Short Communication

Fatal adverse drug reactions: Experience of adverse drug reactions in a tertiary care teaching hospital of North India – A case series

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Abstract

Medical burden of fatal adverse drug reactions (FADRs) is significant. The epidemiological data on FADR do exist from the western world, but there is scanty from India. We hereby report a case series of FADRs recorded in a 2 years period. Point prevalence of FADRs was 0.223%. Point prevalence of all cause death in the hospital was 1.20%. The drugs causing FADRs were injection bupivacaine, amphotericin B, directly observed treatment short-course Category-1, injection streptokinase, and tablet ferrous sulfate. All these FADR were labeled as possible expect one case as probable. All FADR were labeled as type A. In three out of five the central nervous system was involved, while the hepatic system and multiorgan failure accounted for one case each. Two cases each were acute and subacute, while one was latent in nature. Reporting of FADRs shall go a long way in patient safety.

Keywords: Adverse drug reactions, drug safety, fatal ADR, mortality

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Introduction

Adverse drug reaction (ADR) has been implicated as a leading cause of considerable morbidity and mortality. The overall incidence of serious ADRs has been reported 6.7% and of fatal ADRs (FADRs) to be 0.32% of hospitalized patients, which is extremely high.[1] It has been suggested that annual rates of ADR related deaths ranged from 0.08/100,000 to 0.12/100,000 and rate increase significantly over time at a rate of 0.0058/year.[2] Few other studies recorded FADR rate as high as of 6.4% and 1.66%, respectively.[3,4] In studies originating from India, five cases of death were recorded by Nair *et al*. (2005)[5] resulting from drug reaction. Similarly, 1.8% had a FADR rate in the study of Ramesh *et al*. (2003).[6] The epidemiological data on FADR do exist from the western world,[1-4,7,8] but there is scanty data from India. Furthermore, it is important to report FADR as it can go a long way to ensure patient safety and shall help the regulators to take preventive measures to reduce the number of deaths caused by drugs. We hereby report a case series of FADRs recorded in a 2 year period.

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Case Reports

Case 1

A 21-year-old, 52 kg weight, male patient was admitted in the surgery department to undergo elective surgery. His preoperative biochemical and other baseline parameters were within normal limits. On the day of surgery, he was administered 2 ml of 0.5% of injection bupivacaine for spinal anesthesia. Following which he immediately went into shock. His blood pressure (BP) fell drastically to systolic 60 mg of Hg and diastolic not recordable and had thready pulse and tachypnea. His parameters PCO_2-50.6 mm Hg; PO_2-54.00 mm Hg; pH - 7.308; HCO_3-24.5 mmol/L; hemoglobin (Hb) - 15 g/dl; serum Na + 142 mmol/L; serum K^+ 2.7 mmol/L; blood urea 152 mg%, serum cretanine - 4.6 mg%; blood sugar - 126 mg%, serum alanine aminotransferase: 26.17 µkat/L, serum aspartate aminotransferase: 25.12 µkat/L and lipid profile

were normal. Patient was given injection dopamine, mephentramine along with antibiotics and was put on ventilator support, but he succumbed within 1 day.

Case 2

A 35-year-old, HIV positive female patient suffered from difficulty in swallowing solids to start with followed by even liquids for last 2 months. She had a history of significant loss of appetite and weight loss. Endoscopic examination of upper gastrointestinal (GI) tract was carried during hospitalization to know the cause of dysphagia. She was found to be suffering from candida esophagitis with antral gastritis. Her cerebrospinal fluid examination was normal. Her blood sugar was 86 mg/dl; Hb 9 g%, total leukocyte count (TLC) - 8000/cmm, differential leukocyte count - predominant lymphocytosis, platelet count 2.4 lacs/cmm, blood urea 26 mg, serum creatinine 0.7 mg, HbA1c 6.0%, serum cholesterol 154 mg%, serum triglyceride 140 mg%, high-density lipoprotein (HDL) 35 mg%, routine urine examination, C-reactive protein + ve, erythrocyte sedimentation rate 88 mm/h, T3, T4 and thyroid stimulating hormone, LFT, serum uric acid, serum electrolyte levels were within normal limits. HIV status was positive and CD4 count – 100 (cells/μl) at the time of report. She was already on highly active antiretroviral (zidovudine + stavudine + nevirapine) therapy. She was given IV 100 μg/ml of amphotericin B in 5% dextrose for candida esophagitis. Following this she suffered from seizures that converted into status epilepticus. The nature of convulsions was generalized tonic-clonic. The BP was 86/56 mm of Hg and HR was 60 beat/min. The patient was immediately intubated. Injection diazepam - 10 mg intravenous (IV) push over 30–60 s repeated after every 10-15 min up to 30 mg was given. It was followed by loading and maintenance dose of phenytoin 600 mg in 100 ml of NS. IV midazolam loading dose was also given. Thus, patient was immediately shifted to intensive care unit for ventilator support. Patients magnetic resonance imaging done within 2 days showing marked hypoxia with cerebral edema [Figure 1], which may be due to delayed intubation following generalized tonic-clonic seizure. However, she died after 7 days.

