J Young Pharm, 2017; 9(4): 598-604
A multifaceted peer reviewed journal in the field of Pharmacy
www.jyoungpharm.org | www.phcog.net

Original Article

An Intensive Monitoring of Adverse Drug Reactions among Elderly Patients Hospitalized in Medical Wards of a Tertiary Care Hospital

Dinesh Zaverbhai Kamejaliya[1], Jigar Dilipkumar Kapadia[2], Chetna Kalpan Desai[2]*, Mira Kiran Desai[2]
[1]P. D. U. Medical College, Rajkot, Gujarat, INDIA.
[2]Department of Pharmacology, B. J. Medical College, Ahmedabad, Gujarat, INDIA.

ABSTRACT

Objective: To evaluate the pattern of adverse drug reactions in elderly patients hospitalized in medical wards at a tertiary care hospital in India. **Methods**: Elderly patients ≥ 60 years hospitalized in three randomly selected medical units were enrolled and followed up daily till discharge. Detailed information of patients and ADRs were recorded by interviewing patients, doctors and nurses. Appropriateness of drug treatment in patients≥65 years was analyzed using Beer's criteria. ADRs were assessed for incidence, onset, duration, management, outcome, causality, severity, preventability, seriousness and risk factors. **Results**: A total of 1017 patients were enrolled (mean age: 69.5±7.6 years); majority (80.9%) suffered from >1 ailments. Patients received 6.3±0.5 drugs, commonly by oral (48%) and intravenous (41.6%) routes. Inappropriate drug therapy was observed in 76 patients of ≥65 years. ADRs were observed in 107(10.7%) patients, majority occurred within first week, commonly affected GI (29.9%), central and peripheral nervous system (17.8%) and were frequently associated with antimicrobials (44.2%), drugs acting on CVS (13.3%) and endocrine systems (12.5%). Majority of reactions were mild (55.1%), non-serious (73.8%), not preventable (85.9%), recovered completely at discharge (87.8%) and had possible causal association with suspect drug (68.2%). Age>80 years, ≥3 diseases, prescription of >10 drugs and hospitalization for>4 days were risk factors for occurrence of ADRs. **Conclusion**: Adverse reactios are common in elderly and were frequently affect gastrointestinal, central and peripheral nervous systems. Reactions are mild, non-serious and commonly caused by antimicrobials and drugs acting on cardiovascular or endocrine systems. Multiple diseases, polytherapy, age>80 years and hospitalization>4 days increase the risk of ADRs.

Key words: Intensive Monitoring, Elderly Patients, Medical Inpatients, Tertiary Care, Risk Factors.

Key points: The study provides information regarding drug exposure in elderly patients hospitalized to medical units and the pattern of adverse drug reactions in these patients. Causal drugs and associated risk factors are also studied in the present work.

Correspondence

Dr. Chetna Kalpan Desai, Professor, Department of Pharmacology, B. J. Medical College, Asarwa, Ahmedabad- 380016, Gujarat, INDIA.

Phone: +91-9904011644

Email: drdesaichetna@gmail.com

DOI: 10.5530/jyp.2017.9.114

INTRODUCTION

'National Policy on Older Persons' adopted by Government of India defines 'elderly' as person who is of age 60 years or above.[1] A steady increase in elderly population is evident over past decades. Globally, it is estimated that elderly population will become 2 billion by 2050.[2] Elderly persons comprise 8.0% of total population in India[1] and 8.3% of total population in Gujarat.[3]

Elderly persons undergo various physiological changes e.g. decrease in lean body mass, increase in body fat etc. Also, functioning of vital organs is decreased and various pharmacokinetic and pharmacodynamic changes occur.[4] These factors lead to altered response to drugs. Further, multiple diseases in elderly account for polytherapy which increases the risk of ADRs. Incidence of ADRs in elderly (11-32%)[5-8] is higher as compared to general population, which increases the burden on health-care system[7,9] and adversely affects patient compliance.

Intensive hospital-based monitoring, done by a group of doctors, nurses or others screening a defined population, can detect incidence of ADRs and provide detailed and accurate information. Currently, data of ADRs in Indian elderly patients is limited. Hence, the present study was conducted to evaluate the pattern of ADRs in elderly inpatients, using the intensive method of ADR monitoring.

