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Adverse drug reactions & their risk factors among Indian ambulatory elderly patients

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***Background & objectives*: Several studies have reported adverse drug events ranging from 5 to 35 per cent in all age group from outpatient setting. However, adverse drug reactions (ADRs) particularly among a large sample of ambulatory elderly patients in India has not been reported. This study has attempted to identify ADRs and assessed their causality, preventability and severity, and also their risk factors in Indian ambulatory elderly patients.**

***Methods*: A 2 year long term prospective study included 4005 ambulatory elderly patients (60 yr or above; either sex) at a public teaching hospital. Suspected ADRs were assessed for causality, preventability and severity using Naranjo's probability scale, modified Schumock and Thornton's criteria, and modified Hartwig's criteria, respectively.**

***Results*: Of the total 4005 prescriptions, 406 were identified with ADRs, giving the occurrence of 10 per cent ADRs in elderly. The total number of ADRs was 422 in 406 prescriptions. Type A ADRs accounted for 46 per cent of the total ADRs. Majority of the ADRs (88.6%) were classified as 'probable'. The definitely preventable reactions were 22 per cent. The percentage of moderate reaction was 16 per cent. Only 1.6 per cent ADRs was severe in nature. The most common type of ADR was peripheral oedema. The most commonly offending class of drug was cardiovascular drugs (57.6%). Using logistic regression analysis, the risk factors which contributed to ADRs were age above 80 yr (OR=1.7), prescription of multiple drugs (OR=1.8), longer duration of treatment (OR=2.28) and multiple diagnoses (OR=1.8).**

***Interpretation & conclusions*: In this study, 10 per cent ambulatory elderly patients were found to have ADRs. This indicates that the elderly patients should be closely monitored for ADRs, to avoid clinically significant harmful consequences. The awareness of risk factors of ADRs would help physicians to identify elderly patients with greater risk of ADRs and, therefore, might benefit from ADRs monitoring and reporting programme.**

Key words ADRs - ambulatory elderly patient - risk factors

Adverse drug reactions (ADRs) are a major cause of morbidity and repeated ADRs related hospitalizations have consistently increased faster than first-time ADRs among elderly patients[1]. Majority of studies have shown that prevalence of ADRs is higher in the elderly as compared to adult[2].

In USA, more than 90 per cent of adults aged 65 yr and older use one medication per week and 10-25 per cent experience an adverse drug reaction. These ADRs are responsible for 3.4 to 7.0 per cent of hospital admissions[3]. The proportion of outpatients with an ADR ranges from 5 to 35 per cent in all age group of patients[4].

Although, the literature review has shown the lack of Indian studies to identify ADRs especially among Indian ambulatory elderly patients, one study conducted among elderly inpatients has reported that one third of hospitalized elderly experienced 419 ADRs[5]. It has been argued that old age is not a predictor for adverse drug reactions but merely a marker for co-morbidity, altered pharmacokinetics, altered pharmacidynamics and polypharmacy[6]. Of all the factors that are most consistently associated with adverse drug reactions, polypharmacy is considered to be the most important. In the elderly patients, the multiplicity of disorders requires the use of multiple drugs[7]. In addition, their altered pharmacokinetics and pharmacodynamics result in an enhanced sensitivity to many drugs. Studies from overseas as well as India have demonstrated that polypharmacy is prevalent and associated with increased potential for adverse drug reactions, inappropriate prescription and drug interactions[8,9].

Adverse drug reaction (ADR) monitoring and reporting activity is in its infancy in India. The important reason is lack of awareness and lack of interest of healthcare professionals in ADR reporting and documentation. A study conducted to determine the level of awareness of physicians about ADR and the extent of their involvement in pharmacovigilance activities showed that despite good observation and knowledge of ADR among physicians the rate of ADRs reporting and documentation is very low[10]. Therefore, this study was aimed to identify ADRs and assess their causality, preventability and severity, and also their risk factors in Indian ambulatory elderly patients.

Material & Methods

A prospective study was carried out in geriatric clinic of Government Medical College and Hospital (GMCH), Chandigarh. The data of 4115 patients were collected from geriatric clinic between July 2009 to February 2011.

