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Original Article

Evaluation of Predisposing Factors Associated with Suspected Adverse Drug Reactions of Hospitalized Patients

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ABSTRACT

Objectives: To study the incidence and to evaluate the risk factors of suspected adverse drug reactions developed in the hospitalized patients of various departments and to assess the causality and severity of adverse drug reactions (ADRs). **Methods:** It was a retrospective-prospective study conducted in a tertiary care hospital for a period of two years two months, with a specific predefined criterion. A total of 254 subjects with ADRs were identified during the period of study for which 1:1 ratio of subjects with non-ADRs were taken. Subjects of all age groups and of either sex were enrolled. Risk factors included subjects' age group, gender, polypharmacy, comorbidity, intercurrent diseases and concurrent interactive drugs. **Statistical analysis used:** Multiple logistic regression analysis was performed to find the association of risk factors with adverse drug reactions. **Results:** The incidence of suspected adverse drug reactions in hospitalized patients was13% (254/1952, 95%CI). Polypharmacy was the most significant predictor of adverse drug reactions (OR=55.952; 95%CI). Elderly population with multidrug therapy had developed the higher rate of ADRs. Cephalosporin's 27.6%, fluoroquinolones 15.5%, penicillamines 12.1%, anti-hypertensive 8.7%, NSAIDs 8.3% were more frequently implicated. Risk factors for suspected ADRs were: age (more than 60 years) (OR=1.033: 95% CI), gender [Male (OR=55.952; 95% CI)], comorbidity (OR=1.008; 95% CI), intercurrent diseases (OR=19.27; 95% CI). **Conclusion:** Polypharmacy, history of ADR, concurrent interactive drugs and inter current disease were the significant risk factors of adverse drug reactions. The elderly population was the vulnerable age group for ADRs. Multidrug therapy and comorbidity resulted in higher risk of ADRs in an older population. The Higher rate of suspected ADRs were probable and very less severe.

Key words: Adverse drug reaction, Age, Comorbidity, Polypharmacy, Risk factor.

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INTRODUCTION

Adverse drug reactions are one of the significant health problems in the vulnerable age groups.[1] In the day to day modern life, medications became part of the pocket. The rate of drug use is increasing proportionally to the occurrence of new diseases, and multiple drug usage becomes a risk for developing adverse drug reactions. As per the World Health Organization, an adverse drug reaction (ADR) is defined as an "unintended and noxious response to a drug that occurs at doses normally used for the prophylaxis, diagnosis, or therapy of diseases, or for the modification of physiological function".[2] It is the leading cause of morbidity and mortality and has a major impact on the public health by imposing an economic burden on the society and healthcare systems. From the literature survey, about 10 – 20% of the hospitalized patients may experience at least one ADR during their hospitalization stay, and 5% of all hospital admissions are the result of an adverse drug reaction.[3] Prevalence of adverse drug reactions increases with age.[4] A study from the United Kingdom estimates that 1225 hospital admissions were due to ADRs.[5] A prospective spontaneous reporting study from the Indian set up revealed that 3.7% of hospitalized patients experienced the ADRs and 0.7% of hospital admissions were due to the adverse drug reactions.[6] There are various factors which predispose patients to adverse drug reactions. Literature had shown that female gender was considered as the major risk factor for occurrence of adverse drug reaction.[7,8,9,10] Along with this, some other risk factors like age, multiple drug regimen, intercurrent diseases, comorbidity, history of adverse drug reactions to the drug class, concurrent interactive drugs were also considered.[11] But there is diversity in the effect of predisposing factors to the development of adverse drug reactions.[12] It is because of different study settings, study designs, study population, the time duration of the study, statistical methods, ethnicity, race, etc.[13] There are many methods have been developed for assessing the causality relationship between the adverse drug reactions and suspected drugs. But the commonly used causality assessment scale is World Health Organization – Uppsala Monitoring Centre (WHO-UMC) causality categories scheme, but it is a complex process to determine the cause of suspected ADR.[14] Time efficient and simplified probability scale "Naranjo ADR probability scale" is developed for feasibility.[15] The importance of the present study was to study the incidence, to evaluate risk factors, the causality and severity of adverse drug reactions.

