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PREVALENCE OF ADVERSE DRUG REACTIONS IN INDIA – SYSTEMIC ANALYSIS

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ABSTRACT

Nowadays Adverse drug reactions related admissions have significantly increased over past few decades. Antibiotics are most widely misused drugs in developing countries in the form of over the counter use, self medication and irrational prescriptions. ADR was the fourth to sixth most cause of death in India. The objective of this study was to make an overall view on different ADR studies about the incidence and prevalence of ADR in inpatients of various hospitals and also to find out the mortality, causality and most common drugs causing ADRs. 15 articles were taken into consideration for our study from the year 2008-2019 which were obtained from Google Scholar; Medline, Embase and Pubmed from 2008 –2019. A total of 65 articles were found based on the keyword adverse drug related hospital admission. Abstract –only articles, out –patient ADR studies were filtered. Finally 15 articles were taken into consideration for our study. Based on these articles systemic analysis was made and results were outlined. Higher prevalence of ADRs was observed in anti –microbials followed by anti –tubercular and anti –neoplastics. In anti –microbials class cephalosporins and beta-lactams have shown higher incidence of ADRs. For safety and rational use of antimicrobials, implementation of antimicrobial guideline policy and strict adherence to it should be established.

KEYWORDS: Adverse drug reactions, Pharmacovigilance, Anti microbials.

INTRODUCTION

According to World Health Organisation an Adverse Drug Reaction (ADR) is defined as a noxious, unintended and undesirable effect that occurs as a dose normally used in man for diagnosis, prophylaxis, treatment of a disease and modification of physiological function. 10-20% of inpatients will have at least one ADR during their stay in hospital (Kuna Kamala *et al, 2019)*. The ADRs were classified into two categories, the occurrence of ADRs after admission in hospital and its occurrence before admission in hospital (*AnupKumar et al, 2015)*. The complexity and severity of an ADR was affected by drug related factors and patient related factors. Drug related factors include route of administration, type of drug, dosage and duration of treatment, Patient related factors include Age, Sex, Genetic factors and Concurrent disease (Kavitha Dhar *et al*, 2015). ADRs were the fourth to sixth most cause of death in India. Women are more prone to ADRs compared to males (Jayanthi *et al*, 2018).

ADRs were classified into different types. Based on classification of Predictability they were classified as Predictable ADR in which the mechanism of its occurrence is known whereas in Unpredictable ADR the mechanism of its occurrence is unknown. Based on the cause it is classified into 5 types, Type A – Augmented reactions, Type B –Idiosyncratic or Bizarre, Type C –Chronic or Continuous use, Type D –Delayed Onset, Type E –End of use or Discontinuation of use or Sudden withdrawal of effect and Type F –Failure of treatment. Based on the classification of Severity these are classified as MILD, MODERATE and SEVERE. Based on classification of Location these are classified as Systematic ADR and Local ADR in which the drug shows its adverse effect on whole body and only on a particular organ respectively (Peter Ejizokhale Akhideno, *et al*.). The occurrence of an ADR may increase the burden of economy, increase or prolong stay in hospital and may increase the risk of death (*Hiran.R.Trivedi etal*, 2011).

In 1960 after thalidomide tragedy WHO introduced a program for monitoring ADRs was pharmacovigilance (Jayanthi *et al*, 2018). The reporting of ADRs can be done by active participation or through reporting in hospital system *(Hiran.R.Trivedi etal*, 2011). In India the reporting of ADRs is still at an infant stage. There is certain need to create and enhance physicians about detection, management, prevention and reporting of an ADR (Jayanthi *et al*, 2018). Antibiotics followed by antitumor class of drugs were causing most of the ADRs. Antibiotics are most widely misused drugs in developing countries in the form of over the counter use, self medication and irrational prescriptions (S Sharma *et al, 2015).*

OBJECTIVE

The objective of this study was to make an overall view on different ADR studies about the incidence and prevalence of ADRs in inpatient of various hospitals and also to find out the mortality, causality and most common drugs causing ADRs.

