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Original Research Article

Identification, Assessment and Reporting of Adverse Drug Reactions (ADR) in a Large Tertiary Care Hospital in South India using Spontaneous Reporting System (SRS): A Prospective Observational Study

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Abstract:

Background: In most of the countries including India, Pharmacovigilance (PvPI) system relies mainly on spontaneous (or voluntary) reporting which provide the highest volume of information at the lowest maintenance cost, It is flexible and very effective method of collecting information whereby health professionals voluntarily submit case reports of ADR. As there is under reporting of ADRs and very less research is conducted in this area especially in south India, this present study was carried out with an aim to detect, assess (establishing causality relationship using WHO Scale), reporting (Using Spontaneous reporting system) and documentation of various Adverse Drug Reactions that occur in our tertiary care teaching government hospital at Visakhapatnam.

Methodology: The present study was carried out in the in-patient wards of General Medicine department ofKing George Hospital (KGH), a large tertiary care teaching hospital at Visakhapatnam, Andhra Pradesh, India. The present study is a Prospective, Observational study done for a period of four months i.e., from 19-Dec-2017 to 16-Apr- 2018.

A total of 103 Adverse Drug Reactions (ADRs) were identified and reported in 85 patientswho met our study criteria and were enrolled into our study after obtaining the Informedconsent. The present study was aimed to Identify, Assess, Report and document the suspected Adverse Drug Reactions using spontaneous reporting system.

Results: In our study we have screened about 196 patients out of which 85 people developed ADRs and thecausality assessment for each and every ADR was established using WHO probability scale.The details and all data pertaining to our study obtained using MS Excel 2010 work sheet. The most commonly identified reactions were drowsiness, tremor, myalgia and constipationout of 24 different reactions observed. Digestive system (35%) is the most effected organ systemfollowed by integumentary (15%) and muscular (12%). The number of ADRs reported was higherin the age group 46-55. WHO assessment scale revealed that out of 103 ADRs (78.64%) werepossibly drug related, (20.38%) probably drug related and(0.97%)found to be certain.

Conclusion: Health professionals have enough knowledge and awareness of the need to report ADR, but onlysmaller proportions report ADR. It depends on their knowledge, attitude and beliefs. Early identification and management of ADR is essential and special attention is to be taken in elderlypatients, patients with comorbidities and poly pharmacy.

Keywords: Pharmacovigilance, Adverse drug reactions, Causality Assessment, spontaneous reporting system

Introduction

Adverse Drug Reaction (ADR)

WHO Definition

The World Health Organization (WHO) defines an Adverse Drug Reaction (ADR) as:

"Any response to a drug which is noxious and unintended, and which occurs at doses normallyused in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.[1]

American Society of Health-System Pharmacists (ASHP), which defines a significant ADR as "any unexpected, unintended, undesired, or excessive response to a drug that requires discontinuing the drug (therapeutic or diagnostic), requires changing the drug therapy, requires modifying the dose (ex-

cept for minor dosage adjustments), necessitates admission to a hospital, prolongs stay in a health care facility, necessitates supportive treatment, significantly complicates diagnosis, negatively affects prognosis, or results in temporary or permanent harm, disability, or death" (ASHP 1995)[2]

Classification of ADRs

Adverse drug reactions were originally classified into two subtypes.

1. **Type A:** ADRs are dose-dependent and predictable; they are augmentations of known pharmacologic effects of the drug, such as orthostatic hypotension with antihypertensive medications.
2. **Type B**: ADRs are uncommon and unpredictable, depending on the known pharmacology of the drug; they are independent of dose and affect a small population, suggesting that individual patient host factors are important [3]

Type A reactions were later called augmented, and type B reactions, bizarre.