METHODS

This prospective, observational study was conducted in elderly patients hospitalized to three randomly selected medical units of a tertiary care teaching hospital in Gujarat. The study was carried out over a period of 18 months i.e. from December 2013 to May 2015. Prior permissions to conduct the study were obtained from Institutional Ethics Committee (EC/Approval/32/14) and Head of Department of Medicine. All patients of either gender, aged 60 years or more, admitted to selected medical units and willing to participate in the study were enrolled. Patients not willing to participate and those transferred to other medical units or departments after admission were excluded, except if they were transferred for management of an ADR.

Investigator visited the selected units daily and monitored each enrolled patient for treatment details and occurrence of ADRs. Patients were followed up till discharge. Details were collected from case records and interview with patients, doctors and nurses on duty and recorded in a pretested Case Record Form (CRF). Attending doctors and nurses were informed about the study and were requested to inform any ADR observed in these patients. ADRs were classified using WHO Adverse Reaction Terminology.[10] Data were entered in Microsoft Excel® worksheet 2007 and analyzed.

Data analysis: Data were presented as frequency, percentages or mean ± SEM as applicable. Demographic details, diagnosis of patients and incidence of ADRs were analyzed using frequency and percentage analysis. Appropriateness of drug treatment was analyzed using Beer's criteria.[11] Adverse reactions were analyzed for causality using WHO- UMC scale[12] and Naranjo's score,[13] severity using Modified Hartwig & Siegel Scale[14] and preventability using Modified Schumock and Thornton's criteria.[15] Risk factors for occurrence of ADRs were analyzed using Chi square test. P value of <0.05 was considered statistically significant.

RESULTS

A total of 1017 elderly patients were enrolled during the study period (average of 56.6 patients per month). These included 486 males and 531 females (male: female ratio: 1:1.09) with a mean age of 69.5 ± 7.6 years. Age wise distribution of patients was: 60-69 years (620, 60.9%), 70-79 years (255, 25%) and ≥80 years (142, 13.9%).

Most patients (823, 80.92%) suffered from more than one ailments including cardiovascular diseases (683, 67.15%), infectious diseases (538, 52.90%), endocrine disorders (479, 47.10%), respiratory disorders (382, 37.56%) and CNS disorders (254, 24.97%). None of the patients was admitted due to occurrence of an adverse drug reaction.

Mean duration of hospitalization in these patients was 6.33 ± 0.09 days (range: 2 to 20 days). Mean duration of hospitalization in patients suffering from single disorder (5.95±0.20 days) was similar to that in patients with multiple co-morbidities (6.43±0.11 days) (P>0.05, student's t test). Duration of hospitalization in patients suffering from ADR (7.40 ± 0.17 days) was significantly higher than that in patients who did not develop ADRs (6.21 ± 0.10 days) (P=0.0002, student's t test).

A total of 6418 drugs were prescribed to these patients (6.30 ± 0.5 per patient). Most common drugs prescribed were those acting on GIT (1252, 19.51%), antimicrobials (1175, 18.31%), drugs acting on CVS (954, 14.86%) and vitamins, minerals and supplements (848, 13.21%) (Table 1). Drugs were prescribed by oral (3082, 48.02%) intravenous (2667, 41.56%), sublingual (223, 3.47), subcutaneous (214, 3.33), inhalational (172, 2.68%), intramuscular (32, 0.49%) and topical (28, 0.44%) routes. Total drug encounters were 88195 (13.69±0.10 encounters/patient/day), including 41758 and 35452 encounters with oral and i.v. routes respectively.

Appropriateness of drug therapy was evaluated in 733 (72.07%) patients of age ≥ 65 years using Beer's criteria. Therapy was found to be inappropriate in 76 (10.37%) patients. This included category A defects (use of drugs which generally should be avoided in elderly) in 74 patients and category B defects (use of doses that exceed maximum recommended daily dose) in two patients.