All patients aged ≥60 yr who visited the geriatric clinic during the study period, and were prescribed medication(s), were included in the study. Data on demographic details and prescribed medications were collected using structured format. For each patient, a form was completed with regard to patient age, gender, diagnosis, past medications, currently prescribed drugs, their brand names, daily doses, treatment durations, indications for each drug, laboratory investigation reports. Data of 110 patients with incomplete information were excluded. Therefore, a total of 4005 prescriptions were included for analysis.

International Classification of Disease (ICD-10)[11], was used for coding the diagnosis and Anatomical Therapeutic Chemical (ATC)[12] classification was used for medications. The adverse drug reactions based on the causes were classified on the basis of Edward & Aronson classification system. According to this, there are six types of ADRs namely Type A (augmented pharmacologic effects), Type B (bizarre effects), Type C (chronic effects), Type D (delayed effects), Type E (end-of-treatment effects) and Type F (failure of therapy)[13].

Identification of adverse drug reactions: Suspected ADRs were assessed for causality, preventability and severity using Naranjo's probability scale[14], modified Schumock & Thornton's criteria[15] and modified Hartwig's criteria[16], respectively. The degree of association of an ADR with a drug was done with the help Naranjo's algorithm which involves assigning score to a set of questions. The total score for a particular ADR was calculated and the association was termed into one of these categories– definite (score >9), probable (score 5-8), possible (score 1-4) or doubtful (score 0). Modified Schumock and Thornton's criteria[18] have three sections namely definitely preventable, probably preventable and not preventatable, each consists of three questions. Severity was identified using Modified Hartwig's criteria[19] which involve seven severity levels. Severity of the identified ADRs was assessed at different levels, ranging between 1 and 7. Levels 1 and 2 indicated mild, 3 and 4 considered as moderate and level 5 and above, as severe ADRs. The potential risk factors assessed were age, sex, number of medications, number of diagnoses and duration of treatment.

The study protocol was approved by the ethics committee of Government Medical College & Hospital, Chandigarh. Each patient gave written informed consent. Each patient was assigned a sequential identification number.

Statistical analysis: The results are represented as mean ± SEM and percentages as applicable; age, diagnosis, number of medications and duration of treatments were variable for determination of risk factors. Odds ratio was calculated to assess the most common risk factors for ADRs. Statistical significance was determined at 95 per cent level of confidence. The data were analyzed using Sigma Stat package (Ver. 3.5).

Results

A total of 2208 male and 1797 females were included in the study (55 vs 45%). The average age of patients was 68.28 ± 0.11 yr. Of the 4005 patients, 2402 patients belonged to the age group 60-69 yr (60% of total) while 30.8 per cent of the patients belonged to the age group 70-79 yr and the remaining (9.2%) were more than 80 yr of age.

It was found that approximately 69 per cent of the patients suffered from two or more diseases. On an average, each patient had 2.01±0.01 diagnoses; 41 per cent of patients were diagnosed as having 2 co-morbidities; 21 per cent had 3 co-morbid conditions and 7.4 per cent had a range of 4 to 6 co-morbidities. The most common pair of diseases was hypertension-diabetes, coronary artery disease-hypertension or diabetes, hypertension-cerebrovascular disease, diabetes-polyneuropathy and coronary artery disease-digestive disorder. It was found that 97 per cent of the patients suffered from diseases of circulatory system followed by digestive system disorders (48%) and endocrine, nutritional, metabolic diseases accounted for 44 per cent. Hypertension (64.8%), diabetes mellitus (36%) and ischaemic heart disease (24.7%) were the most frequently reported disorders.

The average number of medications prescribed was 6.45±0.04. The distribution of medication followed the normal Gaussian distribution. Over half of the patients (57.9%) received more than five medications concurrently. The average duration of prescribed medication was found to be 36.25±0.42 days.

Most prescriptions (90%) did not have any ADRs. The total number of ADRs was 422 in 406 prescriptions. The most commonly identified ADRs were peripheral oedema, dry cough and drowsiness (Table I). The other ADRs were ataxia, dystonia, eczema, incontinence, oral ulcer, vertigo, sinusitis, xerosis, increased prothrombin time, atrial fibrillation and renal failure. The most common offending class of drug according to ATC classification was the cardiovascular drugs, followed by haematinics, antiplatelet agents and heparin and low molecular weight heparin and drugs used to treat neurological disorders (57.5% >12.7% >10%). Type A ADRs accounted for 46 per cent of the total ADRs.