MATERIALS AND METHODS

This retrospective-prospective study was conducted at a tertiary care hospital in South India. Cases were differentiated from controls with specific predefined criteria. Cases were the subjects' who developed the adverse drug reactions after the prescribed drugs during hospitalization. These cases were identified during the regular ward rounds of various specified departments like General Medicine wards (male and female), Paediatrics ward, OBG ward, Dermatology ward, Psychiatry ward, Orthopaedic ward (male and female) and ICU.[11] Data were collected from the case sheets of the suspected patients. Subject and care-taker

were interviewed about the previous medical and medication history, co-morbid conditions, lifestyle and diet which were also updated inpatient case sheet for future reference. Retrospectively case data was collected from the reported documents which were stored in drug information centre and control data from the medical record database of the hospital. The patients who had no ADR were selected as controls. The severity of suspected adverse effects was assessed as mild, moderate and severe by using the specific standard scale called Hart wig and Siegel's scale, and the Naranjo`s algorithm was used to assess the causal relationship between the suspected drug and ADR. For evaluating the risk factors, in association with information obtained from subjects, various supportive resources like Pharmacology textbooks, databases like Micromedex and Lexi comp were also used.

The qualitative data were presented as frequencies and percentages. The quantitative data were presented as the mean and standard deviation. Chi-square test was used as the test of significance for categorical variables. Independent samples *t*-test for two groups and Analysis of Variance (ANOVA) test was used as the test of significance for quantitative variables. A logistic regression analysis was performed to find the association of predisposing factors for adverse drug reactions. Statistical Package for Social Services (SPSS vs. 20) was used.

Ethical issues

Ethical approval was obtained from the BMCH and RC Institutional Ethics Committee and no objection certificate was taken (BMCH and RC/MS/2016-17/338) from the Medical Superintendent of the hospital BMCH and RC, Chitradurga, Karnataka, India. Written informed consent was received from the subjects before enrolling into the study.

RESULTS

The criteria were fulfilled by 508 subjects, who were included in the study. During the study period, a total of 1,952 subjects were admitted as inpatients to the hospital. A total of 254 subjects had adverse drug reactions and thus had an incidence rate of 13% (254/1952; 95% CI). About 87% of the study subjects had no experience of adverse drug reactions (Table 1). Distribution of the study group according to age had shown that most of the cases and controls belonged to the age group 21 – 50 years. About 20.5% of the adverse drug reactions occurred in subjects of 41 – 50 years of age group followed by 18.1% in 61 – 70 years and 16.1% in 21 – 30 years (Table 2). By the distribution of cases as per gender, females (50.8%) developed more adverse drug reactions than males (49.2%) (Table 3). The Adverse drug reactions were higher when the medication was consumed orally (52.4%). It was followed by intravenous route of administration (31.1%), intramuscular, inhalation, nebulization, subcutaneous and topical routes (Table 4). The association of predisposing factors with adverse drug reactions had shown that Polypharmacy was the premier significant risk factor of adverse drug reactions with an odds ratio of (Odd`s 55.952, 95 CI). Age more than 60 years, male gender comorbidity showed no significant association with the adverse drug reactions. Patients with intercurrent diseases had 19.297 times of higher risk for adverse drug reactions with P-Value 0.001, 95 CI. H/o adverse drug reactions had shown a significant association with adverse drug reaction (Odds 10.285, 95 CI). Concurrent interactive drugs were also a significant risk factor of adverse drug reactions (Odds 2.016, 95 CI) but in our observations comparatively, it showed less risk of ADR occurrence than other factors. (Table 5). The subjects who consumed the drug as tablet form developed more adverse drug reactions (49.2%) followed by injection form (38.6%), ointment (3.5%), nebulizer (3.1%) and syrup (2.8%). Other dosage forms were less frequently resulted in adverse drug reactions. In the study, all the cases underwent causality assessment by using Naranjo`s scale. In this 60.2% cases were probable followed by possible in 32.7% of the cases (Table 6). The severity of adverse drug reactions was assessed by using Hart wig and Siegel's Scale. About 31.9% of the cases had moderate level 3 reactions, 24.4% had mild level 2 reactions, and 16.5% had moderate level 4A reactions. Very less number of cases (3.9 %) had severe reactions (Table 7). ADRs were assessed for the preventability by using Modified Schumock and Thornton scale. Out of 254 (100%), ADR developed patients, 45.7% of cases were preventable, 45.3% of cases were probably preventable and very less proportion were non-preventable cases (4.7%)

Table 1: Incidence of adverse drug reactions in the study group.