Adverse reactions were observed in 107 patients (10.7%) including 52 (10.7%) males and 55 (10.3%) females. ADRs were observed in patients of 60-69 years (75, 70.09%), 70-79 years (24, 22.43%) and ≥80 years (8, 7.48%) (Mean age: 67.28 ± 6.53 years). Patients of ≥80 years suffered significantly more number of ADRs compared to other age groups (P<0.05, Chi square test).

Ninety three ADRs (86.9%) occurred within first week of hospitalization, 10 (9.35%) occurred during second week and four (3.74%) after two weeks (mean duration of onset of ADRs: 5.17 ± 0.36 days) (Table 2). ADRs affecting musculoskeletal, hearing and vestibular and respiratory systems had late onset as compared to ADRs affecting gastrointestinal system, CNS, body as a whole, CVS, skin and appendages, psychiatric and metabolic and nutritional systems (P<0.001, ANOVA). ADRs recovering completely during hospital stay (94, 87.8%) had a mean duration of 2.46 ± 0.12 days. This duration was significantly longer in ADRs affecting skin and appendages, musculoskeletal system and special senses compared to those affecting GIT, CNS, metabolic system, cardiovascular system, psychiatric disorders and general disorders (P<0.05, ANOVA) (Table 2).

ADRs commonly affected GI (32, 29.9%) central and peripheral nervous (19, 17.97%), metabolic and nutritional (10, 9.35%), skin and appendages (9, 8.41%) and psychiatric (9, 8.41%) systems (Table 2). A total of 120 drugs were suspected to cause ADRs (Table 3), including >1 suspect drug in 12 (11.21%) patients. Antimicrobials and drugs acting on CNS were associated with an increased occurrence of ADR as compared to drugs acting on CVS, hematological system, analgesics and vitamins, minerals and supplements (P<0.05, Chi square test) (Table 1). Intravenous route was more commonly associated with ADRs (n=57, 47.5%) compared to oral route (n=46, 38.33%), however, the difference was not significant (P>0.05, Chi square test).

Majority of ADRs (94, 87.8%) recovered during the hospital stay. Few ADRs (9) were continuing i.e. dry cough (4), metallic taste (3), weakness (2) or recovering (4) i.e. hypokalemia (1) and tinnitus (3) at time of discharge. Hospitalization was prolonged in 25 patients due to ADRs (23.36%) which included hyperkalemia (1), hypokalemia (1), rash (9), muscle ache (3), vomiting (5), and diarrhea (6). Adverse reactions requiring withdrawal (20.5%) or additional treatment (42%) are mentioned in Table 4.

Most ADRs were non-serious, mild in severity, not preventable and possibly associated with suspected drugs (Figure 1). Age ≥80 years, prescription of >10 drugs, hospital stay >4 days and presence of ≥ 3

Table 1: Medicines prescribed to elderly medical inpatients at a tertiary care teaching hospital in India (N=1017)

Classification of drugs	Number of drugs (% of total drugs)	Drugs associated with ADRs (% drugs, % of ADRs)
Drugs acting on gastrointestinal tract	1252 (19.51)	-
Antimicrobials	1175 (18.31)	53 (4.51, 44.17)*
Drugs acting on cardiovascular system	954 (14.86)	16 (1.68, 13.3)
Vitamins, minerals, supplements	848 (13.21)	2 (0.24, 1.67)
Drugs acting on hematological system	510 (7.95)	9 (1.76, 7.5)
Drugs acting on endocrine system	495 (7.71)	15 (3.03, 12.5)
Drugs acting on respiratory system	414 (6.45)	-
Drugs acting on renal system	280 (4.36)	11 (3.93, 9.17)
Drugs acting on central nervous system	260 (4.05)	12 (4.61, 10.0)*
Analgesics and anti-inflammatory drugs	195 (3.03)	2 (1.03, 1.67)
Others**	35 (0.55)	-
Total	**6418 (100)**	**120 (100)**

*P<0.05 was considered statistically significant compared to drugs acting on CVS, hematological system, analgesics and vitamins, minerals and supplements [Chi square test] [**zinc calamine lotion, polyvinyl alcohol, hydroxypropyl methylcellulose, boric acid powder, dimethicone]

