Original Article

An analysis of serious adverse drug reactions at a tertiary care teaching hospital

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Abstract

Objective: The objective of this study was to analyze the various aspects of serious adverse drug reactions (serious ADRs) such as clinical presentation, causality, severity, and preventability occurring in a hospital setting. **Materials and Methods:** All serious ADRs reported from January 2010 to May 2015 at ADR Monitoring Centre, Department of Pharmacology, B. J. Medical College and Civil Hospital, Ahmedabad, were selected as per the World health Organization –Uppsala Monitoring Center (WHO-UMC) criteria. A retrospective analysis was carried out for clinical presentation, causality (as per the WHO-UMC scale and Naranjo's algorithm), severity (Hartwig and Siegel scale), and preventability (Schumock and Thornton criteria). **Results:** Out of 2977 ADRs reported, 375 were serious in nature. The most common clinical presentation involved was skin and appendageal disorders (71, 18.9%). The common causal drug group was antitubercular (129, 34.4%) followed by antiretroviral (76, 20.3%) agents. The criteria for the majority of serious ADRs were intervention to prevent permanent impairment or damage (164, 43.7%) followed by hospitalization (158, 42.1%). Majority of the serious ADRs were continuing (191, 50.9%) at the time of reporting, few recovered (101, 26.9%), and two were fatal. The majority of serious ADRs were categorized as possible (182, 48.8%) followed by probable (173, 46.1%) in nature. **Conclusion:** Antitubercular, antiretroviral, and antimicrobial drugs were the most common causal drug groups for serious ADRs. This calls for robust ADR monitoring system and education of patients and prescribers for identification and effective management.

Key words: Causality, preventability, serious adverse drug reactions

INTRODUCTION

The World Health Organization (WHO) defines an adverse drug reaction (ADR) as "one which is noxious and unintended, and which occurs in doses normally used in human for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological functions."[1] ADRs are as old as medicines. The criteria for serious adverse drug reactions (serious ADRs) have been specified by the WHO and include any untoward medical occurrence at

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any dose that results in death, life-threatening, requires or prolongs hospitalization, or results in persistent or significant disability or incapacity.[2] ADRs are the leading cause of mortality and morbidity in health care and have a significant economic impact on health-care resources.[3,4] Serious ADRs account for 6.7% of all hospital admissions and occur in 10–20% of hospitalized patients.[4,5] The impact and the management of ADRs are complex as they may increase costs due to increased hospitalization, prolongation of hospital stay, additional investigations, and drug therapy in more serious cases.[6] This emphasizes the need for early detection of serious ADRs and to quantify the risk associated with the use of drugs through hospital-based ADR monitoring and reporting program. In this context, Pharmacovigilance Programme of India (PvPI) has been launched since June 2010 with the objective to ensure safe use of drugs and generate ADR data in Indian patients.[7] However, little is known about the profile of serious ADRs occurring in resource-limited countries. Hence, an attempt has been made in this study to analyze the clinical spectrum and assess seriousness, outcome, causality, severity, and preventability of the serious ADRs.

MATERIALS AND METHODS

The Department of Pharmacology, B. J. Medical College, Ahmedabad, has been a recognized Adverse Reaction Monitoring Centre since 2010 under the PvPI. The suspected ADRs were diagnosed by treating consultants, and relevant details of each ADR were collected in spontaneous ADR reporting form (www.ipc.nic.in). The details were sent to the National Coordinating Centre via Vigiflow and simultaneously ADR data were entered in the Microsoft Excel sheet. All the serious ADRs reported from January 2010 to May 2015 were identified as per the WHO-UMC criteria and analyzed to find the time relationship with the initiation of drug treatment, causal drug group, and body system as per system organ class (SOC). An association of clinical presentation of serious ADRs with the route of drug administration and number of drugs prescribed, i.e. polypharmacy was also carried out. Causality assessment was done using the WHO-UMC scale and Naranjo's algorithm.[8,9] Severity was assessed using modified Hartwig and Siegel scale whereas preventability was assessed using modified Schumock and Thornton scale.[10,11]

RESULTS

Out of 2977 ADRs reported during the study period, 375 were serious with an occurrence rate of 12.6%. There were 218 men and 157 women with a male:female ratio of 1.38:1. The mean age of patients with serious ADRs was 36.93 ± 0.83 years (mean ± standard error of mean) (95% confidence interval, 35.31–38.55 years).