Particulars	Frequency	%
Adverse drug reactions	254	13.0
No adverse reactions	1,698	87.0
Total	1,952	100

Table 2: Distribution of ADRs according to age group.

Age group	Adverse drug reactions		Total
	No n (%)	Yes n (%)	
0 – 1 Year	24 (9.44%)	11 (4.3)	35
1 – 10 Years	49 (19.29%)	12(4.7%)	61
11 – 20 Years	21 (8.27%)	15 (5.9%)	36
21 – 30 Years	26 (10.23%)	41 (16.14%)	67
31 – 40 Years	41 (16.14%)	33(12.9%)	74
41 – 50 Years	30 (11.9%)	52 (20.5%)	82
51 – 60 Years	27(10.62%)	32(12.6%)	59
61 – 70 Years	26(10.23%)	46 (18.11%)	72
71 – 80 Years	05 (1.96%)	10 (3.93%)	15
81 – 90 Years	5 (1.96%)	2 (0.78%)	7
Total	254	254	508

Table 3: Distribution of ADRs according to gender.

Gender	Adverse drug reactions			Total
	No	Yes	%	
Female	125	129	50.8	254
Male	129	125	49.2	254
Total	254	254	100	508

Table 4: Distribution of ADRs according to drug route of administration.

Route of administration	ADRs	%
Intra Muscular (IM)	07	2.8
Inhalation (INH)	05	2.0
Intravenous (IV)	79	31.1
Intravenous + Per Oral (IV + PO)	03	1.2
Nebulization (NEB)	03	1.2
Nebulizer + Intravenous (NEB + IV)	01	0.4
Per Oral (PO)	133	52.4
Per Oral + Intravenous (O + IV)	04	1.6
Subcutaneous (SC)	10	3.9
Topical (T)	09	3.5
Total	254	100.0

Table 5: Predisposing factors for Adverse drug reactions.

	Predisposing factors	Adverse drug reactions		Odds ratio	P value
		Yes n (%)	No n (%)		
Age	More than 60 years	37 (14.6)	36 (14.2)	1.033	0.072, NS
	Less than 60 years	217 (85.4)	218 (85.8)		Reference
Gender	Male	125 (49.2)	129 (50.8)	1.209	0.338, NS
	Female	129 (50.8)	125 (49.2)		Reference
Poly pharmacy	Yes	4 (18.1)	1 (0.4)	55.952	0.000, Sig
	No	208 (81.9)	253 (99.6)		Reference
History of ADR	Present	15 (5.9)	2 (0.8)	10.285	0.001, Sig
	Absent	239 (94.1)	252 (99.2)		Reference
Concurrent interactive diseases	Present	4 (1.6)	0	2.016	0.045, Sig
	Absent	250 (98.4)	254 (100)		Reference
Intercurrent drugs	Present	18 (7.1)	1 (0.4)	19.297	0.001, Sig
	Absent	236 (92.9)	253 (99.6)		Reference
Multiple illness	Yes	3 (1.2)	1 (0.4)	1.008	0.315, NS
	No	251 (98.8)	253 (99.6)		Reference
Others	Present	4 (1.6)	1 (0.4)	1.818	0.178, NS
	Absent	250 (98.4)	253 (99.6)		Reference

Table 6: Assessment of causal relationship by Naranjo`s scale.

Naranjo`s Scale	Frequency	Percentage
Definite	14	5.5
Not done	04	1.6
Possible	83	32.7
Probable	153	60.2
Total	254	100.0

Table 7: Assessment of severity by Hart wig and Siegel's Scale.