Table 2: Onset and duration of ADRs (n=107) affecting different organ systems in elderly medical inpatients at tertiary care teaching hospital in India

Organ system classification	Clinical manifestations	Onset of ADRs in days (Mean± SEM)	Duration of ADRs in days[@] (Mean± SEM)
Gastrointestinal system disorder	Nausea (12), diarrhoea (6), vomiting (5), epigastric pain (4), abdominal pain (3), constipation (2)	3.31 ± 0.33	2.31 ± 0.17
Central and peripheral nervous system disorder	Headache (12), giddiness (7)	3.32 ± 0.29	2.10 ± 0.15
Body as a whole – general disorders	Chills (2), shivering (1)	3.67 ± 1.33	1.33 ± 0.30
Cardiovascular disorders	Palpitation (5)	4.2 ± 1.2	1.60 ± 0.24
Skin and appendages disorders	Rash (9)	4.44 ± 0.24	4.11 ± 0.26[#]
Psychiatric disorders	Sedation (8), drowsiness (1)	4.63 ± 0.53	2.22 ± 0.22
Special senses disorders	Metallic taste (5)	5.2 ± 0.37	4.30 ± 0.33[#]
Metabolic and nutritional disorder	Hypoglycemia (8), hypokalemia (1), hyperkalemia (1)	6.1 ± 0.41	1.44 ± 0.33
Musculoskeletal disorders	Muscle ache (3), weakness (3), fatigue (1)	10.28 ± 1.14**	4.50 ± 0.64[#]
Hearing and vestibular disorder	Tinnitus (3)	13.67 ± 2.33**	-
Respiratory system disorders	Dry cough (4)	16.0 ± 1.47**	-
Application site disorder	Swelling at injection site (1)	-	-

[@]Duration was calculated for those ADRs which recovered completely during hospitalization: **P< 0.001 compared to gastrointestinal system, CNS, body as a whole, CVS, skin and appendages, psychiatric and metabolic and nutritional disorders (ANOVA) [#]P< 0.05 as compared to general, metabolic and nutritional, cardiovascular, CNS, psychiatric and GIT disorders (ANOVA)

Table 3: Drugs suspected to cause ADRs (n=120) in elderly medical inpatients at a tertiary care teaching hospital in India

Name of Drug	Number of patients receiving the drug	Number of patients developing ADRs (%)	ADRs according to system affected (number of ADRs observed)
Chloroquine	121	10 (8.26)	Gastrointestinal system disorders (10)
Insulin	169	10 (5.92)	Metabolic and nutritional disorders (9), application site disorders (1)
Metronidazole	107	9 (8.41)	Skin and appendages (6), gastrointestinal system disorders (3)
Ciprofloxacin	96	8 (8.33)	Skin and appendages (6), gastrointestinal system disorders (2)
Ceftriaxone	213	7 (3.29)	Gastrointestinal disorders (6), skin and appendages disorders (1)
Cetirizine	86	7 (8.14)	Psychiatric disorders (7)
Isosorbide dinitrate	196	6 (3.06)	Cardiovascular disorders (4), central and peripheral nervous system disorders (2)
Amoxicillin + clavulanic acid	234	5 (2.14)	Gastrointestinal system disorders(4), skin and appendages disorders (1)
Mannitol	72	5 (6.94)	Central and peripheral nervous system disorders (5)
Metformin	163	5 (3.07)	Special senses disorders (5)
Amlodipine	232	4 (1.72)	Central and peripheral nervous system disorders (4)
Enalapril	369	4 (1.08)	Respiratory system disorders (4)
Furosemide	142	4 (2.82)	Musculoskeletal system disorders (4)
Phenytoin	52	4 (7.69)	Central and peripheral nervous system disorders (4)
Amikacin	71	3 (4.22)	Hearing and vestibular system disorder (3)
Atorvastatin	391	3 (0.77)	Musculoskeletal system disorders (3)
Azithromycin	136	3 (2.2)	Gastrointestinal system disorders (3)
Cefixime	194	3 (1.55)	Gastrointestinal system disorders (3)
Clopidogrel	175	3 (1.71)	Central and peripheral nervous system disorders (3)
Artesunate	126	2 (1.59)	Gastrointestinal system disorders (2)
Aspirin	274	2 (0.73)	Gastrointestinal system disorders (2)
Iron salts	36	2 (5.55)	Gastrointestinal system disorders (2)
Parenteral fluids	451	2 (0.44)	Body as a whole- general disorders (2)