MATERIALS

The relevant literature search was obtained from Google scholar, Medline, Embase and Pub med from 2008 – 2019 were collected. All the studies which were obtained in the search results were considered for the study irrespective of speciality department. A total of 65 articles were found based on the keyword adverse drug related hospital admission. Abstract – only articles, out –patient ADR studies and Non –English studies were filtered from 25 articles. Finally 15 articles were taken into consideration for our study. On these articles systemic analysis was made and resulted were outlined.

Study No	Study	State	Study design	setting	Study group	Duration of study
1	Hiren R. Trivedi *et al*, 2011	Ahmedabad	Prospective cohort study	Multi centre	General population	6m
2	Jayanthi C R *et al*, 2018	Bangalore	Prospective observational study	Multi centre	General population	48m
3	R.Vijaishri *et al*,2017	Coimbatore	Prospective interventional	Multi centre	General population	6m
4	Ambili Remesh *et al*, 2013	Kerala	Prospective cross sectional	Multi centre	General population	1m
5	Kavita Dhar *et al,2015*	Ghaziabad	Retrospective observational non –interventional	Multi centre	General population	6m
6	Snehal Anturlikar *et al*, 2017	Gujarat	Prospective cross sectional	Multi centre	Adults	1y
7	Anup Kumar *et al*, 2016	Himachal Pradesh	Retrospective observational study	Multi centre	Adults and geriatrics	1y
8	S.V.Desai *et al*,2008	Jaipur	Retro –prospective	Multi centre	Adults and geriatrics	6m
9	S. Sharma *et al, 2015*	Jammu Kashmir	Retrospective cross sectional	Multi centre	General population	3y
10	Palanisamy S *et al*,2013	Coimbatore	Prospective observational	Multi centre	General population	3y 8m
11	M. Shamna *et al*,2014	Kerala	Prospective study	Multi centre	General population	1y
12	Manju Agarawal *et al*, 2018	Raipur	Prospective observational	Multi centre	General population	11m

13	Ponnusankar Sivasankaran e*t al*,2015	Tamil Nadu	Prospective study	Multi centre	General population	1y 10m
14	Kunakanala *et al*, 2019	Vishakhapatnam	Prospective observational	Multi centre	General population	2y
15	G. Meghana *et al*, 2018	Warangal	Prospective observational	Single centre	General population (Females)	8m

RESULTS AND DISCUSSION

Out of 15 studies 5 were prospective observational in which 4 were conducted at multi centre and 1 was at single centre study. Two studies were conducted by excluding paediatrics, one study was conducted only in female population and twelve studies were conducted in general population. Retrospective cross –sectional and observational studies were conducted at Jammu Kashmir, Himachal Pradesh respectively whereas both retro- prospective study was conducted at Sree Krishna Hospital at Jaipur. Studies conducted at Ghaziabad, Kerala and Jammu Kashmir was showing only the patterns of prescribing and occurrence of ADRs due to Anti microbials only. Most of the studies were assessing ADRs through causality and severity by utilising WHO Scale and Naranjo Scale.

The study at Guru Gobindh Singh hospital, Jamnagar, Ahmedabad was conducted on 830 subjects and 47 ADRs were found. Based on causality assessment 28 were certain, 14 were possible, 2 were unlikely, 2 were unassesble, and 1 was possible. Based on severity assessment 30 require hospitalisation, 14 were life threatening and 2 were fatal. In this study males were prone to higher risk of ADRs than females. In anti microbial group, Chloroquine phosphate was the common drug causing ADRs and in anti tubercular drugs streptomycin causing 2 fatal reactions and anti cancer drugs were causing immune suppression.

A study conducted at Vain Vilas Hospital, Bangalore. A total of 100 ADRs were found. Based on causality assessment 61 were probable and 39 were possible. Based on severity assessment 57 were mild, 43 were moderate. In this study the main drugs involved for causing ADRs were Haematinics and anti microbial. The most common ADRs presented in pregnant women are with anaemia. Allergic reactions were mostly presented in patients taking anti microbial. Gastro intestinal system was most commonly affected system followed by immune system.