Two further types of reactions were eventually added: chronic reactions, which relates to both dose and time (type C), and delayed reactions (type D). Reactions after withdrawal ofdrug later became the fifth category (type E), and most recently, unexpected failure of therapy became the sixth (type F) (Rohilla 2013; Edwards 2000) [4,3]

An ADR is a type of ADE whose cause can be directly attributed to a drug and its pharmacological properties. ADRs are the major cause for morbidity, leading to hospital admissions, posing an immense burden on health care resulting in the increase in significant number of deaths [5,6]. Studies have shown that around l0-20% of patients are admitted with ADRs in hospital of UK and more than l, 00, 000 (one lakh) deaths are resulted due to serious adverse drug reactions in United States of America, annually [7,8]

ADRs are the 7th most common cause of death according to a Swedish study and almost 50% of all ADRs are preventable and care should be taken in their detection and management [7,6]. Also, the health-related quality of life was adversely affected by the ADRs and may lead to increase in the health care costs of the patients and lose the confidence in HCPs, increased physician visits, hospitalizations and even death [8,5]

Patients who were hospitalized at general medicine wards are considered to be more predisposed to suffer from ADRs, as the majority of patients admitted are likely to be elderly and have several co morbidities which are needed to be treated with multiple drug regimens during hospitalization [3,6].

Identification of ADRs

In the inpatient setting, patients may inform attending nurse or treating physician about the new symptom they developed. Asking detailed questions about the patient's symptoms, ratherthan immediately providing a treatment recommendation, could uncover an ADR and prevent unnecessary drug therapy or further ADR symptoms. A laboratory or diagnostic procedure has been ordered may indicate that an ADR has occurred.

In a community, patients often seek advice from the nearby pharmacist to treat various symptoms which can be adverse effects of drugs. This can be an opportunity for the pharmacist to inquire about the patient's symptoms to determine whether they might have beencaused by an ADR.

When an ADR occurs, a patient may need transfer to a higher level of care, such as from a general surgery ward to an intensive care unit or an unexpected change in a patient's clinical condition warrants transfer to a higher level of care.

Causality Assessment of Suspected ADRs

A causality assessment, performed for each potential ADR, can help determine future drug therapy options. It provides a degree of likelihood to the relationship between a drug and an adverse reaction. The widely used causality assessment scale in United States is the World Health Organization - Uppsala Monitoring Centre (WHO-UMC) Causality Categories scheme, which is described below:

- Clinical event or laboratory test abnormality that occurs in a plausible time relation to drug administration.
- Cannot be explained by underlying concurrent disease or other drugs or chemicals.
- Response to withdrawal of the drug is clinically plausible.
- The event is definitive pharmacologically or phenomenologically (an objective, specific medical disorder, or a recognized pharmacologic phenomenon)
- If necessary, a rechallenge is satisfactory.

Probable/Likely

- Clinical event or laboratory test abnormality that occurs in a reasonable timerelation to drug administration.
- Unlikely to be attributed to underlying concurrent disease or other drugs orchemicals.
- Response to withdrawal of the drug is clinically reasonable.
- Rechallenge is not required.

Possible

- Clinical event or laboratory test abnormality that occurs with reasonable time inrelation to drug administration.
- Could also be explained by underlying con-

current disease or other drugs or chemicals.
- Information on drug withdrawal may be lacking or unclear Unlikely.
- Clinical event or laboratory test abnormality with a time to drug administration that makes a relationship improbable, but not impossible.
- Underlying concurrent disease or other drugs or chemicals provide plausible explanations.

Conditional/Unclassified

- Clinical event or laboratory test abnormality
- Reported as an adverse reaction.
- More data needed for proper assessment or additional data being examined Unassessable/Unclarifiable
- Report suggesting an adverse reaction.
- cannot be judged because of insufficient or contradictory information.
- Data cannot be supplemented or verified.

The other more commonly used scoring system because of their simplicity and time efficiency; one is the Naranjo ADR Probability Scale shown in Table 1-2 (Naranjo 1981). By answering 10 questions about the ADR and assigning a numeric score to each answer, the ADR probability classification can be determined.