Over 88.6 per cent of the ADRs were probable (n=374) with a score of 5-8. Only 11 were definite (with score equal or over 9) and 37 ADRs were possible type with score range of 1-4. Of the total 422 ADRs, most (73%) belonged to the category of "not preventable". Definitely preventable ADRs were 22 per cent and probably preventable were only 6 per cent. Based on modified Hartwig severity scale, most of the reactions were categorized as mild (348 of 422), 67 ADRs were moderate type and only seven ADRs were 'severe' in nature.

Using logistic regression analysis, it was found that patients of more advanced age (over 80 yr) were at significant risk for ADRs as compared to the patients of age group 60-69 yr. In this study, patients with multiple diseases, multiple medications and longer duration of treatment were more likely to have ADRs. There was no difference in the occurrence of ADRs in female as compared male patients (OR=1.09; CI=0.88-1.35). The effect of variables on the ADRs is depicted in Table II.

Discussion

ADRs were found in 10 per cent of elderly patients in this study which was lower as compared to 21 per cent reported by Schneider *et al*[17]. A recent study has reported the ADRs related hospitalization rate as 5-12 per cent among elderly and increase in ADR-related hospital admissions in elderly by 143 per cent[18].

Adverse drug reactions and non-compliance are important causes of hospital admissions in the elderly patients. Other studies reported high proportion (30.4%) of hospital admissions were ADRs related among elderly patients[19]. In the present study, 11 patients required hospitalization to manage the condition. The possible reason for these differences may be differences in ADRs reporting and documentation and use of broad definition of ADRs. It is known that frail elderly patients appear to be particularly at risk of ADRs. It is known that elderly patients have reduced renal clearance and literature supports the use of low dose of digoxin. In this study, five patients were prescribed high dose and

Table I. List of commonly identified adverse drug reactions (ADRs) and drugs/class

Identified ADRs	Identified drugs/Class	Frequency (No./422)
Peripheral oedema	Amlodipine, Pioglitazone	89
Dry cough	ACE inhibitors, Imipramine	46
Drowsiness, daytime sleep, dependence	Benzodiazepines, Amitryptyline, Chlordiazepoxide, Gabapentin	29
Constipation	Ferrous supplement	26
Hypotension & hypertension	Prednisolone, ARBs, ACE inhibitors, Diuretics, α blockers, β blockers	35
Bleeding	Warfarin, Aspirin	24
Bradycardia	Amiodarone, β blockers	20
Fall	Benzodiazepines	18
Skin reactions	Tramadole, Torsemide, Phenytoin, Glimipride, Gatifloxacin	17
Blurred vision and dryness of mouth	Amitryptyline	17
Hypovolemia	Diuretics, ARBs	17
Gastritis	Risodronate, Alendronate, NSAIDs, Simvastatin, Warfarin, Aspirin, Diacerin	16
Myopathy	Atorvastatin, Rosuvastatin, Simvastatin	10
Hyperkalemia & Hypokalemia	ACE inhibitors, Digoxin, Diuretics	10
Headache	Isosorbide mononitrate	9
Digoxin toxicity	Digoxin	5
Raised LFT & hepatitis	Atorvastatin, Rosuvastatin, Anti-tuberculosis drugs, Methotrexate	5
Hyperglycaemia & hypoglycaemia	Hypoglycaemic agents, Prednisolone, Gatifloxacin, Glucosamine, Insulin	5
Thrombocytopenia and thyrotoxicosis	Amiodarone, Methotrexate	5
Tachycardia, dizziness	Prazosin, Thyroxine, Gabapentin, doxophyllin, Theophylline, ARBs	4
Ataxia, dystonia, eczema, incontinence, oral ulcer, vertigo, sinusitis, xerosis, increased prothrombin time, raised TLC atrial fibrillation and renal failure	Diuretics, Azithromycin, Aspirin, Phenytoin, Orlistat, Acenocoumarol, Imatinib, Glycazide, Isosorbide dinitrate, Metoclopromide, Amiodarone, digoxin	15

ADR, adverse drug reactions; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; NSAIDs, non-steroidal anti-inflammatory drugs; LFT, liver function test; TLC, total leukocyte count

experienced digoxin toxicity. This can be reduced by increasing the awareness among healthcare professionals regarding drugs.