A study conducted at PSG Hospital, Coimbatore. In this study prescription with antibiotics were analysed in 1138 subjects out of which 143 ADRs were found. Based on causality assessment 129 were possible, 14 were possible. Based on severity assessment 127 were mild and 15 were moderate. In these study beta lactam antibiotics shows maximum number of ADRs. Gastro intestinal system was most commonly affected followed by dermatology. In this study males were prone to higher risk of ADRs than females and also >45 years were highly affected.

A study conducted at Kovai Medical Care and Hospital. A total 950 were found. Based on causality assessment 759 were probable, 165 were possible, 20 were definite and 6 were unlikely. Based on severity assessment 583 were moderate, 308 were mild, 55 were severe. In this study Predictable ADRs were commonly found. Most of the ADRs were found in dermatology department as maculopapular skin rashes followed by general medicine. Antibiotics produced more number of ADRs followed by NSAIDS. Females were highly prone by ADRs than males and also 41-50 years were highly affected.

A study conducted at tertiary care teaching hospital, Ghaziabad, UP. A total 126 ADRs were found. Based on causality assessment 78 were possible, 32 were probable, 10 were unlikely and 6 were certain. Severity assessment was not included in the study. In this study beta lactams shows maximum number of ADRs followed by Quinolones. Males were prone to higher risk of ADRs than females and also adults followed by children were highly affected. ADRs were mostly affected to gastro intestinal system followed by respiratory system.

A study conducted at GMERS Medical College and Hospital, Gujarat. A total of 269 ADRs were reported by students of this college and 180 ADRs were found by Physicians. ADRs were analysed by causality assessment by students and physicians. In this study ADRs reported by students as 172 were probable, 97 as possible where as physicians reported as 141 were possible, 38 were probable and 1 was certain. Serious ADRs reported by students and physicians were 12 and 13 respectively. Mean age reported by physician was 35.40 ± 16.30 where as by students as 37.31±16.22. By comparing the results type A reactions were mostly obtained. Students reported that gastro intestinal system followed by dermatology was highly affected due to ADRs where physicians reported that dermatology followed by gastro intestine system was affected. The study determined that the major class of drugs causing ADRs were antibiotics and anti neoplastics.

The study at Dr. Rajendra Prasad Government Hospital was conducted on 6922 subjects and 526 ADRs were reported. Based on causality assessment 61.2% were probable, 32.3% were possible, 5% were unlikely and 1.5% was certain. Based on severity assessment 74.2% were moderate, 13.6% were severe and 12.1% were mild. In this study Type-A reactions were commonly found. Males were more prone to ADRs than females and age group of 41-60 years were mostly affected. Gastrointestinal system was affected followed by central nervous system. Major class of drugs causing ADRs were antimicrobials followed by NSAIDS and hypoglycemics.

The study at Sree Krishna Hospital was conducted on 600 subjects and 18 ADRs were reported. Based on causality assessment 11 were probable, 6 were possible and 1 was definite. In this study patient receiving more than 10 drugs were showing higher incidence of ADRs. Gastrointestinal system followed by liver was affected due to ADRs. The major class of drugs causing ADRs were anti infective followed by anti tubercular drugs.

A study was undertaken using suspected adverse drug data collection form available under Pharmacovigilance Programme of India (PvPI). A total of 2586 ADRs were reported. Based on causality assessment 290 were probable, 102 were Possible. Based on severity assessment, 352 were moderate, 27 were severe and 13 were mild. In this study Type-A reactions were most commonly found. The mean age of the males affected by ADRs was and 36.6 for females. Males were more prone to the ADRs than females. The class of dugs which mainly causing ADRs were anti microbial. Adults followed by geriatrics and paediatrics were mostly affected.

A study at 500beded tertiary care hospital, Trivandrum was conducted on 100 patients and 12 ADRs were found. Based on causality 9 were possible and 3 were probable. Based on Naranjo scale 9 were possible and 3 were probable. Based on severity 9 were mild and 3 were moderate. In this study the class of drugs which causing ADRs were beta lactams followed by amino glycosides. Dermatology followed by gastrointestinal system was commonly affected by ADRs. The mean age of paediatrics included in this study was 4.04± 3.91 and for adults 44.4± 17.56.