Reporting of ADRs

Spontaneous Reporting System (SRS)

Spontaneous (or voluntary) reporting of adverse effects is when health professionals or patients decide that they will report suspected harm from a drug to their local or national pharmacovigilance Centre. It is a system that relies entirely on the motivation of individuals to record and send information about something bad that has happened to a patient to the organization responsible for collecting reports of adverse effects (usually a local or national pharmacovigilance center). ADR forms (hard copy) are the commonest method of communication, but online reporting and apps (mobile applications) are also now available in most of the places and are an important development to increase rate of reporting. In most of the countries including India, national [pharmacovigilance] systems relies mainly on spontaneous (or voluntary) reporting, which provide the highest volume of information at the lowest maintenance cost, and have proven their value in the early detection of patient safety issues related either to the products themselves or to their use. As a source of unique data, spontaneous reporting remains important, but complementary methods are essential for pharmacovigilance to realize its potential in the prevention of harm to patients. In our study we have adopted SRS for reporting the ADRs. All ADRs were reported to the ADR monitoring center located at the department of pharmacology in the study site. All ADRs were documented in a well-designed ADR form in a prescribed format, provided by Indian Pharmacopoeia Commission (IPC), under the National Coordination Centre• Pharmacovigilance Program of India (NCC-PvPI) and reported.

As there is under- reporting of ADRs and very less number of researches were conducted in this area and therefore, our present study was carried out with an aim to detect, assess (establishing causality relationship using WHO Scale), report (Using Spontaneous reporting system) and documentation of various Adverse Drug Reactions that occur in a large tertiary care teaching hospital at Visakhapatnam.

Methodology

Study Site

The present study was planned to be carried out in the in-patient wards of General Medicine department of King George Hospital (KGH), a large tertiary care teaching hospital at Visakhapatnam, Andhra Pradesh, India. It is a 1300 bedded hospital with an occupancy rateof 100%.

On an average about 60-70 patients are admitted to the In-Patient ward of General Medicineunits every day, and therefore this site was selected to carry out our present study.

Study Design and Duration

The present study is a Prospective, Observational study carried out for a period of four months i.e., from 19-Dec-2017 to 16-Apr- 2018.

Study Approval

Prior approval for the study was obtained from Institutional Ethics Committee (IEC), King George Hospital (KGH), Visakhapatnam, Andhra Pradesh.

Study Objectives

1. To identify, assess and report the Adverse drug reactions occurring in the in-patients admitted in the General Medicine department of KGH.
2. To assess the severity of ADRs, organ system affected and the drug class responsible for ADRs.

Study Criteria

Inclusion Criteria

1. Patients of either sex, who are admitted to the In-Patient wards of the department of General Medicine were enrolled into our study.
2. Patients of age >14 years.
3. Patients who gave Informed consent form (ICF) and participated voluntarily in our studywere included.

Exclusion Criteria

1. Patients who do not meet the Inclusion Cri-

teria were excluded from our study.
2. Woman who are pregnant and lactating and patients who are below 14 years of age were excluded from the study as most of them were referred to the Pediatric unit and likely hood of lost to follow -up is more with them.
3. Adverse events resulted from transfusion of Blood and its products, or IV fluids were not considered as ADRs as they are studied as a separate entity known as Hemovigilance.
4. Patients who are referred to general medicine unit from other units or shifted to other units from General medicine were excluded.
5. Subjects who are discharged within one day are excluded from our study.

Study Procedure

1. After obtaining the approval from the IEC, the data pertaining to the patient including the Patient's demographics, presenting complaints, past medication history, other details including Over the-counter drugs, current medications, laboratory investigations if done any were entered in a well-designed ADR data collection and documentation form.
2. Data pertaining to the ADR was obtained from sources like Patient's Medical records or case sheets, medical reports and by interviewing the patient or their care takers (if necessary) nursing staff or doctors on duty regarding the side effects experienced by them.
3. The collected data was then analyzed for identification of ADRs using Spontaneous Reporting System (SRS) and causality assessment of each ADR was established using WHO Probability Scale.
4. Finally, the ADR's identified were reported to the ADR monitoring center using Spontaneous Reporting system (SRS)which is the regional Pharmacovigilance Centre (AMC) in the department of Pharmacology, Andhra Medical College, located in the campus and documented.

Termination of the Study

The investigators are determined to terminate the study for safety reasons at any time and the reasons for this termination were planned to be provided to IEC and the subjects.