Hartwig and Siegel's Scale	Frequency	Percent
Mild level 1	22	8.7
Mild level 2	62	24.4
Moderate level 3	81	31.9
Moderate level 4 a	42	16.5
Moderate level 4 b	23	9.1
Not done	14	5.5
Severe level 5	10	3.9
Total	254	100.0

Table 8: Assessment of ADRs as per Modified Schumock and Thornton's scale.

Modified Schumock and Thornton's scale	Frequency	Percent
Definitely preventable	116	45.7
Non-preventable	12	4.7
Not done	11	4.3
Probably preventable	115	45.3
Total	254	100.0

(Table 8). ADRs affected the various organs of the body, which were classified according to the WHO-ART classification. The highest proportion of ADRs was developed in the organ skin and appendages (74) followed by general disorder (57), gastrointestinal system (46) and central and peripheral nervous system disorder (21) (Table 9). From the observations of the study, it was identified that 43.7% of cases underwent additional treatment. The patients with adverse drug reactions were observed for the dechallenge or alteration of the dosage of the drug. dechallenge was not done in 69.3% of the cases, about 15.7% of the cases did not improve, and 9.8% of the cases were improved. About 46.5% of subjects with adverse drug reactions recovered during the hospital stay before discharged. The duration of recovery from the adverse drug reactions had shown that about 11.4% of the cases had recovered within 1 days itself, followed by 10.2% of cases had recovered within 4 days, 9.4% and 8.7% of cases were recovered within 2 days and 4 days, 4.7% of cases were recovered within 05 days, 4.3% of cases recovered within 06 days. About 53.9% of cases developed adverse drug reactions to the suspected drugs consumed at a frequency of twice a day. The suspected drug was withdrawn after occurrence of adverse drug reactions in 50.4% of the patients and continued in 49.6% of the patients. 7.9% of subjects with adverse drug reactions underwent drug alteration. About 83.9% of subjects developed ADRs to suspected drugs within a week duration of drug exposure, followed by 5.9% cases with in the duration of one week to 01 month of suspected drug exposure, 3.1% of cases had developed ADRs after 1 month to 1 year of drug use and 4.3% of cases had developed ADRs after more than one year of suspected drug exposure. The higher proportion of ADRs were developed by antibiotics (29.5%), followed by anti-hypertensive (8.7%) and NSAIDs (8.3%). Cephalosporin's (27.6%) are majorly identified suspected drug class of antibiotics followed by fluoroquinolones (15.5%) and penicillamines (12.1%). In the cephalosporin's the drug ceftriaxone with ATC code J01DD04 induced adverse drug reactions at a frequency 27 as follows abdominal pain, angioedema, cough, diarrhoea, dysentery, skin rashes, itching with redness of the skin, urticarial. Among fluoroquinolones, ofloxacin and ciprofloxacin

Table 9: Distribution of ADRs according to Organ system.

Organ affected	Frequency	ADRs
Skin and appendages	74	Steven Johnson syndrome, hyperpigmentation, urticaria, skin rashes
General disorder	57	Fever, swelling of limbs, edema
Gastrointestinal system	46	Vomiting, constipation, diarrhea
Central and peripheral nervous system disorder	21	Drowsiness, headache, tremors
Vision disorder	10	Blurred vision, lacrimation, conjunctivitis
Respiratory system disorder	9	A cough, breathlessness, asthma
Psychiatric disorder	8	Anxiety, depression
Metabolic and nutritional disorder	6	Hyperglycemia, hypoglycemia
Cardiovascular system	5	Chest pain, hypertension hypotension
Liver and biliary system	5	Hepatitis
Platelet, bleeding and clotting disorder	5	Bleeding
Endocrine disorder	3	Cushings syndrome
Vascular disorder	3	Thrombocytopenia, Lymphadenopathy Vasculitis
Red blood cell disorder	1	Anemia
Urinary system disorder	1	Kidney damage

induced adverse drug reactions such as chest pain, arthralgia, skin disorders, and diarrhoea repeatedly. In anti-hypertensive, amlodipine (13.8%) induced ADRs had higher proportion followed by telmisartan (3.4%).

