

Assessment of Adverse Drug Reactions, Severity, Preventability Status, and Its Determinants among Inpatients in Tertiary Care Hospitals in South India

Sir,

This observational study was done to assess the pattern of adverse drug reactions (ADRs), its severity, determinants, and preventability status among inpatients at a government and private hospital in Mangalore in May 2019. Institutional ethics committee approval was taken before the commencement of this study. Inpatients were enrolled by a convenience sampling method. The sample size was calculated at 95% confidence intervals, 20% relative precision, and assuming 32.8%^[1] of the patients to have ADRs. With a 10% buffer, the sample size was calculated as 216. All inpatients aged ≥ 18 years and those giving written informed consent for participation were included. Those severely or mentally ill; those admitted for deliberate drug intoxication, accidental poisoning, or drug abuse; pregnant mothers; and outpatients were excluded. Data were collected by interviewing each participant using a content and language validated interview schedule. The socioeconomic status (SES) of the patients was assessed using modified Kuppuswamy's classification of 2019. The severity of ADRs was assessed using modified Hartwig criteria and preventability status by modified Schumock and Thornton criteria. The patients were followed up to ascertain the length of hospital stay. Reaction time was defined as the time taken for the reaction to appear since the last exposure to the suspected drug. Regular medications were defined as those medications which the patients took daily over the recent 6 months. The mean age of the patients was 36.6 ± 13.7 years. Majority of them were males (121 [56%]), were unskilled workers (68 [31.5%]), and were from urban areas (127 [58.8%]). SES was known among 188 patients. Among them, 3 (1.6%) were of upper, 20 (10.6%) were of upper middle, 46 (24.5%) were of lower middle, 109 (58%) were of upper lower and 10 (5.3%) were of lower SES. Family history of allergy was present among 4 (1.8%) and family history of ADRs among 3 (1.4%) patients. History of allergy to dust particles and to food substances was present among 7 (3.2%) and 2 (0.9%) participants, respectively. The Charlson Comorbidity Index scores were 1–2, 3–4, and 5 among 69 (31.9%), 9 (4.2%), and 1 (0.5%) participants, respectively. Among the 216 patients, 22 (10.2%) gave a positive history of ADRs. Each incident of ADR involved the usage of a particular drug among the participants. The ADRs reported were mood changes and irritability with hydroxychloroquine in one patient; redness of the skin due to ibuprofen, montelukast, and metronidazole in one patient each; loss of appetite and pruritus with levetiracetam in one, bleeding with aspirin in one; pruritus and redness of the skin due to folic

acid tablets in one; nausea, vomiting, and gastritis due to iron tablets among five; nausea and blurring of vision due to digoxin in one; constipation due to dicyclomine in one; redness of the skin and pruritus due to isotretinoin in one and only redness of the skin in one; sedation due to diclofenac in one; drowsiness due to cetirizine in one; redness of the skin due to heparin in one; swelling of the hands due to pregabalin in one; diarrhea due to ceftriaxone in one, and nasal irritation due to fluticasone in one. The median number of episodes of ADRs experienced by the patients was 2 with interquartile range (IQR) (1, 3). The number of episodes ranged from 1 to 15 among the patients. More than three episodes of ADRs were reported among three patients. This comprised 15 episodes of diarrhea due to ceftriaxone in 1 patient, 6 episodes of bleeding due to aspirin in one patient, and 4 episodes of nasal irritation due to fluticasone nasal spray in 1 patient. The median time from administration of the drug to the development of drug reactions was 30 min with IQR (20 min, 135 min). It ranged from 5 min to 7 days. A proportion of patients with ADRs were seen more (16.7%) among patients aged 18–20 years. It was present among 11.6% of females and 9.1% of males. Redness of the skin [7 (31.8%)] was the most common presentation among patients with ADRs [Table 1]. Severe ADR was reported involving ceftriaxone, whereas ADR of moderate severity was reported involving drugs such as ibuprofen, aspirin, iron tablets, digoxin, diclofenac, and heparin. Thirty-nine patients gave a history of taking one or other medicines regularly at home. The mean number of drugs taken regularly by patients ($n = 7$) who developed ADRs was 1.71 ± 0.49 in comparison to 1.44 ± 0.56 among patients ($n = 32$) who did not develop ADRs ($t = 1.2$, $P = 0.238$). ADRs among majority of the patients occurred due to change in medications [Table 1]. An Italian study reported ADRs due to drug overdose in 0.15%, due to medication error in 0.17%, due to drug-to-drug interactions (DDIs) in 0.19%, and due to drug abuse in 0.21% of the patients.^[2] DDIs in this study were the cause of ADR in one patient. It was present in 1 (10%) out of 10 patients on ≥ 4 medications in comparison to none among 206 patients on treatment with < 4 drugs ($P = 0.0463$). This was similar to the findings of a study done in Gujarat, India, where DDIs were significantly seen more when the number of drugs prescribed was > 5 .^[3] The median reaction time was 30 min IQR (20, 135). It ranged from 5 min to 7 days. Reaction for the ADR was reported ≤ 15 min for drugs such as iron tablets, folic acid tablets, heparin injection, and fluticasone nasal spray. It was reported > 3 h for drugs such as digoxin, ceftriaxone,

Table 1: Distribution and severity of adverse drug reactions experienced by the patients