In our study, no one was identified with serious health deterioration while the study was being carried out.

Results and Discussion

The present study was aimed to Identify, Assess, Report and Document the suspected Adverse Drug Reactions using Spontaneous Reporting System.

The demographic details of each and every patient i.e., Age, Gender and weight were collected along with the current medical condition, treatment given, the type of adverse reaction identified, the organ systems affected, drugs which are implicated in the ADRs, causality assessment using WHO causality assessment scale.

The outcomes of each ADR were then assessed and were reported to the ADR monitoring center at the study site and are finally documented by the Pharmacovigilance Technical associate in the Vigiflow WHO database for future reference.

The data pertaining to our study were analyzed using MS -Excel 2010 work sheet.

Patient Demographics

A total of 103 Adverse Drug Reactions (ADRs) were identified and reported in 85 patients who met our study criteria and were enrolled into our study after obtaining the Informed consent form.

Out of 85 patients enrolled, 42(49.41%) were found to be male and 43(50.58%) were found to be female patients, with ADRs slightly more pronounced in female patients, suggesting that there was no much significance in occurrence of ADRs with respect to gender in our study.

The results obtained in our study were similar when compared to the study results obtained from the other studies conducted by Palaniswamy S et al of India in 2009 and Juan Fco Sanchez et al of Spain in 2011 which is probably due to the less sample size and study duration in both the studies.

Table 1: Gender distribution with respect to occurrence of ADRs in the study population.

S. No.	Gender	No of ADRs	Percentage (%)
L	Male	42	49.41
2	Female	43	50.58
3	Total (n)	85	100

Age distribution

Patients of different age groups between 16-72years were enrolled into our studyand the mean age was found to be 44.6 years. The youngest patient enrolled in our study 16 years of age and the patient with highest age was found to be 72 years.The age distribution was analysed in our study and is represented in the table 2

Table 2:

S.no	Age distribution (Class)	No of Patients	Percentage
1	16-25	09	10.58%
2	26-35	20	23.52
3	36-45	14	16.47
4	46-55	25	29.41
5	56-65	14	16.47
6	66-75	03	3.52
	Total	85	100

Types of reactions observed from reported ADRs About 24 different reactions have been observed in patients. The most commonly identified reactions were Drowsiness 6(5.8252), tremors 4(3.809524), Myalgia 4(3.809524), constipation4(3.809524), dry cough 4(3.809524), slurred speech 3(2.857143)

Table 3:

S.No	Name of Reaction	No. of Patients
1	Vomiting	2(1.904762)
2	Tremor	4(3.809524)
3	Sweating	2(1.904762)
4	Slurred Speech	3(2.857143)
5	Shivering	1(0.952381)
6	Polyarthritis	1(0.952381)
7	Pain In Upper Limbs	1(0.952381)
8	Numbness In Toes	1(0.952381)
9	Myalgia	4(3.809524)
10	Joint Pain	1(0.952381)
11	Headache	1(0.952381)
12	Fatigue	2(1.904762)
13	Excessive Salivation	2(1.904762)
14	Epigastric Burning	2(1.904762)
15	Dryness Of Mouth	2(1.904762)
16	Drowsiness	6(3.809524)
17	Cough	4(3.809524)
18	Burning Sensation In Abdomen	1(0.952381)
19	Burning Micturition	1(0.952381)
20	Abdominal Distension	2(1.904762)
21	Gastric Irritation	2(1.904762)
22	Redness Of Skin	1(0.952381)
23	Constipation	4(3.809524)
24	Others	55(45.7201)