The study at tertiary care referral hospital, Kerala was conducted on 15,037 subjects and 49 ADRs were reported. Based on the causality assessment using Hart wig and Siegel scale 35 were probable, 9 were possible and 5 were definite. Based on severity assessment using

shumock and Thornton scale 31 were moderate, 14 were mild and 4 were severe. In this study type A reaction were reported commonly based on Rawlin and Thomson classification. The most affected organ system was gastro intestinal and dermatology. In this study the most common class of drugs causing ADRs were cephalosporin's followed by fluoroquinolones. Males were more prone to ADRs compared to females. In this study the ADRs majorly affecting the age groups were geriatrics followed by adults and children respectively.

A total 450 were hospitals were included in pharmacovigilance program in India. A total of 532514 subjects were included in the study out of which 242 ADRs were identified. Based on causality assessment 156 were probable, 64 were possible, 11 were certain and 1 was likely. The occurrence of ADRs was mainly observed through parentral followed by oral and topical route. In this study females were prone to higher risk of ADRs than males. The age group commonly affected to ADRs was 31-60years. Skin reactions were highly observed in this study. The reporting frequency of ADRs was high by physicians whereas low by nursing staff and patients.

A study was conducted at 4200beded secondary care hospital, Ootacamund, Tamilnadu. A total 1000 patients were included in the study out of which 80 ADRs were observed among which 77 were reported by pharmacist and 3 were reported by physician. Based on causality assessment 78.75% were probable and 21.25% were possible. Based on severity assessment 45 were mild and 35 were moderate. Based on Thornton Preventability scale 73.75 were preventable, 25% were not preventable and 1.25% was definite preventable. The higher incidence of ADRs was observed in patients >60years of age and mean age of population was considered as 52.2years. The most common class of drugs causing ADRs were Diuretics followed by antibiotics. Gastrointestinal system followed by Haematological system was mostly affected due to ADRs. Based on wills and Brown classification these reactions were classified as type A reactions.

A study was conducted at King George Hospital, Vishakhapatnam. A total of 327 ADRs were reported out of which females were more than males. Based on causality assessment scale 51.99% were possible, 47.09% were probable and 0.91% was certain. Majority of ADRs were observed at an age group of 18-44 years and the mean age was defined as 31.472±15.499. Anti microbial followed by Anti psychotics were the common class of drugs causing ADRs in this study. Dermatology followed by Central nervous system was mostly affected. Out of 327 ADRs 20.18% were serious and death occurred in 5 patients by

ceftriaxone induced severe anaphylactic reactions.

The study at a Private Cancer hospital, Telangana was conducted on 254 female patients and 2342 ADRs were reported. Based on causality assessment by Naranjo scale 1273 were definite, 863 were probable and 206 were possible. Based on severity assessment by Hart wig and Siegel scale 1971 were moderate, 312 were mild and 59 were severe. The mean age group affected by ADRs were 51-60 years. Gastrointestinal system followed by musculo skeletal system was majorly affected due to ADRs. Among anti neoplastic drugs cisplatin followed by Adriamycin+cyclophosphamide with paclitaxel were responsible for causing ADRs in this study.

CONCLUSION

In conclusion of our study the results indicate that ADRs occur during hospitalisation. Males were more affected to ADRs than females. The wide spectrum of ADRs affecting the most was gastrointestinal system followed by dermatology and central nervous system. In majority of these studies ADRs observed were classified under Type A reactions. The higher prevalence of ADRs were observed in anti microbials followed by anti tubercular and anti neoplastics. In anti microbial class cephalosporins and beta lactams have shown higher incidence of ADRs. For safety and rational use of antimicrobials, implementation of antimicrobial guideline policy and strict adherence to it should be established. The main limitation of these studies was the rate of ADR related hospitalisation due to miss classification or under reporting in India. So there is a need to develop a positive attitude towards pharmacovigilance among pharmacist and other healthcare professionals to reduce drug related reactions.

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