Table 3: Con

Nitroglycerine	27	2 (7.4)	Cardiovascular system disorders (1), central and peripheral nervous system disorders (1)
Spironolactone	109	2 (1.83)	Metabolic and nutritional disorders (1), psychiatric disorders (1)
Diclofenac	82	2 (2.44)	Gastrointestinal system disorders (2)
Cefotaxime	73	1 (1.73)	Skin and appendages disorders (1)
Chlorpheniramine	11	1 (9.09)	Psychiatric disorders (1)
Primaquine	42	1 (2.38)	Gastrointestinal system disorders (1)
Vancomycin	62	1 (1.61)	Body as a whole-general disorders (1)

Table 4: ADRs requiring withdrawal of drug/change in treatment (n=22) and requiring additional treatment (n=45)in elderly medical inpatients at tertiary care teaching hospital in India

ADRs (n)	Suspected drugs that were withdrawn or replaced (number of ADRs observed)
Diarrhea (4)	Cefixime (3), Amoxicillin+Clavulanic acid (1)
Headache (4)	Amlodipine (4)
Dry cough (4)	Enalapril (4)
Rash (3)	Cefotaxime (1), Amoxicillin+Clavulanic acid (1), Ceftriaxone (1)
Tinnitus (3)	Amikacin (3)
Vomiting (2)	Chloroquine (2)
Hyperkalemia (1)	Spironolactone (1)
Hypokalemia (1)	Insulin (1)
ADRs (n)	**Drugs used for management of ADRs**
Rash (15)	Chlorpheniramine
Nausea, vomiting (14)	Ondansetron
Hypoglycemia (8)	Dextrose 5%, 10%
Diarrhea (4)	Oral rehydration salt
Epigastric pain (3)	Famotidine
Hypokalemia (1)	Potassium chloride

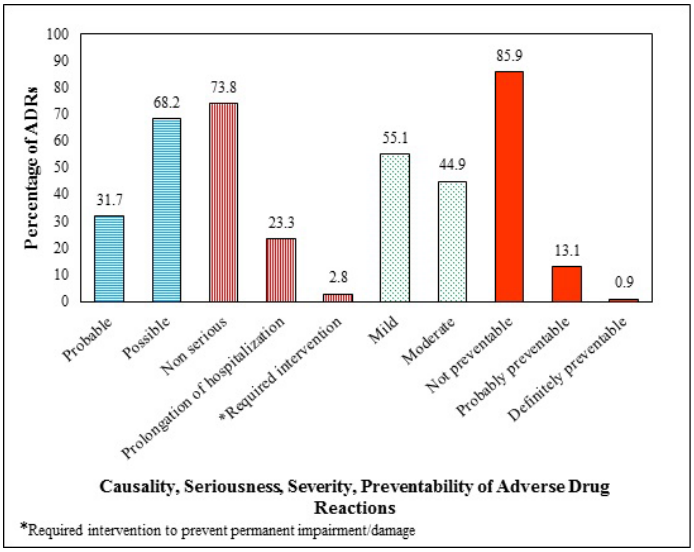

Figure 1: Causality, seriousness, severity and preventability of Adverse Drug Reactions (n=107) among elderly medical inpatients at a tertiary care hospital in India. [Causality: WHO-UMC scale, Severity: Modified Hartwig and Seigel scale, Preventability: Modified Schumock and Thornton's criteria].