Case 3

A 70-year-old, 80 kg postmenopausal female a known case of hypertension stage 1 as per JNC-7 with pulmonary TB Category-1 was on directly observed treatment short-course (DOTS) antitubercular therapy started 17 days before along with telmesartan presented with history of altered sensorium and loss of appetite for last 1 day. She was on isoniazid, rifampin, ethambutol, and pyrazinamide containing

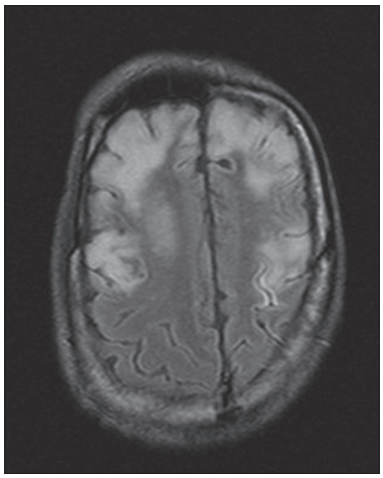

Figure 1: Magnetic resonance imaging of the case 2 done within 2 days showing marked hypoxia with cerebral edema with cerebral atrophy following seizure

regimen under DOTS. In addition, she was also taking pantoprazole and calcium as and when required. A chest X-ray showed pulmonary tuberculosis (TB) with pleural effusion. Her baseline LFT, lipid profile, renal function test (RFT), complete blood count, and HIV status were normal. Gammaferon gold test for TB was positive. Electrocardiography (ECG) and ultrasonography (USG) abdomen was normal suggestive of postmenopausal status. Examination at the time of admission revealed BP 126/78 mmHg, pulse - 66/min, serum glutamic oxaloacetic transaminase 325 IU/L, serum glutamic-pyruvic transaminase - 132 IU/L, serum bilirubin 2.9 mg%. Based on these investigations, she was diagnosed as the case of antituberculosis therapy (ATT) induced hepatitis. Her ATT was stopped immediately. However, her condition deteriorated further. On 8th day of hospitalization, she went into hepatic encephalopathy followed by coma. Patient was given injection dopamine, along with antibiotics and was put on ventilator support. On day 10, she was in shock with BP 70/50 mm of Hg, pulse - 104/min, serum bilirubin 4.9 mg%, RFT – normal, blood sugar 87 mg% and she died after 20 days of admission in hospital in spite of all the medical intervention.

Case 4

A 70-year-old male a known case of hypothyroidism with stage 3-systolic hypertension as per seventh report of the Joint National Committee presented to emergency with pain chest not relieved by sublingual nitrate. ECG examination revealed acute inferior wall myocardial infarction with positive 10 h troponin-T assay. Pulse rate was 94/min, regular, normal volume, no radio-femoral delay and vessel wall not palpable. BP measured in both limbs was 190/90 mmHg. Laboratory

