Diclofenac	1	1.42	
		Efavirenz	1	1.42	
		linezolid	1	1.42	
	hypersensitivity	combiflam	1	1.42	
	Fever	Metronidazole	1	1.42	
		D-penicillamine	1	1.42	
		Cefixime	1	1.42	
		Linezolid	1	1.42	
	Itching	Vancomycin	1	1.42	
		Metronidazole	1	1.42	
		Paracetamol	1	1.42	
	Chills	Ceftriaxone	1	1.42	
		D-penicillamine	1	1.42	
	Rashes	Vancomycin	1	1.42	
		fluconazole	1	1.42	
		Ampicillin	11	1.42	
		Pantoprazole	1	1.42	
		Ceftriaxone +amikacin	2	2.85	
		Ceftriaxone	2	2.85	
		Cetirizine+PCT	1	1.42	
		Abacavir +Lamivudine	1	1.42	
Musculoskeletal	Muscle pain	D-penicillamine	1	1.42	2 (2.85%)
		Ceftriaxone + Amikacin	1	1.42	
Renal System	Red colored urine	ATT	1	1.42	1(1.42%)

Table 7: Type of Adverse drug Reaction according to Rawlins and Thompson criteria

	COUNT	NUMBER	%
TYPE OF ADR	A	63	90%
	B	5	7.14%
	C	2	2.85%
	RARE	0	0

Figure 6: Type of Adverse drug Reaction according to Rawlins and Thompson criteria

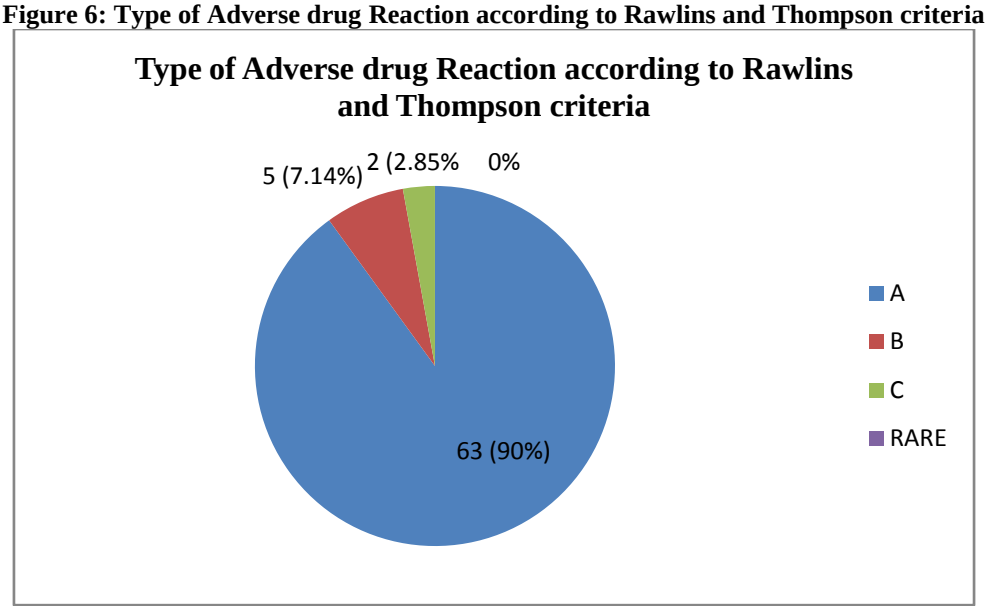


Table 10: ADR reporting percentage or reporting awareness among different groups of people

REPORTED BY	NUMBER	%
HEALTH CARE PROFESSIONAL	47	67.14%
PATIENT	5	7.14%
PHARMCOVIGILANCE ASSOCIATE	12	17.14%
STAFF NURSE	6	8.57%

Figure 9: ADR reporting percentage or reporting awareness among different groups of people