Time for appearance of serious adverse drug reactions

Majority of the serious ADRs (196, 52.2%) occurred within 4 weeks of drug therapy. Out of these 196 ADRs, 62 (16.53%) occurred within a day, 54 (14.4%) occurred between 1 day and 1 week, and 80 (21.33%) occurred between 2 and 4 weeks of therapy. While 179 (47.7%) serious ADRs such as hepatitis, anemia, visual impairment, loss of hearing, and joint pain occurred after 4 weeks of drug therapy.

Clinical presentation of serious adverse drug reactions

The most common affected body system (as per system organ class [SOC]) was skin and appendages disorders (71, 18.9%) followed by liver and biliary system disorders (41, 10.9%) [Table 1].

Causal drug groups

The most common drug group causing serious ADRs was antitubercular agents (129, 34.4%) followed by antiretroviral agents (76, 20.3%) [Figure 1]. Among anti-tubercular agents, rifampicin, pyrazinamide, and kanamycin were the most common causal drugs causing hepatitis, joint pain, and impaired hearing, respectively. While in antiretroviral agents, zidovudine and tenofovir were the most common causal drugs. The antiretroviral regimens causing serious ADRs were zidovudine + lamivudine + nevirapine (51), stavudine + lamivudine + nevirapine (11), and tenofovir + lamivudine + efavirenz (09), however the details of antiretroviral regimens were not available in five cases. In addition, antimicrobials ranked the third common causal group resulted into serious ADRs in 31 (8.26%) cases. The causal agents were co-trimoxazole, co-amoxiclav, clindamycin, gentamycin, vancomycin, doxycycline, piperacillin, levofloxacin, dapsone, metronidazole, ceftriaxone, ceftazidime, etc. Further, among diuretics (16, 4.26%) and antipsychotic (15, 4%) groups, furosemide and olanzapine topped the list, respectively [Figure 1]. Other causal antipsychotics were haloperidol, risperidone, trifluoperazine, and aripiprazole.

Dechallenge

Dechallenge was positive in 134 (35.7%) patients and negative in 26 (6.93%) patients while the information was not known in majority of the patients (138, 36.8%). Moreover, dechallenge was not attempted in 77 (20.53%) patients.

Routes of administration

Out of 375 serious ADRs, in 271 (72.3%) patients, the causal drug was administered orally, 36 (9.6%)

Table 1: Details of affected body system and clinical presentation of the serious adverse drug reactions (*n*=375)

Body system affected (as per SOC)	Clinical presentation of the affected system (number of ADRs)	Number of ADRs (%) (*n*=375)
Skin and appendages	Steven-Johnson syndrome (28), maculopapular rash (26), angioedema (7), vesicular lesion (3), erythroderma (3), toxic epidermal necrosis (2), Nicolau syndrome (1), dermatitis (1)	71 (18.9)
Liver and biliary system	Hepatitis (41)	41 (10.9)
Metabolic and nutritional	Hypokalemia (13), hypoglycemia (11), weight gain (5), hypercholesterolemia (3), lactic acidosis (3), hyponatremia (2), hyperkalemia (1), hyperglycemia (1), uremia (1)	40 (10.7)
Hearing and vestibular	Tinnitus (19), loss of hearing (9), decreased hearing (5)	33 (8.8)
Gastrointestinal	Nausea and vomiting (11), diarrhea (8), abdominal pain and vomiting (4), gastritis (3), abdominal pain (2), pancreatitis (2), constipation (1)	31 (8.3)
Red blood cell	Anemia (31)	31 (8.3)
Body as a whole general	Edema (6), anaphylaxis (4), hypersensitivity reaction (3), weakness (2), chills (2), drug reaction with eosinophilia and systemic symptoms (1), laryngospasm (1), malignant hyperthermia (1)	20 (5.3)
Central and peripheral nervous system	Tremor (7), convulsion (4), peripheral neuropathy (4), giddiness (2), extrapyramidal symptoms (2), acute muscular dystonia (2), seizure (2), unconsciousness (2)	25 (6.7)
Musculoskeletal	Joint pain (19), myopathy (2), muscle pain (2), avascular necrosis (1)	24 (6.4)
Vision	blurring of vision (19)	19 (5.1)
Psychiatric	Psychosis (4), altered sleep (3), talkativeness (2), suicidal tendency (1), depression (1)	11 (2.9)
Urinary system	Nephrotoxicity (4), azotemia (2), Fanconi syndrome (1), urinary retention (1), hematuria (1)	9 (2.4)
Cardiovascular	Hypotension (5)	5 (1.3)
Application site	Abscess (4)	4 (1.1)
White cells and reticuloendothelial system	Leucopenia (2), neutropenia (2)	4 (1.1)
Endocrine	Hypothyroidism (2), moon face (1)	3 (0.8)
Vascular	Deep vein thrombosis (1)	1 (0.3)
Heart rate and rhythm	Cardiac arrhythmia (1)	1 (0.3)
Red and white cell	Leukopenia (1)	1 (0.3)
Respiratory	Respiratory depression (1)	1 (0.3)

