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Original Research Article

A retrospective study of serious adverse drug reactions and associated risk factors in a tertiary care hospital

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ABSTRACT

Background: Serious adverse drug reactions (ADRs) cause physical, psychological and economic harm to patients and society. This study was undertaken to understand serious ADRs in a tertiary care hospital and risk factors associated with it.
Methods: The serious adverse reactions that occurred over a one-year period were assessed. The serious adverse drug reactions, action taken, outcome, predictability, suspect drug, causality, patient demographics and risk factors for the reaction was collected. Chi-square test was applied for observing relationships of predisposing factors for serious ADRs.
Results: Out of a total of 984 reported adverse drug reactions, 94 (9.55%) were serious. Hematological disorders (41.05%) were the common serious ADRs followed by electrolyte disturbances (18.94%). Anticancer agents were the suspect drugs for majority of serious ADRs. Serious ADRs contributed to 39 (0.05%) admissions in the hospital. Recovery occurred in 97.87% of the patients. The causality was possible in 91.48% (n=86) and probable in 8.51% (n=8) of the serious adverse drug reactions. Males, patients even with a single concomitant disease and those with more than 2 concomitant medications were at increased risk ($p<0.05$) for developing serious ADRs.
Conclusions: Serious ADRs are a significant problem in health care. Measures should be taken to detect and treat them at the earliest to reduce suffering of the patient.

Keywords: Cancer, Hematological, Causality, Predictability

INTRODUCTION

Drugs save life but they can also cause adverse drug reactions (ADRs). They place an economic burden on the patients and the health care sector. A lot of hospital resources and manpower have to be put in managing the same. If the ADR results in death, hospitalization, increase in duration of stay, disability or is life threatening, it is a serious ADR.[1] Serious ADRs resulted in 3.1% to 6.2% of hospital admissions.[2] In emergency department, ADRs of various severity were responsible for 2.5% of all visits, of which 16.7% required hospitalization.[3] A study in a secondary care hospital in India reported an incidence of 9.8% for adverse drug reactions, 3.4% of which resulted in hospital admissions.[4]

To reduce these figures and to minimize the patient suffering because of serious ADRs, it is important to

recognize them early, establish the causal relationship with drug, identify risk factors and implement measures to treat and prevent the adverse reactions. Hence, the serious ADRs in the hospital were studied along with risk factors associated with it. The objective was to identify the suspect drug, causality, action taken, outcome, predictability, and hospital admissions due to the reactions.

METHODS

The study was carried out following approval by the Institutional Ethics Committee. The one year data was collected from Medical records section of Kasturba hospital, Manipal and Department of Pharmacology which monitors adverse drug reactions. This was a retrospective study. The study period was January 2014 to December 2014. The demographic data that includes age, sex, date of diagnosis of disease, serious adverse drug reaction, action taken and outcome of reaction any suspect drug details, any other concomitant medication being taken, any coexisting disease, number of serious ADRs calculated for the specified period was collected.

Anatomical therapeutic and chemical (ATC) classification system was used for drug categories.[5] Causality of the adverse reaction was assessed using WHO-UMC system for standardized case causality assessment.[6]

The total number of hospital admissions due to serious ADRs was calculated after obtaining total number of admissions for the year. Predictability was based on Rawlins and Thompson system.[7] Risk factors, if any, for the serious adverse reactions were identified.

Statistical analysis

Mean and standard deviation (mean±SD) was used for variables with normal distribution while those without normal distribution were summarized using the median, the lower (Q1) quartile, and upper (Q3) quartile. Chi-square test was applied for observing relationships of predisposing factors for serious ADRs.

RESULTS

Overall, 984 adverse drug reactions were reported. Serious ADRs were 94 (9.55%). The median duration (days) of disease for which suspect drug was prescribed was 150 (60,170).

Gender and age

About 48.94% (n=46) were males and 51.06% (n=48) were females. The age (mean±SD) of patients with serious ADRs was 48.63±15.59 years. The age (mean±SD) of males and females who developed serious ADRs was 47.68±16.56 years and 49.56±14.70 years, respectively.

Criteria for serious adverse drug reactions

About 41.49% (n=39) of the serious ADRs (n=94) resulted in hospitalization, 41.49% (n=39) in prolonged hospitalization, 17.02% (n=16) were life threatening.

Hospital admissions

The total number of hospital admissions was 75,219. Of this, 39 admissions (0.05%) were due to serious adverse drug reactions. The median duration of hospital stay due to serious adverse drug reaction (in days) was 7 (4, 11).

Suspect drugs and serious adverse drug reactions observed

Hematological disorders (41.05%) were the common serious ADRs followed by electrolyte disturbances (18.94%). Anticancer drugs constituted the majority of serious adverse drug reactions (Table 1).

Table 1: Suspect drugs and serious ADRs.