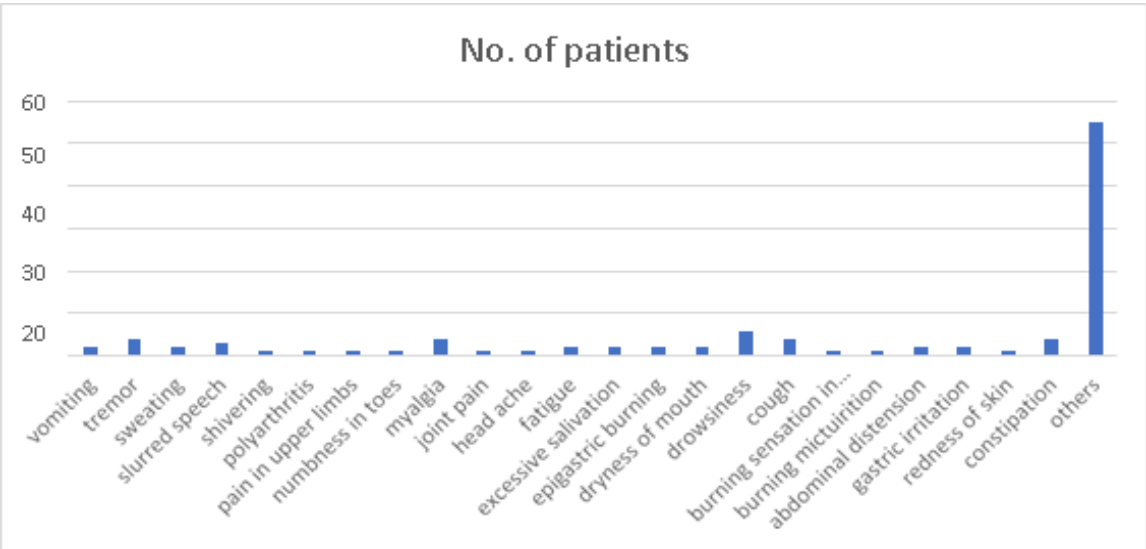

Figure 1: Types of reactions observed from reported ADRs

Classes of drugs involved in ADRs (table 4)

The most frequently drug classes associated with ADR'S are ACE inhibitors 11(10.48), Atypical anticonvulsants 10(9.52), Anti histamines 9(8.57), salicylates 7(6.67), HMG-CoA enzyme reductase inhibitors 6(6.67), PPI inhibitors 6(6.67).

Table 4: Classes of drugs involved in ADRs

Class of Drugs	No. of ADRs	Percentage	Class of Drugs	No. of ADRs	Percentage
Anticonvulsants	1	0.95	Beta blocker	2	1.90
5-HT3 4ntagonist	2	1.90	Biguanide	3	2.86
ACE inhibitors	11	10.48	butyrophenone	1	0.95
Adrenergic	1	0.95	ca blocker	2	1.90
Amino penicillin's	1	0.95	Cobalamin	1	0.95
Anti- Tubercular	1	0,95	diuretics	1	0.95
Anti-Coagulant	4	3.81	Dopamine antagonist	1	0.95
Anti-Convulsant	4	3.81	DPPA-4 inhibitor	3	2.86
Anti-Epileptics	4	3.81	HMGCO-A	6	5,71
Antihistamines	9	8.57	insulin	1	0.95
Anti-Pyretic	1	0.95	loop diuretic	2	1.90
Anti-Tubercular	1	0.95	NSAIDS	1	0.95
Anti-Tuberculosis	1	0.95	phenothiazine	2	1.90
Antibiotic	3	2.86	PPI	6	5.71
Anticoagulant	1	0.95	protectant	1	0.95
Anticonvulsants	4	3.81	quinolones	1	0,95
Antimanic Agent	1	0.95	salicylates	7	6.67
Atypical Antipsychotic	10	9.52	sulfonylurea	2	1.90
Azoles	1	0.95			