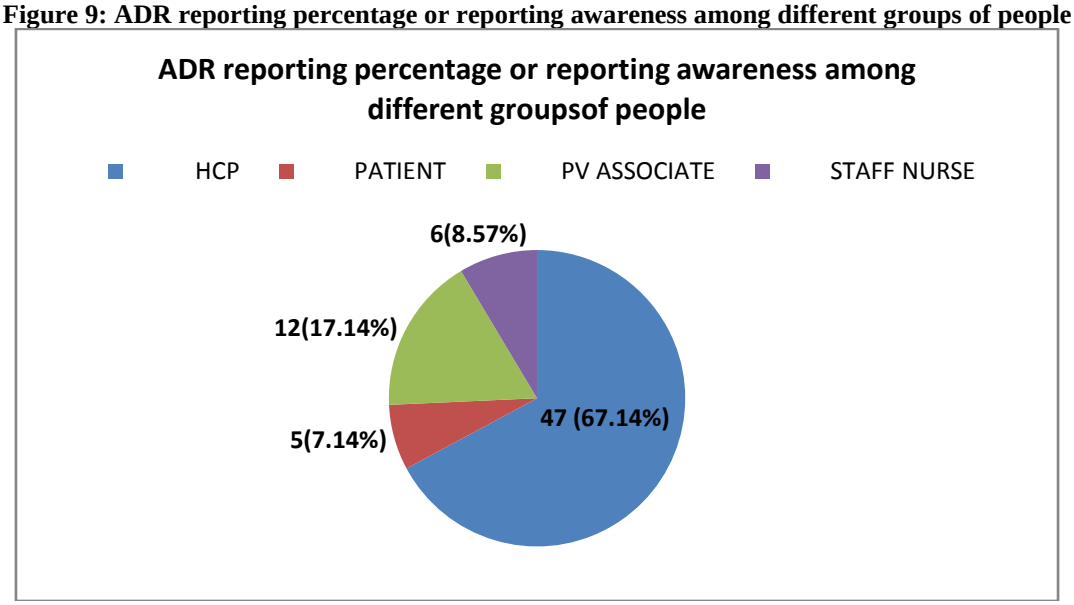


Table 12: Causality assessment of ADRs according to WHO-UMC scale in the study

		Number	%
UMC Scale	CERTAIN	3	4.28%
	POSSIBLE	35	50.0%
	PROBABLE	31	44.2%
	UNLIKELY	1	1.42%

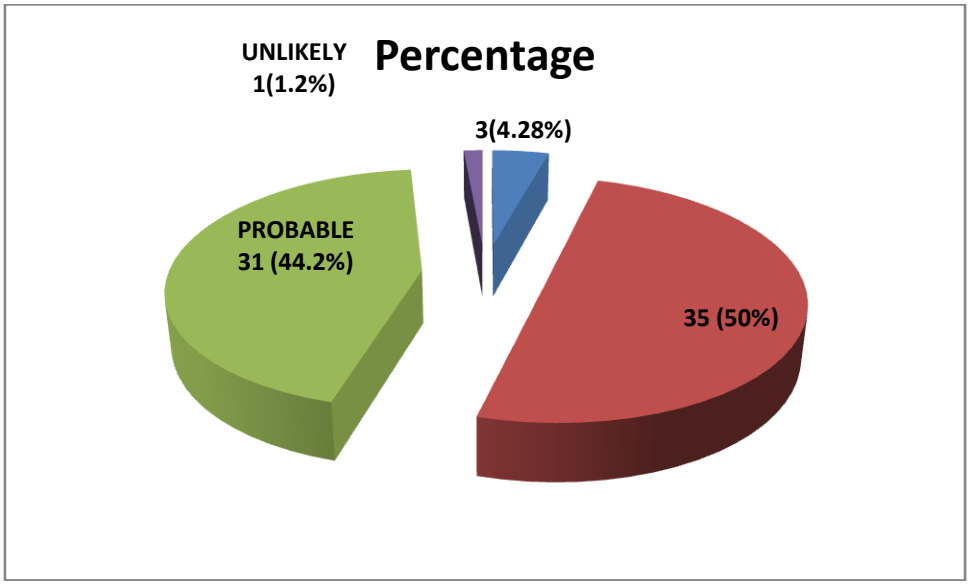
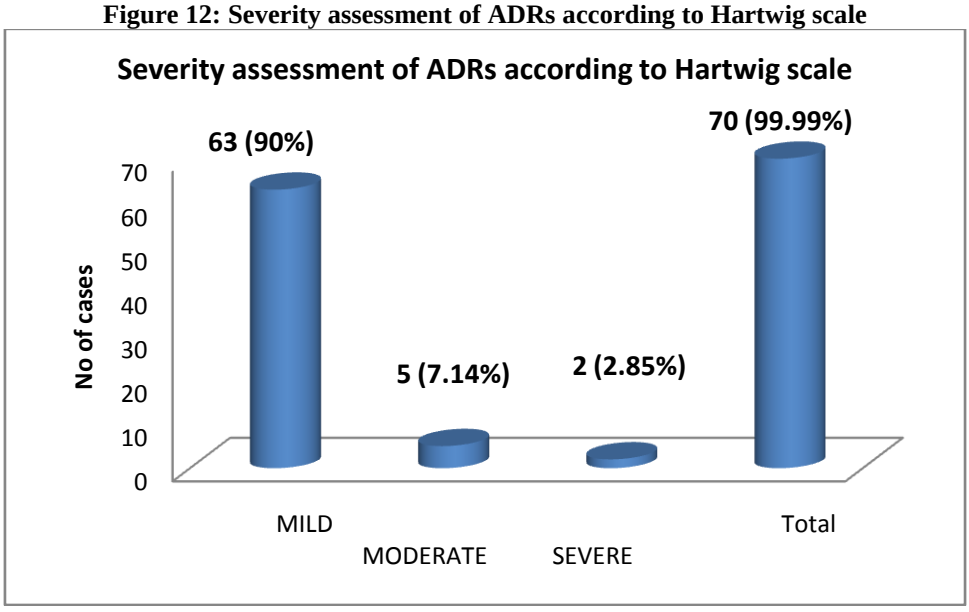