DISCUSSION

In day to day life, medication is playing a significant role both positively and negatively. In the regular clinical practice, while prescribing, the clinicians should consider the potential benefits and risks of the treatment. The adverse drug reactions are the salient cause of complications, morbidity and mortality in all age groups of patients.[13,16-19] Many predisposing factors predispose to adverse drug reactions including sex, increased number of drug exposures, advanced age, length of hospital stay and functions of excreting organs.[20] This study aimed to determine the incidence of adverse drug reactions and their predisposing factors in a south Indian tertiary care hospital setting. The following predisposing factors were considered in the study, age, gender, polypharmacy, comorbidity, intercurrent disease, history of ADR to the drug class, concurrent interactive drugs.

The current study shows that the incidence of adverse drug reactions was 13% which is higher than ADR incidence reported in South Africa.[21] Another study[22] showed that, the incidence of adverse drug reactions was 11.75% which is almost similar to this study. The incidence of definite and probable ADR was 15.9% and 17.7%.[23] Comparatively, it is lesser than the UK study which showed an incidence of a 16% and German study had an incidence of 38% of ADRs.[19,24]

Predisposing factors were considered based on patient related factors, disease related factors and drug related factors. Drug related factors are the drug dose, frequency and Polypharmacy. Patient related factors are the age, gender, pregnancy, foetal development, renal function, and allergy. Disease related factors are the comorbidities, intercurrent disease. Based on the limitations of study design we only included the following predisposing factors.

Age was not a significant risk factor of identified adverse drug reactions in our study. But higher proportion of adverse drug reactions was developed in the patients aged above 40 years. The age greater than 40 years can be attributed to the increase in number of diseases and thus increased use of drugs and thus increasing the number of ADRs. Another explanation can be due to low body water and larger body fat in elderly persons than younger ones which increases the concentration of the drugs. In a similar study the median age of the patients with adverse drug reactions was 30 years ranging from 24 – 42 years.[25] Literature showed that the mean age of the patients was 61 years with age ranging from 1 to 98 years.[26] In an another study on children, the age was a significant factor for the occurrence of ADRs.[23]

Females outnumbered males in an occurrence of adverse drug reactions in this study. But gender was not a significant predisposing factor for adverse drug reactions. A higher number of ADRs in female population was because of lower body weight and more body fat than men and lower concentration of hepatic enzymes.[27] In contrary to these results, males outnumbered females.[22] Another similar study showed that sex was not the significant predisposing factor for adverse drug reaction among children.[23,5] Observed that females (70%) were commonly involved in adverse drug reactions than males (30%).[25]

Polypharmacy was the premier significant risk factor identified in our study with an Odds ratio (Odds 55.952, 95 CI). The patients with five to seven prescribed drugs during the hospital stay had a higher risk of adverse drug reactions. Our study findings showed 18.1% of cases developed adverse drug reactions due to polypharmacy. Comparatively, it is lesser than the study conducted in the elderly patients 70%.[28] This difference could be due to the difference in the methodological aspects of the study particularly the study population and the direct supervision of healthcare team over the patient in the wards. The geriatric population of 61-70 years age group developed 38.6% of adverse drug reactions due to polypharmacy comparatively lesser than the study conducted where it was 70%.[28] The synergistic effect of two or more drugs can be toxic even more than the drug when administered alone. The risk of peptic ulcers in the elderly patient's increases by 10% with the use of NSAIDs compared to others. The simultaneous use of NSAID with corticosteroid increases

the risk of peptic ulcer by 15 times than people who are not using any drugs.[29]

Multiple diseases in a patient make him/her more vulnerable to adverse drug reactions.[27] In the current study, very less percentage (1.2%) of population developed adverse drug reactions due to comorbidity with an odd's ratio of 1.008 and showed no significant association with adverse drug reactions. Another study from India had noted that each additional diagnosis increases the odds of experiencing ADR by 1.2 times.[30]

History of ADR, concurrent interactive drugs and intercurrent disease had an odd's ratio of more than 1 and shown significant association with adverse drug reactions. The history of ADR causes drug independent cross-reactive antigens which can trigger the sensitizations and becomes drug allergy and cross sensitivity. The stimulation of the T cell and antibodies increase the chance of subsequent ADRs.