investigations revealed Hb 13 g%, TLC 9400/cmm, platelet count 2.6 lacs/cmm, blood urea 39 mg, serum creatinine 0.9 mg, blood sugar - 100 mg%, HbA1c 6.8%, serum cholesterol 245 mg%, serum triglyceride 185 mg%, and HDL 35 mg%. Angiography was not done. Patient was treated with oxygen, morphine, beta blocker, ACE inhibitor, statins, aspirin, and clopidogrel. He was allowed to continue thyroxine 25 µg/day. Injection monocef 1 g IV and for hypertension he was given IV metoprolol. He was administered IV streptokinase after which he developed purpura and extensive ecchymosis [Figure 2]. Patient also developed epistaxis as well as macroscopic hematuria. Patient on subsequent investigations showed platelet count 350,000/cmm and Hb 6.9 g%. There were no signs of deep venous thrombosis, pulmonary embolism, gangrene or retroperitoneal bleed in the patients as suggested by USG abdomen. However, his condition continued to deteriorate further and computed tomography examination revealed major intracerebral hemorrhage [Figure 3]. Patient was started four units of platelet fraction and two units of blood transfusion. He was placed on a ventilator, but the patient died after 6 days.

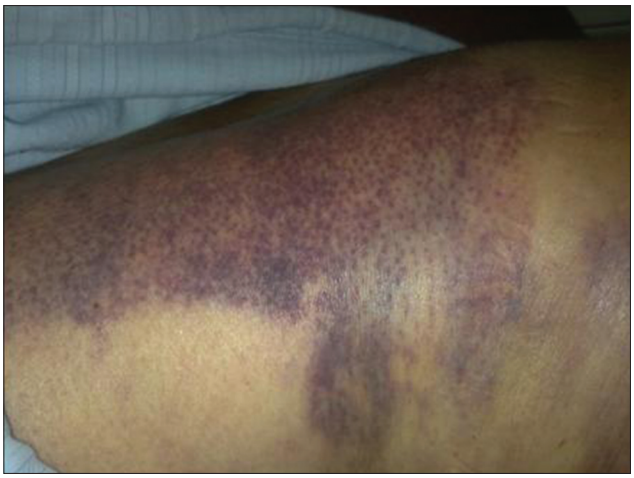

Figure 2: Extensive echymosis in case 4

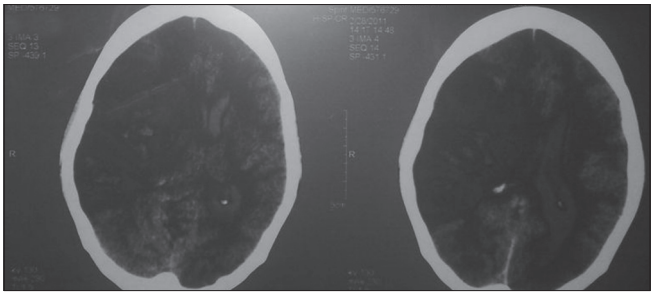

Figure 3: Computed tomography examination showing major intracerebral hemorrhage in case 4

Case 5

A 2½-year-old female child was admitted with history of intake of one tablets of iron which her mother was taking for pregnancy induced anemia. The child presented with drowsiness, intractable vomiting, and passage of dark colored black stools. She had major episodes of hematemesis and passage of malena. She presented with ocular hemorrhage. She went into shock. Endoscopy revealed massive GI bleed [Figure 4]. Immediately treatment for and severe anemia was instituted. Child was given desferrioxamine 150 mg/kg/h in 100 ml of normal saline at the rate of 30 ml/h. Patient developed signs of Congestive cardiac failure for which injection lasix 20 mg was given. However, patient deteriorated further and developed multi organ failure and died on the 2nd day.