Characteristics	n (%)
Common adverse drug reactions*	
Redness of the skin	7 (31.8)
Nausea	6 (27.3)
Pruritus	3 (13.6)
Systems involved*	
Cutaneous system	9 (40.9)
Gastrointestinal system	9 (40.9)
Central nervous system	4 (18.2)
Respiratory system	1 (4.5)
Hematopoietic system	1 (4.5)
Site of involvement in skin lesions (n=9)*	
Legs	4 (44.4)
Trunk	2 (22.2)
Face	2 (22.2)
Forearms	1 (11.1)
Hands	1 (11.1)
Number of episodes of ADRs	
1	8 (36.4)
2	6 (27.3)
3	5 (22.7)
>3	3 (13.6)
Reaction time (min)	
≤15	4 (18.2)
16-30	9 (40.9)
31-180	5 (22.7)
>180	4 (18.2)
Severity of ADRs	
Mild	15 (68.2)
Moderate	6 (27.3)
Severe	1 (4.5)
Reason for ADRs	
Change in medication	5 (22.7)
Drug-to-drug interaction	1 (4.5)
Not known	16 (72.8)
Action taken following ADRs	
Drug continued but with a reduced dosage	10 (45.4)
Immediate stoppage of the drug	6 (27.3)
Drug continued without change in dosage	6 (27.3)
Medications used to manage ADRs	
Ranitidine	2 (9.2)
Cetirizine	2 (9.2)
Ondansetron	1 (4.5)
Ranitidine and ondansetron	1 (4.5)
Diazepam	1 (4.5)
Topical antihistaminic agents	1 (4.5)
Lactulose	1 (4.5)
None	13 (59.1)
Outcome with management (n=9)	
Complete recovery	7 (77.8)
Partial recovery	2 (22.2)
Preventability status of ADRs	
Definitely preventable	6 (27.3)
Probably preventable	13 (59.1)
Not preventable	3 (13.6)
Total	22 (100.0)

*Multiple responses. ADR: Adverse drug reactions

Table 2: Association between determinants and adverse drug reactions among patients (n=216)

Determinants	ADRs present, n (%)	ADRs absent, n (%)	OR (95% CI)	P	AOR (95% CI)	P
Socioeconomic status (n=188)						
Upper/middle	11 (15.9)	58 (84.1)				
Lower	9 (7.6)	110 (92.4)				
		$\chi^2=3.226$, $P=0.072$	2.318 (0.909-5.914)	0.072	2.856 (1.012-8.058)	0.047
Family history of ADRs						
Present	2 (66.7)	1 (33.3)				
Absent	20 (9.4)	193 (90.6)				
		$P=0.028$	19.3 (1.675-32.236)	0.028	26.536 (1.725-40.826)	0.019
Diabetes mellitus						
Present	6 (17.7)	28 (82.3)				
Absent	16 (8.8)	166 (91.2)				
		$\chi^2=2.46$, $P=0.117$	2.223 (0.802-6.166)	0.117	4.572 (1.359-15.38)	0.014
History of taking iron tablets regularly						
Yes	4 (28.6)	10 (71.4)				
No	18 (8.9)	184 (91.1)				
		$P=0.041$	4.089 (1.164-14.365)	0.041	4.304 (0.972-19.052)	0.055
History of taking calcium tablets regularly						
Yes	4 (28.6)	10 (71.4)				
No	18 (8.9)	184 (91.1)				
		$P=0.041$	4.089 (1.164-14.365)	0.041	0.969 (0.02-47.135)	0.987
Total	22	194				

ADR: Adverse drug reactions

montelukast, and aspirin. Previous history of allergy to the same drug was reported in a patient using isotretinoin. In another patient, metronidazole therapy was not indicated for treating the present condition. Toxic drug concentration test and therapeutic drug monitoring test were performed for the drug digoxin in a patient before its usage. History of ADRs during the current hospital stay was reported among 12 (54.5%) out of the 22 patients with ADRs. Among them, eight developed mild ADRs, whereas four developed moderate/severe ADRs. The mean number of drugs currently taken by patients ($n = 8$) who developed mild ADRs was 2 ± 0.756 in comparison to 3 ± 1.826 among patients ($n = 4$) who developed moderate/severe ADRs during the hospital stay ($t = 1.38$, $P = 0.198$). Partial recovery with diazepam was reported by a patient presenting with mood changes and irritability due to hydroxychloroquine intake and by another patient managed with cetirizine for pruritus and redness of the skin due to folic acid tablet intake. There was no association between development of ADRs during hospital stay and duration of

admission in the hospital among the patients ($Z = 0.933$, $P = 0.351$). Moderate-to-severe ADRs were present among 5 (55.6%) out of 9 patients of lower SES in comparison to 1 (9.1%) out of 11 patients of upper/middle SES ($P = 0.0498$). The median duration of hospital stay in patients with mild ADRs ($n = 15$) was 3 days IQR (2, 7) and for those with moderate/severe ADRs ($n = 7$) was 4 days IQR (2, 14) ($Z = 0.392$, $P = 0.731$). Multivariable analysis identified upper/middle SES, family history of ADRs, and the presence of diabetes mellitus (DM) as independent determinants of ADRs among the patients [Table 2]. DM affects renal function which impairs drug metabolism making diabetic patients more vulnerable to develop ADRs.^[4] Increased vulnerability of better SES groups could be due to their faulty lifestyle habits. Positive family history of ADRs as a determinant indicates the possible role of genetic factors in its development. In other studies, elderly patients,^[5] females,^[1,2] the presence of hypertension,^[2] the presence of DM,^[6] the presence of urinary tract infections,^[6] multiple comorbidities,^[1,4] polypharmacy,^[1,2,4,6] and unnecessary usage of antimicrobial agents^[1] were associated with the development of ADRs among patients. These risk groups, therefore, need to be closely monitored for the development of ADRs. Majority of the patients had probably/definitely preventable status of ADRs indicating the need of interventions to avoid ADRs.

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Conflicts of interest

There are no conflicts of interest.

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