The suspected drug wise distribution had shown that ceftriaxone (27) resulted in the higher proportion of ADRs which belonged to general anti-infective with ATC J01DD04. Acetaminophen followed it in 17 patients, Ipratropium bromide and ambroxol in 10 patients each. Bisoprolol and Carvedilol were implicated in cardiac failure, Fentanyl, Midazolam, Promethazine and choral hydrate resulted in sedation withdrawal, warfarin for raised INR and haemorrhage, Diaz oxide for pulmonary enema, Fentanyl, Ketamine and Midazolam for respiratory depression, Fentanyl, Sevoflurane, Isoflurane, and Ketamine were implicated in respiratory arrest and Vincristine was implicated in peripheral neuropathy.[23] Agents affecting cardiovascular system including cardiac stimulants glycosides/ similar drugs and antihypertensive drugs were commonly implicated in adverse drug reactions. Among the analgesics/ antipyretics/ anti-inflammatory drugs, NSAIDs and anti-rheumatics, Opioids and related analgesics were involved in the causation of adverse drug reactions.[31] Another similar study showed that cardiovascular drugs accounted for 26.6% of the ADRs followed by antibiotics (20.1%), anticoagulants (26.6%) and Opioids (10.6%).[26]

The suspected adverse drug reactions affected various organs of the body and are classified according to the WHO ART classification. The organ skin and appendages developed the higher proportion of adverse drug reactions (73) followed by general disorder (57), GI system (46). But the literature shows that GI system is most commonly involved organ followed by cardiovascular disorders, body general disorders, skin, and appendages.[22,25] It could be due to the difference of drug exposure duration, geographical area, race, ethnicity and climatic conditions.

In the current study, causality assessment was done for suspected ADRs, which showed that 60.2% of cases were probable followed by 32.7% of the cases were possible. From the study of Shah *et al*., causality results were observed as 66.66% of the cases fell into a possible group, 28.07% in the probable category and while in 5.26% of the cases it was found to be "certain".[25] Another study observed that the 42.0% ADRs were probable, possible in 30.5% and 20.2% were unlikely in children.[23] From the reported suspected adverse drug reactions, about 31.9% of the cases had moderate level 3 reactions, 24.4% had mild level 2 reactions, and 16.5% had moderate level 4A reactions. Very less number of cases (3.9 %) had severe reactions. Another similar study had shown that 19.29% had a severe reaction, 68.42% had moderately severe, and 12.28% had mild reactions.[22,5] Noted that 44% of the patients had moderate drug reactions, 43% had mild, 12% had severe and 1% had life-threatening adverse drug reactions.[25]

The ADRs were assessed for the preventability by using Modified Schumock and Thornton scale. Out of 254 (100%), ADR developed patients, 45.7% of cases were preventable and very less proportion were non-preventable cases (4.7%). In an another similar study findings it was that the majority of the ADRs were not preventable (45.61%), 36.84% were preventable, and 17.54% were probably preventable.[22,10] It was noted that 7% of the reactions were preventable, 29.2% were probably preventable and 63.8% were not preventable at all.[26]

CONCLUSION

This ambispective study concluded that the risk of suspected adverse drug reactions was high in the geriatric population with multidrug therapy. Polypharmacy was a significant risk factor of ADRs. History of ADR to the drug class and intercurrent diseases were statistically significant, but they do not impose much risk for the occurrence of adverse drug reactions. A Higher proportion of adverse drug reactions was notified in the population with tablet dosage form through oral route followed by intravenous route of administration. Majority of ADRs were probable followed by possible. A Higher proportion of ADRs was moderate and very less proportion of ADRs was serious.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ADR: Adverse drug reaction; **AE:** Adverse event; **CI:** Confidence Interval; **DIC:** Drug Information Centre; **DUE:** Drug utilization evaluation; **M&E:** Monitoring and evaluation; **NSAIDS:** Non Steroidal Anti-Inflammatory Drugs; **OR:** Odds Ratio; **PEM:** Prescription event monitoring; **PVC:** Pharmacovigilance Centre; **SJS:** Steven Johnson Syndrome; **TB:** Tuberculosis; **TEN:** Toxic Epidermal Necrolysis; **UMC:** Uppsala Monitoring Centre; **WBC:** White Blood Cells; **WHO:** World Health Organization.

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