The most commonly identified ADR was peripheral oedema (89 of 422) due to amlodipine. Calcium channel blocker (CCB) related oedema is caused by preferential arteriolar or pre-capillary dilation without commensurate dilation in the venous or post-capillary circulation. Reported frequency rates for peripheral oedema with CCB therapy are quite varied ranging from 5 per cent to as high as 70 per cent[20]. Correction of oedema was done by physician with dose reduction or drug withdrawal.

The second most common ADR was ACE inhibitors induced dry cough. Cough may occur within hours of the first dose of medication, or its onset can be delayed for weeks to months after the initiation of therapy. The prevalence of ACE inhibitor-induced cough has been reported to be 5-35 per cent in patients treated with these agents[21]. Women, individuals with ACE genotype II, and those of black or Asian ethnicity have been reported to be at increased risk of ACE inhibitor-induced cough. Angiotensin II receptor blockers (ARBs) confer many of the same haemodynamic benefits as ACE inhibitors, but these do not directly inhibit ACE activity or inhibit the

Table II. Risk factors associated with adverse drug reactions (ADRs)

Variable	Total no. of patients	Patients with ADR	Odds ratio (95% confidence interval)	*P* value
All	4005	406		
Age (yr)				
60-69	2402	215	1 (reference)	
70-79	1232	138	1.3 (1.02-1.6)	0.03
≥80	371	53	1.7 (1.21-2.37)	0.001
No. of medication				
<6	1678	138	1 (reference)	
6-10	1912	211	1.4 (1.10-1.75)	0.005
≥11	415	57	1.8 (1.26-2.50)	0.001
Duration of treatment (month)				
<1	661	34	1 (reference)	
≥1	3344	372	2.28 (1.6-3.4)	0.00
No. of diagnosis				
Single	1263	83	1 (reference)	
Double	1623	183	1.80 (1.37-2.39)	0.00
Multiple	1119	140	2.03 (1.52-2.73)	0.00
Gender				
Male	2208	216	1 (reference)	
Female	1797	190	1.09 (0.88-1.35)	0.41

breakdown of bradykinin. ARBs should be acceptable substitute for ACE inhibitors in patients who have adverse events such as kinin-mediated cough[22].

The most commonly offending class of drug was the cardiovascular drugs. The drugs included in this class were CCBs (type C), ACE inhibitors (type C), digoxin (type A) and diuretics (type A). Cardiovascular medications prescribed for cardiovascular disease is challenging because treatment often requires more than one medication, which may be one of unavoidable reasons for multiple drug use and dose variation in the elderly. The finding of this study was consistent with other results where cardiovascular drugs were most often associated with ADR admissions in adults and elderly patients[23]. Drug classes like antidiabetics, oral anticoagulants and antiplatelets and narrow-therapeutic index drugs accounted for most of the ADRs in present study, as reported earlier also[24]. Majority of the reactions were type A (46%) which has also been reported by other researchers[25]. The second most common ADR was type C because elderly patients have chronic disorders. There is no published report showing prevalence of Type C reactions in elderly outpatients.

In this study the causal relation for 88.6 per cent ADRs with drug was probable; corroborating with other results showing majority of reactions as probable[26]. Only in 11 cases drugs were established with certainty for ADR as causal reason; 73 per cent of the ADRs were not preventable as patients were on chronic medications. Most of the ADRs observed in this study were found to be mild (82.5%).

In this study the suspected ADRs were not identified, but the possible risk factors related to the occurrence of ADRs were determined. The risk factors

were more advanced age (>80 yr), multiple diseases, prescription of multiple medications and longer duration of treatment. Advance age was a significant risk factor for ADRs. Possible reasons could be the changes in pharmacokinetics with advancing age.

Higher prescribing rates of medicine among elderly are associated with severity of illness and severe morbidity may influence their susceptibility to ADRs through alterations in pharmacokinetics. The results of this study also found that increased number of medications and co-morbidity increases the risk of occurrence of ADRs, which is consistent with other results[27,28].

One report has suggested that pharmacological, immunological and hormonal differences and the fact that women take more medications may explain some gender differences[29]. However, our study showed no difference in the occurrence of ADRs in male and female patients in concordance with the study by Patel *et al*[30] from England.

In conclusion, the results of our study indicate that the elderly patients should be closely monitored for ADRs, to avoid clinically significant harmful consequences. The awareness of risk factors of ADRs can help physicians to identify elderly patients with greater risk of ADRs.

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