Table 5: Risk factors for the occurrence of ADRs in elderly medical inpatients at tertiary care teaching hospital in India (N=1017)

Risk factor	Number of patients with ADR (%)	Number of patients without ADR (%)	
Gender			
Male	52 (10.7)	434 (89.3)	
Female	55 (10.3)	476 (89.7)	0.91
Age			
60-69 years	75 (12.1)	545 (87.9)	
70-79 years	24 (9.4)	231 (90.6)	0.29
≥ 80 years	8 (5.6)	134 (94.4)	0.02*
Number of drugs			
≤ 5	3 (3.95)	73 (96.05)	
6-10	79 (9.73)	733 (90.27)	0.14
≥ 11	25 (19.38)	104 (80.62)	0.001#
Number of disorders			
1	11 (5.67)	183 (94.33)	
2	23 (8.39)	251 (91.61)	0.28

Table 5: Con

3	41 (12.58)	285 (87.42)	0.01@
4	20 (14.08)	122 (85.92)	0.01@
5	12 (14.81)	69 (85.19)	0.01@
Duration of hospitalization (days)			
1-4	1 (0.3)	308 (99.7)	
5-9	94 (17.7)	438 (82.3)	0.000$
≥ 10	12 (6.8)	164 (93.2)	0.000$

*p< 0.05 as compared to 60-69 years, #p< 0.05 as compared to less than 5 and 6-10 drugs, @p<0.05 as compared to 1 disorder, $p< 0.001 as compared to 1-4 days (Chi square test)

diseases were identified as risk factors for occurrence of ADRs in these patients (Table 5).

DISCUSSION

The present study was conducted to evaluate the pattern and characteristics of ADRs in elderly inpatients at a tertiary care teaching hospital in Gujarat, India. The study was conducted in three randomly selected medical units using an intensive method of ADR monitoring over a period of 18 months.

Most patients in the present study belonged to the age group of 60 to 69 years (~ 61%) and 70 to 79 years (25%). Lourdu *et al* also reported a similar pattern of age distribution in a study conducted to evaluate drug utilization pattern in geriatric medical inpatients at Puducherry.[16] Pattern of age distribution contributed to the mean age of 69 years in the current study, similar to that (72.6 years) reported by by Jhaveri *et al* in a study conducted at Bhavnagar to evaluate the drug utilization pattern and pharmacoeconomics in geriatric medical inpatients.[17]

Majority (80.9%) of patients suffered from more than one ailment which increases the risk of development of ADRs, similar to the findings of Nayaka *et al* in a study conducted to evaluate drug utilization pattern in geriatric medical inpatients at Bengaluru, India[18] and Shah *et al* in a study conducted to evaluate drug utilization pattern in geriatric patients in Gujarat, India.[19] A loss of functional reserve in the elderly renders them prone to development of multiple disorders, the commonest manifestation in the current study being cardiovascular disorders (67.1%). Prevalence of cardiovascular diseases increases from about 40% in 40-59 years of age to 70-75% in 60-79 years of age.[20] Infections (52.9%) were also frequent in the study population and can be contributed by a reduction in immunity with aging.[21] Metabolic disorders (47.1%), common with increasing age, were also frequent. These disorders, often associated with complications such as hypertension, ischemic heart disease or vascular complications, influence the morbidity pattern in elderly. Incidence of CNS disorders (24.9%) in the study population was higher than younger age groups.[22] These diseases are more frequent with an advancing age, particularly after the age of 75 years.[23] Jhaveri *et al,* in a study conducted at Gujarat, India, reported cardiovascular disorders as major cause of hospitalization (80%) followed by CNS (22%), hematological (19%), endocrine (19%), respiratory (18%) and renal diseases (16%).[17] Further studies are required to determine the pattern and cause for regional variations in the disease patterns observed.

Elderly patients were hospitalized for nearly one week, however, the duration was prolonged in patients suffering from ADRs and hospitalization of more than 4 days was identified as a risk factor for ADRs. Increased hospital stay poses an extra burden on the healthcare system and can be challenging in a developing country like India. Harugeri *et al*., in a study to evaluate the frequency and nature of ADRs in elderly inpatients at two medical colleges in India, estimated 2.2% of bed occupancy due to ADRs, accounting for 18000 bed days and 24.84 million Rs. at any given time in India.[8]

Multidrug therapy in study population (average 13.6 exposures/patient/day) was primarily attributable to multiple co-morbidities. GIT drugs (19.5%) were frequently prescribed although patients did not suffer from GI disorders primarily and use can be presumed to prevent or treat GI ADRs. Also, infections, treated with multiple antimicrobials (average 2.18 antimicrobials/patient), contributed to the number of drugs prescribed. Optimal use of antimicrobials can help reduce cost, ADRs and risk of antimicrobial resistance. Drugs acting on CVS (14.8%) were also frequently used since CVS disorders were frequent in the study population. Frequent use of vitamins, minerals and supplements (13.2%), however, requires further evaluation. Multidrug therapy is usually associated with an increased risk of ADRs, however, in the current study, risk was found to be increased only in patients receiving more than 10 drugs. Further studies are recommended to substantiate this finding.