Table 13: Assessment of severity of ADRs according to Hartwig scale

HARTWIG	NUMBER	%
MILD	63	90%
MODERATE	5	7.14%
SEVERE	2	2.85%
Total	70	99.99%

Figure 12: Severity assessment of ADRs according to Hartwig scale



IV. Discussion

The burden of adverse drug reactions in the global scenario is high and accounts for considerable morbidity and mortality, and extra-cost to patients. Incidence of ADRs worldwide is 5% and in INDIA is about 1%. In England, 0.9% of the total hospital admissions were due to ADRs during the year 1999-2008, in Australia they contribute to 1% of hospital admissions, in the United States of America, ADRs contribute 3.4%-7% of hospital admissions.[6]

ADRs contribute to 10% of hospital admissions in many of the other countries. NCC (National Coordination Centre) has played significant role in creating awareness among health care professionals about reporting of ADRs which were more than 1,49,000 ADRs till December 2015. Currently the contribution of INDIA to the WHO global ICSRs (Individual Case SafetyReports) database is 3%. In Kurnool Medical College, the incidence of ADRs is of 0.6% during the period June 2016-May 2017. While the No of OP (Out Patient) 2000/day and IP (In Patient) 200/day. [7]

Signs suggestive of serious adverse drug reactions include the presence of fever, mucous membrane lesions, lymphadenopathy, joint tenderness and swelling, or an abnormal pulmonary examination. A detailed skin examination is essential in this regard.[8]

General Criteria for Drug Hypersensitivity Reactions:

1. The patient's symptomatology is consistent with an immunologic drug reaction.
2. The patient was administered a drug,be known to cause such symptoms.
3. The temporal sequence of drug administration and appearance of symptoms is consistent with a drug reaction
4. Other causes of the symptomatology are effectively excluded.
5. Laboratory data are supportive of an immunologic mechanism to explain the drug reaction. It may not be present or available in all cases.[9]

Hapten hypothesis: Drug metabolism typically occurs in 2 different steps, phase 1 and phase 2 reactions. Most often the reactive metabolite formed by phase1 metabolism is promptly detoxified and eliminated. However, reactive drug metabolites may act as haptens that bind covalently with cellular macromolecules such as serum proteins or cell surface membranes. Such binding results in the formation of large multivalent immunogens that may initiate an immune response.e.g:antibiotics .[10]

V. Conclusion

In the present study, the total number of ADRs reported were 70 from the period of August 2018 -January 2019.

- Incidence of ADRs is of 0.6%.
- Mortality was 0.2%.
- Among them higher percentage of ADRs were noted with antimicrobials (43.2%) and with antiretrovirals(22.6%).
- Immune system is associated with most of the ADRs (29.89%).
- According to WHO- UMC scale of causality assessment, majority of ADRs were POSSIBLE(50.9%).
- Males(55.4%) are affected due to ADRs more than females.
- Type A (69.9%) reactions are commonly associated with ADRs.
- Polypharmacy is associated with 60% of cases.
- Past H/O drug allergy is present in 1.2%cases.
- One rare ADR is detected with imatinib which induced hyperthyroidism.
- According to HARTWIG scale of severity, majority of ADRs are moderate in severity (52.4%).
- Preventable ADRs are 30.3%.
- Finally, Indian contribution of ADRs to global data base is 3%, where as in KMC Kurnool, it is only 0.6%.
- There is a need to identify the ADRs and improve their reporting by doctors, nurses, pharmacists and patients.

Acknowledgment

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