Serious adverse drug reactions	Number	Suspect drug (no. of reactions)
Haematological disorders (n=39)		
Leucopenia	15	Cyclophosphamide (7), cisplatin (4), docetaxel (1) carboplatin (1), mycophenolate mofetil (1), tacrolimus (1)
Febrile neutropenia	12	Cyclophosphamide (4), doxorubicin (2), paclitaxel (2), docetaxel (1), cisplatin (1), vinblastine (1) 5-fluorouracil (1)
Thrombocytopenia	07	Carboplatin (2), cisplatin (2), cyclophosphamide (1) melphalan (1), lenalidomide (1)
Anaemia	03	zidovudine
Bone marrow suppression	02	Azathioprine, cyclophosphamide
Electrolyte abnormalities (n=18)		
Hyponatraemia	11	Furosemide (5), torsemide (3), hydrochlorothiazide (3)
Hypokalaemia	05	Budesonide (2), cisplatin (1), furosemide (1), prednisolone (1)
Hyperkalaemia	02	Enalapril, potassium chloride

Continued.

Serious adverse drug reactions	Number	Suspect drug (no. of reactions)
Hypersensitivity reactions (n=13)		
Stevens - Johnson syndrome	08	Methotrexate, aceclofenac, diclofenac, nimesulide, cefexime, nevirapine, phenobarbitone, phenytoin
*DRESS syndrome	02	Dapsone, phenytoin
Anaphylactic shock	1	Ceftriaxone
Anaphlylactoid reaction	1	Human albumin
Erythema multiforme	1	Phenytoin
Liver abnormalities (n=10)		
Hepatitis	10	Chlorpromazine (1), pyrazinamide (8), zidovudine (1)
Renal abnormalities (n=04)		
Renal failure	02	Ibuprofen, tenofovir
Nephritis	01	Amikacin
Nephropathy	01	Diclofenac
Others (n=10)		
Seizures	02	Chlorpromazine, clozapine
Hypoglycaemia	01	Glimepiride
Glaucoma	01	Methylprednisolone
Pancreatitis	01	Stavudine
Pleural effusion	01	Dasatinib
Hypotension	01	Indapamide
Rhabdomylosis	01	Atorvastatin
Venous thrombosis	01	Ethinyl estradiol
Diarrhoea	01	Capacitabine

*Drug Rash with Eosinophilia and Systemic Symptoms.

ATC classification of suspect drugs

The suspect drugs were classified as per ATC classification. Antineoplastic and immunomodulating agents were the major class (Table 2).

Table 2: ATC classification of suspect drugs.

L=Antineoplastic and immunomodulating agents	16
J=Antiinfectives for systemic use	09
C=Cardiovascular system	06
N=Nervous system	08
H=Systemic hormonal preparations, excluding sex hormones and insulin	03
G=Genitourinary system and sex hormones	01
A=Alimentary tract and metabolism	01
B=Blood and blood forming organs	01
V=Various	01

Action taken for the serious adverse drug reactions

Suspect drug was either stopped or continued with/ without specific treatment for almost equal number of ADRs (Table 3).

Outcome of the serious adverse drug reactions

Recovery was seen in (97.87%) of the patients while others were recovering when data was recorded.

Table 3: Action taken for adverse drug reactions.

Action taken	Number of ADRs (%)
Drug not stopped but specific treatment given	35 (37.23)
Drug stopped and specific treatment given	30 (31.91)
Drug stopped but no specific treatment given	18 (19.14)
No action - drug continued, no specific treatment given	08 (8.51)
Dose of drug reduced and specific treatment given	02 (2.13)
Dose of drug reduced, no specific treatment given	01 (1.06)

Causality of serious adverse drug reactions

This was assessed using WHO causality assessment scale. The causality was possible in 91.48% (n=86) and probable in 8.51% (n=8).

Predictability of serious ADRs

Of the 94 serious ADRs, 81 (88.42%) were predictable and 13 (11.57%) were non-predictable.

Coexisting disease and concomitant medications

Patients were receiving more than one medication either for the primary disease or coexisting disease. The primary

disease which required more than one drug were cancer, bronchial asthma, tuberculosis, AIDS, leprosy, hypertension, congestive cardiac failure and road traffic accident. The coexisting diseases were hypertension, ischemic heart disease, diabetes mellitus, bronchial asthma, HIV and epilepsy. Concomitant medications were anticancer drugs (gemcitabine, rituximab, cisplatin, vincristine, etoposide), antimicrobials, steroids, analgesics, antidiabetic agents, antiasthma drugs and drugs for cardiovascular disorders.

Suspect drug and indication

The indications for the suspect drugs ranged from cancer, cardiovascular diseases, respiratory disorders, renal diseases, electrolyte imbalance, infections, pain relief, metabolic disorders, psychiatric illness, joint diseases, fever, hypoalbuminemia, seizures, irregular menstrual cycles etc. The route of administration varied from oral, intravenous, intramuscular and inhalation. The doses of drugs were as per treatment guidelines.