While frequent use of oral drugs (48%) was a good prescribing practice[24] observed in the current study, intravenous drug use was also high (40.2%) and needs further evaluation. Use of intravenous drugs can increase the cost of treatment and ADRs. Other routes were less commonly employed, primarily attributed to selection of drugs. Jhaveri *et al* also reported frequent use of oral (47.2%) and parenteral drugs (45.1%) in their study.[17]

Adverse reactions were more frequent (10.7%) in elderly inpatients when compared to the general population i.e., 3-6%.[25] While multidrug therapy increased the risk of ADRs in elderly, PK-PD changes are also suggested to play a role in this population.[4] A similar incidence (14.6%) was reported by Gray *et al* in a study conducted in Wisconsin to evaluate ADRs in 157 hospitalized patients of 70 years or more.[5]Although gender difference was not present in elderly with regards to incidence of ADRs, age ≥ 80 years was associated with an increased risk as compared to age 60-69 years in the current study. This is also supported by findings of Mandavi *et al.*[26]

Inappropriate drug therapy was less frequent (10.4%) and suggested a good prescribing practice. Shah *et al.* had reported a 23% incidence of inappropriate drug therapy in elderly,[27] however, the study included both inpatients and outpatients (400).

Majority of ADRs (87%) occurred within a week of hospitalization and coincided with the duration of hospital stay. Also, serious and non-serious ADRs demonstrated a similar onset, which is important with regards to management and reporting of ADRs. Short duration (average 2.46 days) and recovery of ADRs during the hospital stay (88%) suggested mild nature and effective management. This also reflected in severity assessment suggesting mild to moderate severity of majority of ADRs. Of note, ADRs affecting skin and appendages, musculoskeletal system and special senses lasted for longer duration and contributed to increased duration of hospitalization.

GI adverse reactions were most common (30%) in the study population similar to the pattern in general population. Similar incidences of GIAEs were reported by Harugeri *et al.* (29%) and Gray *et al.* (32%) also, suggesting that drugs used in elderly frequently lead to GIAE. Treatment and prevention of these ADRs is crucial to ensure patient compliance. Central and Peripheral nervous system ADRs (18%) i.e., headache (11.2%) and giddiness (6.5%) were common with drugs like isosorbide dinitrate, mannitol and amlodipine and reflected action of these drugs on hemodynamics. Such ADEs, however, are nonspecific, often being associated with disease process, which needs consideration during causality assessment.

Metabolic and nutritional disorder ADRs (9.35%) included hypoglycemia and hypokalemia with insulin and hyperkalemia with spironolactone. Protective mechanism against hypoglycemia is impaired in elderly[28] which increases the risk of hypoglycemia with insulin. Since it is commonly precipitated by missing meal after insulin injection, it can be effectively addressed by patient education. Disturbance in serum potassium levels, however, requires close monitoring as it can lead to complications such as arrhythmias. These ADRs can be potentially serious and often require treatment or withdrawal of suspect drug, which was also observed in study population. Rash (8.4%) was the only ADR affecting skin and appendages. The ADR was associated with antimicrobials, however, it can occur with any drug being a hypersensitivity type of reaction. Psychiatric disorder ADRs (8.4%) i.e. sedation and drowsiness were primarily associated with antihistamines having significant CNS penetration. These reactions are often associated with adverse events such as falls in elderly and warrants caution.