SOC=System organ class, ADRs=Adverse drug reactions

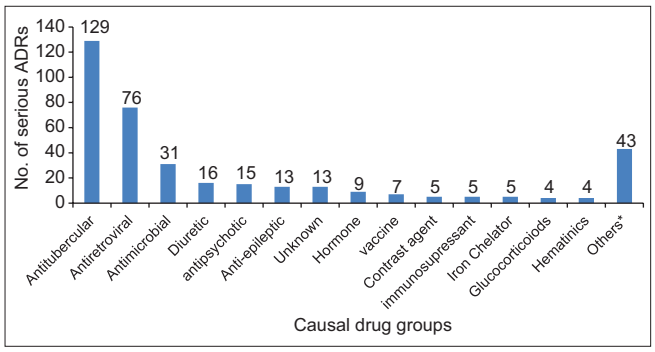

Figure 1: Details of causal drug groups causing serious adverse drug reactions (*n* = 375) (others*: Anti-amoebic, anti-diabetic, anti-cancer, anti-arrhythmic, anti-cholinergic, anti-diarrheal, anti-emetic, antitussive, anti-serum, plasma expanders, blood components, disease-modifying anti-rheumatic drugs, hematinics, nonsteroidal anti-inflammatory drugs, crystalloids, mucolytics, etc.)

received intravenously, while 58 (15.5%) received intramuscularly. In addition, 10 (2.7%) patients were treated by the routes other than oral, intravenous, or intramuscular.

Polypharmacy

Out of 375 serious ADRs, polypharmacy (≥5 drugs per prescription) was observed in 168 (44.8%) patients. Out of 168 patients, 57 received 7 drugs, 50 were prescribed 6 drugs, 40 were prescribed 5 drugs, and 21 received 8 or more drugs. In addition, 140 patients were prescribed 2–4 drugs, while 67 patients received single drug.

Criteria for serious adverse drug reactions

Out of 375 serious ADRs, majority required intervention to prevent permanent impairment/damage (164, 43.7%) followed by initial or prolongation of hospitalization (158, 42.1%). Moreover, there were 31 (8.3%) life-threatening ADRs manifested as anaphylaxis, laryngospasm, Steven–Johnson syndrome, anemia, lactic acidosis, cardiac arrhythmia, hypotension, etc., Some of them also resulted in hospitalization [Figure 2].

Outcome at the time of reporting

Majority of the serious ADRs were continued at the time of reporting (191, 50.9%), while 101 (26.9%) recovered,

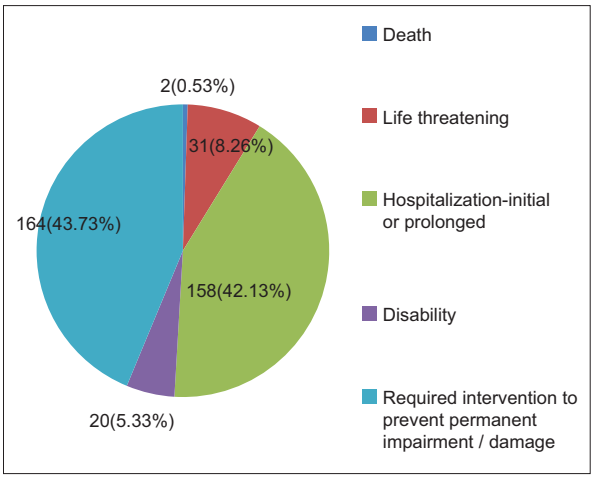

Figure 2: Details of criteria of serious adverse drug reactions (*n* = 375)

71 (18.9%) were recovering, and two were fatal due to Steven–Johnson syndrome and anaphylaxis. Outcome of 10 (2.7%) was not known due to lost to follow-up.