Risk factors for serious adverse drug reactions

Chi square test was used. Patients with serious ADRs were compared with those who were on the suspect drugs but had either no ADRs or nonserious ADRs. Males, patients even with a single concomitant disease and those with more than 2 concomitant medications were at increased risk ($p<0.05$) for developing serious ADRs (Table 4).

Table 4: Risk factors for serious adverse drug reactions.

Variable	Odds ratio (95% CI)	P value
Gender		
Male	(reference)	
Female	0.63 (0.40-0.98)	0.042
No of concomitant diseases		
1	(reference)	
>1	0.08 (0.04-0.13)	0.000
Number of concomitant medications		
≤ 2	(reference)	
>2	2.09 (1.16-3.70)	0.013

DISCUSSION

Our study assessed serious ADRs occurring in a tertiary care hospital in one year. Serious ADRs constituted 9.55% of total ADRs that occurred during this period. This is higher than 5.42% of serious ADRs reported in another study.[8] This could be due to the fact that our study was for one-year duration and recorded serious ADRs across all departments unlike other studies which were conducted for short duration or in a particular department.[9] Studies conducted in India have put the number of hospital admissions due to ADRs at 0.12% to 0.7% of all hospital admissions.[10,11] The numbers reported are lower compared to the west- 3.2-6.5% in the USA - on account of poor reporting of ADRs in India.[12] Hospital admissions was lower (0.05%) in our study as compared to another study in India which had 0.7% ADR related admissions.[11] In another study, 73% of ADRs caused an increase in duration of stay in the hospital which is more than 41.49% in our study.[13]

Rawlins and Thompson described adverse effects as type A and type B.[7] A majority of serious ADRs in this study were type A (predictable) as they are documented in literature and dose dependent. The remaining reactions were type B as they cannot be predicted. They were the hypersensitivity reactions which can be immediate type, type II or type III reactions.

Adverse reaction can occur with any class of drugs and can affect any system. In our study, anticancer drugs were the most common suspect drug. The immediate common effect of most of the anticancer drugs is nausea and vomiting due to gastric irritation and stimulation of chemoreceptor trigger zone. Some of the ADRs due to anticancer drugs results from their pharmacological action, which affects not only cancer cells but also the normal cells.[14]

Antimicrobials are used commonly for treatment and prophylaxis of infections. They have different mechanism of action and adverse effects. Most of the patients admitted in hospitals receive antimicrobials which results in 20-50% of drug related cost. About 70% of patients in intensive care are prescribed antimicrobials either as empiric or definitive treatment. The cost of treatment due to antibiotic use includes cost of the antimicrobial and ADRs to it.[15] Diuretic use is frequently associated with side effects like electrolyte disturbances, hypotension, etc which can result in hospitalization. The patients should be monitored to detect and treat the ADR at the earliest.[16]

Age, alcohol, gender, race, pregnancy, renal impairment, hepatic dysfunction, coexisting disease, concomitant mediations, genetics, etc. also contribute to development of ADRs.[17] Advancing age increases co-morbidities, polypharmacy, alters pharmacokinetics and pharmaco-dynamics.[17] In elderly patients, comorbidities results in use of more than one medication. Also, the change in pharmacokinetics and pharmacodynamics could increase the risk of ADRs. Studies have shown that polypharmacy increases risk for ADRs and drug interactions.[18,19] In our study, gender was a risk factor as females were more prone to serious ADRs. This could be due to physiological, pharmacological, and hormonal factors.[20] All these factors should be kept in mind while prescribing so as to minimize adverse effects wherever possible.[17]

For a majority of reactions, the suspect drug was withdrawn with or without specific treatment in our study. In almost an equal number of serious ADRs, the suspect drug was continued which indicates that the benefit

associated with the use of such drugs outweighed the risk due to their adverse effects. A majority of patients recovered - this could be due to early identification of the adverse drug reaction and proper management of ADRs. Immediate measure is crucial for reactions like anaphylactic shock. If the medicine is critical to the patient, the benefit and risk from use of such drugs should be considered. The need for the drug, availability of alternatives, the treatment of ADR can guide the decision. A decrease in dose can also resolve the reaction. Otherwise, symptomatic treatment should be provided while the drug is continued.[1] If patient is on multiple drugs, the most likely suspect drug can be withdrawn first and patient observed for resolution of reaction.[1]

The management of serious ADRs has a financial implication for the patient and society. Thus, while determining success or failure of treatment, financial impact should be assessed.[21]

The limitation of the study was that it could not capture the actual figures of patients on suspect drugs in the hospital due to lack of electronic record.

To conclude, a drug produces both beneficial and harmful effects. Yet, they are prescribed as a benefit from their use is more than risk. Serious ADRs pose a problem to the quality of life of the patient. Early recognition and management of the reactions will add to the wellbeing of the patient and help to decrease cost of healthcare.

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