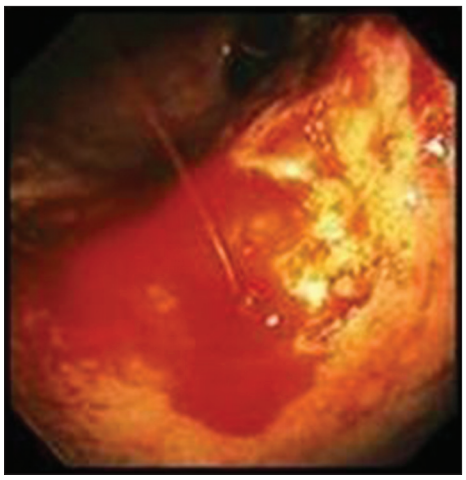

Figure 4: Massive gastrointestinal bleed on endoscopy in case 5

Discussion

All these FADR are labeled as probable expect one case as possible as per causality assessment with the Naranjo's score 6 and 4, respectively.[9] Since these ADRs were not studied for dose dependent response and were predictable as per known mechanism of action; hence, they all could not be clearly labeled as type A.[10] In three out of five cases, the central nervous system (CNS) was involved, whereas in one each case hepatic system and multiorgans were involved. Two cases each were acute subacute as well as one was latent in nature. Two patients were 70-year-old and one from pediatric age group; while other, two patients were of young age in the current case series. In the current study mild ADRs were 992 (41.8%), moderate 1300 (54.7%), severe 84 (3.5%), and fatal 5 (0.223%) out of the total 2376 ADR reported during this study period. Point prevalence of FADR reports in the current study was 0.223% (5/2242).

Table 1: Profile of FADRs

Parameters	*n*(%)
Total number of ADRs reported	2242
Total number of ADR events	2381
Analysis of ADR according to severity	Mild 992 (41.8%), moderate 1300 (54.7%), severe 84 (3.5%), fatal 5 (0.223%)
Total number of patients inward and outward for 2 years	500,000
Point prevalence of ADR reports	0.448% (2242/500,000)
Point prevalence of ADR events	0.476% (2381/500,000)
Total number of fatal reports	5
All cause death for 2 years	6000
Point prevalence of fatal reports	0.223% (5/2242)
Point prevalence of all cause death fatal reports	1.20% (6000/500,000)

Detail of FADR with causality assessment

Age	Sex	Specialty	Route	Drug	Mode of onset of ADR	Type of reaction	Organ system involved	Cause of death	Naranjo's scale
2.5	Female	Pediatrics	Oral	Iron	Subacute	A	Multiorgan	ALVF with multi organ failure	4 - Possible
35	Female	Medicine	IV	Amphrotericin-B	Subacute	A	CNS	Seizure disorder leading to coma and death	6 - Probable
70	Female	Chest diseases	Oral	ATT (DOTS Category 1)	Latent	A	Liver and CNS	Acute fulminate hepatitis leading to hepatic enceplapathy and death	6 - Probable
70	Male	Cardiology	IV	Streptokinase	Acute	A	CNS	Intracranial hemorrhage and cardiopulmonary death	6 - Probable
21	Male	Anesthesia	Spinal	Bupivacaine	Acute	A	CNS	Spinal shock with multi organ failure and cardiopulmonary arrest	6 - Probable

FADR: Fatal adverse drug reaction; ADR: Adverse drug reaction; ALVF: Acute left ventricular failure; CNS: Central nervous system; ATT: Antituberculosis therapy; DOTS: Directly observed treatment short-course; IV: Intravenous

Point prevalence of all cause death fatal reports in the hospital was 1.20% (6000/500,000). The drugs causing FADR in our case series were injection bupivacaine, IV amphotericin B, DOTS Cat-1, IV streptokinase and tablet ferrous sulfate [Table 1].

In one of the recent study GI hemorrhages, CNS hemorrhages, cardiac disorders, drug-induced myelo suppression, and antimicrobial-related enterocolitis were the common causes of fatal disorders due to ADRs. The drugs most frequently implicated in a FADR were antithrombotic drugs, nonsteroidal antiinflammatory drugs, and corticosteroids. The only risk factors associated with FADRs in this population multiple-drug therapy and advancing age.[10]

Similarly, in another study the most common suspected FADRs were GI hemorrhages, CNS hemorrhages, cardiovascular disorders, other hemorrhages, and renal dysfunction. The drugs most commonly implicated in FADRs were antithrombotic drugs, followed by nonsteroidal antiinflammatory drugs, antidepressants, and cardiovascular drugs.[3]

However, systemic antiinfective drugs' was associated with the highest percentage of FADRs (21.9%), followed by antineoplastic and immunomodulating agents (18.8%), and then by nervous system drugs (14.8%) in this study of Leone, *et al*.[4] The main distribution of suspected FADRs in another study was: Hemorrhages, blood, and bone marrow dysfunction, sudden death, and pulmonary embolism. Antithrombotic agents were the drugs most frequently implicated in the FADRs.[8]

The current small case series of FADRs impress upon a need of creating a separate national database on FADRs, which shall go a long way in enhancing patient safety.

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