Musculoskeletal system disorder ADRs (6.54%) i.e. muscle ache, weakness and fatigue were associated with furosemide and atorvastatin. Weakness and fatigue are known ADRs associated with diuretic treatment. Also, muscle related symptoms are the commonest ADRs with statins [29] and require monitoring for early detection of myopathy. Cardiovascular disorder ADRs (4.6%) i.e. palpitations were observed with nitrates and reflected reflex tachycardia due to vasodilation by nitrates. Special senses disorder ADRs included metallic taste (4.6%) associated with metformin (4.2%). Being non-serious in nature, it did not warrant special attention. Dry cough (3.7%), a respiratory system disorder ADR was observed with enalapril. It is caused due to inhibition of breakdown of bradykinin by ACE inhibitors and requires discontinuation of drug in 10-15% patients. Withdrawal was also required in the present study in patients developing dry cough. Hearing and vestibular system disorder ADRs included tinnitus (2.8%) with amikacin. Since it represents an early sign of ototoxicity, amikacin was withdrawn in these cases. ADRs affecting body as a whole-general disorder (2.8%) i.e., chills and shivering were associated with parenteral fluids and vancomycin. These reactions, however, are often not preventable. Application site disorder ADRs included swelling at the injection site of insulin (1) and can be addressed by patient education. Common suspect drugs in the current study were antimicrobials and drugs acting on CVS and endocrine system, although the risk was more with antimicrobials and drugs acting on CNS. In their study, Shah *et al.* reported antimicrobials, drugs acting on CVS and CNS as common causal drugs,[9] however, the pattern is likely to vary according to local prescribing practices and selection of drugs.

Causal association with suspect drug was "possible" in majority of cases (68.2%), owing to lack of dechallenge, presence of co-morbidities which produce similar symptoms and more than one suspect drug. Shah *et al* reported a 66.6% possible causal association of ADRs with suspect drugs in elderly.[9] Serious ADRs (26%) in the present study usually prolonged the hospital stay i.e. hyperkalemia, hypokalemia, rash, muscle ache and vomiting or diarrhea. Some serious ADRs required intervention to prevent permanent damage e.g. tinnitus. A similar incidence of serious ADRs (30%) was reported by Bates *et al.*[30] Treatment of serious ADRs is particularly important to limit morbidity in elderly hospitalized patients.

ADRs which required additional treatment or prolonged the hospital stay (45%) were classified as moderately severe (modified Hartwig and Seigel scale). Remaining ADRs did not require drug withdrawal, additional treatment/antidote and were mild in nature. Moderately severe ADRs (67-69%) have been reported in elderly patients by Harugeri *et al* and Shah *et al*[8,9] and contribute to increased cost of therapy. Only 14% ADRs were preventable, which is a positive finding when compared to the incidence (30-70%) reported by other studies.[8,9]

CONCLUSION

Adverse drug reactions are common in elderly inpatients, usually within first week of hospitalization. Reactions, mostly mild and non-serious, are common with antimicrobials, drugs acting on cardiovascular and endocrine system and frequently affect gastrointestinal and central and peripheral nervous systems. Comorbidities, polypharmacy, age more than 80 years and longer duration of hospitalization increase the risk of adverse reactions.

FUNDING

This study was funded by none.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ACKNOWLEDGEMENT

The authors would like to thank Dr. Asha Shah, Professor and head, Department of Medicine, Civil Hospital, Ahmedabad for permitting to conduct the study in the Department of Medicine and all the patients who participated in the study and supported the research.

ABBREVIATION USED

ACE: Angiotensin converting enzyme; **ADR:** Adverse drug reaction; **ANOVA:** Analysis of variance; **CNS:** Central nervous system; **CVS:** Cardiovascular system; **GIT:** Gastrointestinal tract; **GIAE:** Gastrointestinal adverse event; **PK-PD:** Pharmacokinetic-pharmacodynamic; **SEM:** Standard error of mean; **WHO-UMC:** World health organization- Uppsala monitoring center.

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Article History: Submission Date : 22-05-2017 ; Revised Date : 27-06-2017; Acceptance Date : 19-08-2017.
Cite this article: Kamejaliya DZ, Kapadia JD, Desai CK, Desai MK. An Intensive Monitoring of Adverse Drug Reactions among Elderly Patients Hospitalized in Medical Wards of a Tertiary Care Hospital. J Young Pharm. 2017;9(4):598-604.