Causality assessment

According to the WHO-UMC scale, majority of the serious ADRs were categorized as possible (183, 48.8%) followed by probable (173, 46.1%) in nature, whereas 251 (66.9%) were probable followed by possible (122, 32.5%) as per Naranjo algorithm [Table 2].

Severity assessment

Majority of the serious ADRs (234, 63.7%) were categorized as level 2, i.e., required immediate stoppage of the ongoing treatment. Surprisingly, 92 (24.5%) serious ADRs were either the cause of hospitalization or prolongation of initial hospitalization [Table 3].

Preventability assessment

Out of 375 serious ADRs, majority (360, 96%) were not preventable; however, two ADRs were definitely preventable (previous history of drug allergy). While 13 ADRs were not assessed as patients had no prescription records and were not aware of the name or nature of the drug consumed.

DISCUSSION

This retrospective analysis of serious ADRs showed that reporting rate of serious ADRs was 12.6%. The most common clinical presentation involved skin and appendageal disorders. The common causal drug group was anti-tubercular followed by antiretroviral agents administered by oral route. The most predominant departments in reporting ADRs were antiretroviral therapy (ART) center, tuberculosis (TB) and chest disease, medicine, dermatology, and psychiatry in order of reporting. Intervention to prevent permanent impairment or damage followed by hospitalization was the most common criterion for serious ADRs. A substantial number of these ADRs continued at the time of reporting and occurred within 1 month of therapy. Majority of the ADRs were not preventable.

Table 2: Causality assessment of serious adverse drug reactions (*n*=375)

Causality	Number of serious ADRs (%) (*n*=375)	
	WHO-UMC scale	Naranjo's algorithm
Certain	7 (1.8)	1 (0.3)
Possible	183 (48.8)	122 (32.5)
Probable	173 (46.1)	251 (66.9)
Unclassified	12 (3.2)	1 (0.3)

WHO-UMC: World health Organization–Uppsala Monitoring Center, ADRs=Adverse drug reactions

Our study showed that men were commonly affected. However, Agaard *et al.* reported 60% ADRs in female,[12] and Doshi *et al.* showed that both genders were equally affected.[13] We also observed that adults were most commonly affected by serious ADRs. While it has been reported by Arulmani *et al.* that pediatric and geriatric are more commonly affected.[14] The occurrence of serious ADRs (12.6%) in our study is little less as compared to the study by Agaard *et al.* (16%) in 2012.[12]

Our findings showed that majority of the serious ADRs occurred after 1 month of initiating drug therapy whereas few occurred within a day of treatment. This can be attributed to serious ADRs due to anti-tubercular and antiretroviral drugs, which are immunologically mediated hypersensitivity reactions and not dose-dependent in nature.[15] This indicates that a close monitoring and follow-up of patients is essential for initial month for early detection and prevention of serious ADRs. This information should help the prescriber to remain vigilant during this period and also educate the consumers. Interestingly, skin and its appendages along with liver and biliary system are the common targets for serious ADRs. Our observations are synonymous with Agaard *et al.* and Arulmani *et al.* [Table 4].[12,14] However Kamalaraj *et al.*[16] and Sriram *et al.*[17] shows most common system affected is GIT. This also substantiates our findings that anti-tubercular and antiretroviral drugs are known to cause skin reactions and liver damage.[18-20] Probably, this supports cohort monitoring and integration of Revised National Tuberculosis Control Programme and ART programme with nationwide PvPI. In addition, it has been reported by Agaard *et al.* that drugs acting on nervous system and cardiovascular medicines are the frequent causes of serious ADRs in higher income countries while anti-infectives top the list in resource-limited countries, which further supports our observations.[12]

Table 3: Severity assessment of serious adverse drug reactions (*n*=375)