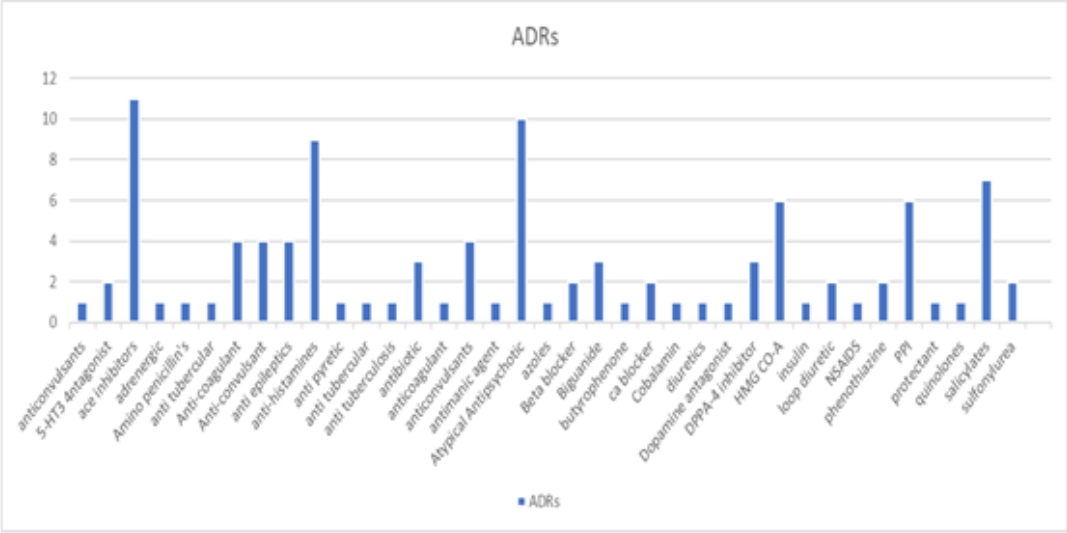

Figure 2: Graphical representation of drug classes causing ADRs

Organ systems effected due to ADRs

Digestive system has been the most effected organ system followed by Integumentary and muscular systems. CNS have been moderately affected, other systems effected were endocrine, hematological, lymphatic, reproductive system, respiratory, skeletal and urinary.

Table 5: Organ systems effected due to ADRs

S.no	Organ system affected	Percentage(%)
1	CNS	21
2	Digestive	35
3	Endocrine	4
4	Haematological	2
5	Integumentary	15

6	Lymphatic	1.5
7	Muscular	12
8	Reproductive	1
9	Respiratory	1.5
10	Skeletal	4
11	Urinary	3

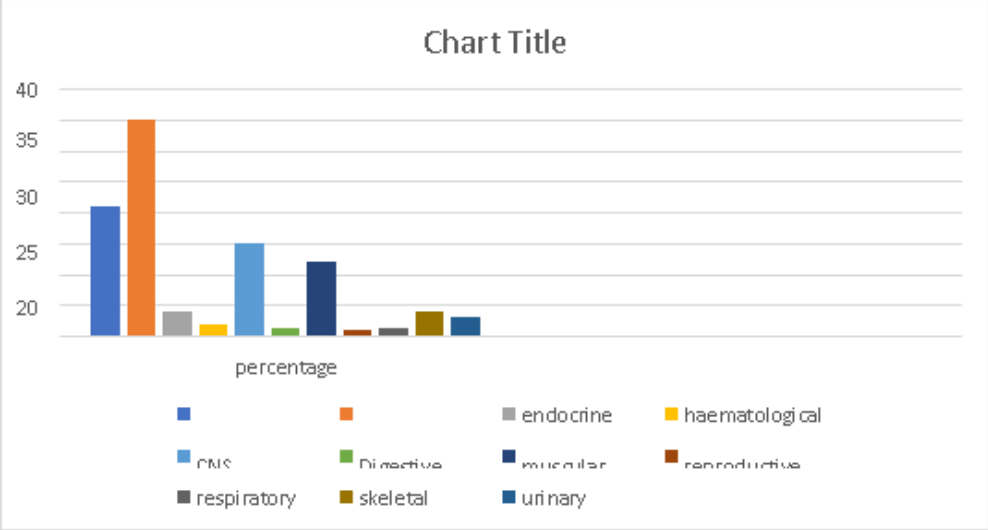

Figure 3: Graphical representation of organ systems affected due to ADR

WHO probability assessment scale

The assessment done by using WHO scale revealed that out of 103 ADRs 81(78 64%) were possibly drug related, 21(20 38%) ADRs were probably drug related and 1(0.97%) are found to be certain.

Table 5 contains the WHO probability assessment scale results.