Severity level	Inference	Number of serious ADRs (%)
Level 1	An ADR occurred, but required no change in treatment with suspected drug	36 (9.6)
Level 2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment was required. No increase in LOS	239 (63.7)
Level 3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR an antidote or other treatment was required. No increase in LOS	0 (0)
Level 4	Any level 3 ADR which increases length of stay by at least 1 day or the ADR was the reason for the admission	92 (24.5)
Level 5	Any level 4 ADR which requires intensive medical care	6 (1.6)
Level 6	The adverse reaction caused permanent harm to the patient	0 (0)
Level 7	The adverse reaction either directly or indirectly led to death of the patient	2 (0.53)

LOS=Length of stay, ADRs=Adverse drug reactions

Table 4: Comparison of characterization of adverse drug reactions with available literature

	Our study (*n*=375) (%)	Doshi *et al*.[13] (*n*=140) (%)	Kamalaraj *et al*.[16] (*n*=49) (%)	Sriram *et al*.[17] (*n*=57) (%)	Arulmani *et al*.[14] (*n*=164) (%)
Affected body system	Skin (19)	Gastrointestinal (34)	Gastrointestinal (25)	Gastrointestinal (37)	Skin (34.1)
Causal drug group	Anti-tubercular (35)	Antibiotics (36.4)	Antibiotics (79.29)	Antibiotics (23)	Antibiotics (10.9)
Causality					
Certain	1.86	3	18.36	30	6.1
Possible	48.8	42	61.22	42	31.7
Probable	46.13	55	20.40	23	62.2 (as per
Unclassified	3.2	0	-	15	Naranjo)
Preventability					
Definitely preventable	0.53	35		28	Not done
Probably preventable	0	25	Not done	7	
Not preventable	96	40		65	

Polypharmacy is ubiquitous for the development of ADRs.[21] Our study showed that majority of the patients were prescribed five or more drugs. Although this can be justified as majority of these patients were receiving anti-tubercular or antiretroviral drug regimen under National Health Programme. Majority of the serious ADRs were continued, two were fatal, and rest were either recovered or recovering. Of these two deaths reported, the suspected drugs prescribed were ceftriaxone, metronidazole, and doxycycline.

The association of majority of serious ADRs to causal drugs was possible in nature. This can be attributed to alternative factors that could have contributed to ADRs. As majority of patients in our study were prescribed multidrug therapy, rechallenge was not done, and the underlying disease process could also have played an important role. In 26% of the cases, it required intensive medical care, prolonged hospitalization, or the ADR itself was the reason for the hospitalization. All these findings are important for all stakeholders of health care system as it leads to significant morbidity and financial burden on patients and hospitals. Surprisingly, majority of serious ADRs were not preventable in our study. This can be explained by the fact that most of the reactions involving skin and its appendages are idiosyncratic [Table 4].[22] The nonpreventability of these ADRs also indicates that drug treatment in the hospital is reasonably rational. This information is essential for prescribers and patients, as serious ADRs may affect confidence of prescribers, program managers, and patients' compliance.

This was a large retrospective study, wherein all reported ADRs were recorded as precisely as possible. However, considering the number of patients seeking medical treatment at our center and number of drugs available, there was definitely underreporting of ADRs. Moreover, due to spontaneous reporting system, the actual incidence rate cannot be estimated. Further, lack of follow-up data till recovery, lack of information about substituted drugs or treatment of ADRs, lack of information on recently introduced drugs, and single center are the major limitations. In spite of these limitations, the strength of our data leads to some important conclusions.

Following are the new findings in our study:

- This is one of the longest (5 years) retrospective analysis of 3000 spontaneously reported ADRs in a tertiary care teaching hospital
- A detailed analysis of data is undertaken with clinical manifestation of ADRs as per system organ class (SOC)

- Anti-tubercular and antiretroviral and other antimicrobial agents are the most common causal drug groups, which justifies the integration of PvPI to National Health Programme of TB and HIV
- Polypharmacy is one of the risk factors contributing in serious ADRs.

It can be concluded that serious ADRs occur within 1–30 days of starting drug therapy in adult men prescribing multi drug therapy. Anti-tubercular, antiretroviral, and antimicrobials are the main causal group of drugs that require intervention, hospitalization, and cause life-threatening serious ADRs. A robust ADR monitoring system and education of prescribers to closely monitor patients can help prevent, identify, and manage serious ADRs effectively.

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Conflicts of interest

There are no conflicts of interest.

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