Table 5:

S.no	Reaction	ADR(%)	Male(%)	Female(%)
1	Certain	1(0.97)	1(2.38)	0
2	Possible	81(78.64)	32(76.19)	30(69.76)
3	Probable/likely	21(20.38)	9(21.42)	13(30.23)
4	Unlikely	0	0	0
5	Unassessable /unclassifiable	0	0	0
6	Conditional/unclassified	0	0	0

Outcomes of ADRs

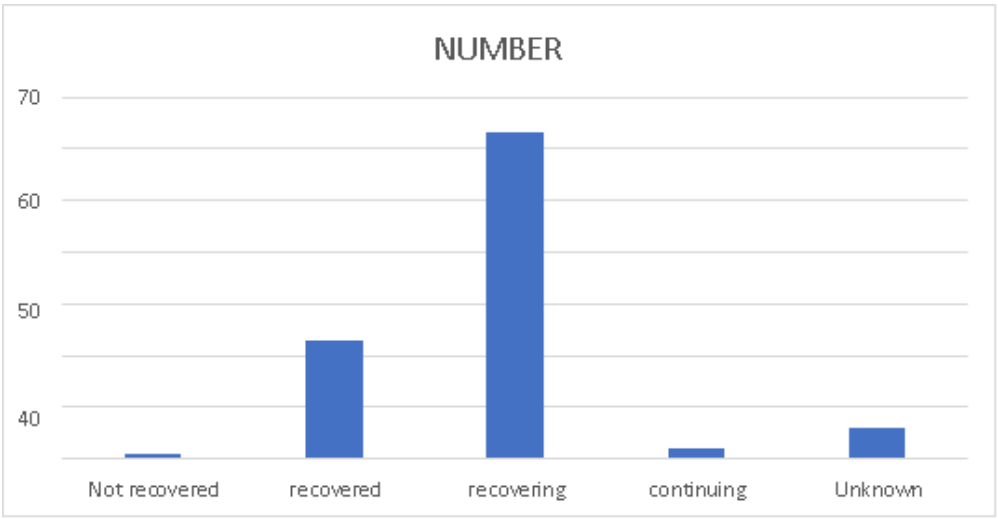

Figure 4: Represents the outcomes in different patients effected by ADRs

Table 6 contains the outcomes caused to the patients effected by ADRs

Table 6:

Adr Outcome	Number	Percentage
Not recovered	1	0.952381
Recovered	23	21.90476
Recovering	63	60
Continuing	2	1.904762
Unknown	6	15.2381

Out of 85 patients enrolled 42(49.41%) were male and 43(50.58%) were female patients similar to Juan Fco Sanchez et al [6]

Patients of age between 46-55 developed higher no of ADRs, (29.41%) which is on par with Palanisamy et al study.[5]

ADRs were more frequent with ACE inhibitors and anticonvulsant group of drugs and gastrointestinal system, next is CNS and integumentary. ADRs were more pronounced like vomiting, epigastric burning, abdominal distention and constipation. WHO probability scale reaction was possible in 78.64% and probable in 21%.

At the end of the study 22% recovered from ADR and 60%of patients were recovering.

Conclusion

In our study we have screened about 196 patients out of which 85 people developed ADRs. Digestive system is the most effected organ system in our cases of study followed by integumentary and muscular.

The number of ADRs reported in the age group *46-55* were prominent. Early identification and management of ADRs is essential and special attention is to be taken in caseof polypharmacy.

Drug withdrawal or dose reduction is usually the first step to be employed for the management ofADR's.

Among the different pharmacovigilance methodologies Spontaneous reporting system remain thebasis of the system, and one of the main sources of information for decision making, drug withdrawals from the market and with advantages of low cost and ease of implementation.

ADRs are preventable and can reduce hospital admissions, morbidity, mortality and treatment cost.

What really matters is reporting culture and proactive approach and a strong PV system to ensure medicine safety. Apart from health care professionals, reporting by patients themselvesadds new information and perspective about ADRs in a way otherwise unavailable, can contribute to better decision-making processes in regulatory activities, and strengthening of safety signals and increase the knowledge about ADRs.

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