

An analysis of adverse drug reactions in extremes of age group at tertiary care teaching hospital

Saloni Amin, Samidh Shah, Mira Desai, Asha Shah¹, K. M. Maheriya²

Departments of Pharmacology, ¹Medicine and ²Paediatrics, B. J. Medical College, Ahmedabad, Gujarat, India

Abstract

Objectives: To analyze clinical spectrum, seriousness, outcome, causality, severity and preventability of ADRs in geriatrics and pediatric patients.

Materials and Methods: All ADRs reported in geriatrics (≥ 65 years) and pediatrics (≤ 12 years) indoor as well outdoor patients from January, 2010 to April, 2016 at ADR monitoring centre, Department of Pharmacology, B. J. Medical College and Civil Hospital were identified. A retrospective analysis was carried out for clinical presentation, causality (as per WHO-UMC scale and Naranjo's algorithm), severity (Hatwig and Seigel scale) and preventability (Schaumock and Thornton criteria).

Results: Out of 3690 ADRs, 160 were in geriatric patients (4.33%) while 231 in pediatric patients (6.26%). The most commonly affected body system was gastrointestinal (53, 33.13%) followed by neurological disorders (26, 16.25%) in geriatric patients. While in pediatric patients, the most commonly affected body system was skin and appendages (73, 31.60 %) followed by gastrointestinal disorders (58, 25.11%). The most common causal drugs in geriatric patients was cardiovascular (38, 23.75%) followed by antimicrobials (28, 13.25%). While in pediatric patients, the most common causal drug group was antimicrobials (85, 33.46%) followed by blood products (36, 14.12%). Total 17 ADRs reported following vaccination, 7 (41.17%) were injection site abscess and 11 (64.70%) were due to pentavalent vaccine. Polypharmacy was common in geriatrics (31, 19.37%). Causality assessment for majority of ADRs in geriatrics (83, 52.5%) and pediatrics (171, 67.32%) were probable.

Conclusion: ADRs are common in geriatric and pediatric patients usually within four weeks of oral therapy. Active surveillance of drug safety monitoring in these vulnerable population is recommended.

Keywords: Adverse drug reaction, geriatric, pediatric, pharmacovigilance

Address for correspondence: Dr. Samidh Shah, Department of Pharmacology, B. J. Medical College, Ahmedabad - 380 016, Gujarat, India.
E-mail: samidhshah@yahoo.com

INTRODUCTION

Adverse drug reactions (ADRs) are the one of the leading cause of repeated hospitalization and adversely affects the quality of life.^[1] The prevalence of ADR is higher among geriatric (5%) and pediatric (9.5%) patients as compared to adults including 2.1% of hospital admissions.^[2-4] The

possible reasons for higher prevalence of ADRs in geriatric patients are other comorbidities, polypharmacy, and altered pharmacokinetic and altered pharmacodynamics.^[5] In addition, infants and very young children are at high risk of ADRs because their capacity to metabolize the drug is not fully evaluated. Similarly, neonates are at high risk of ADRs due to immature hepatobiliary and renal tubular functions.

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Thus, elderly and pediatric patients are vulnerable to ADRs because of immature, altered, and unpredictable physiological changes that occur in extremes of age.

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.^[6] The practice of PV requires special attention for geriatric and pediatric patients because diseases in these patients are qualitatively and quantitatively different from the adult patients.

Hence, an attempt has been made in this study to analyze the clinical spectrum and assess seriousness, outcome, causality, severity, and preventability of the ADRs in the geriatric and pediatric patients.

MATERIALS AND METHODS

Department of Pharmacology, B. J. Medical College is a recognized Adverse Reaction Monitoring Centre and regional training centre under pharmacovigilance program of India. The suspected ADRs from indoor as well as outdoor patients were diagnosed by treating consultants, and relevant details of each ADR were collected in spontaneous ADR reporting form. Each report was sent to the National coordinating centre through Vigiflow and simultaneously entered in the Microsoft Excel sheet. All ADRs reported in geriatric (≥ 65 years) and pediatric (≤ 12 years) patients from January 2010 to April 2016 were identified. Data were analyzed to find the time relationship between the event and the initiation of drug treatment, number of adverse events, causal drug groups and involved body system as per system organ classification (SOC) in both groups. An association of clinical presentation of geriatric and

pediatric ADRs with the route of drug administration, other concomitant conditions and number of drugs prescribed, i.e., polypharmacy was also carried out. Causality assessment was done using WHO-UMC scale and Naranjo's algorithm.^[7,8] Severity was assessed using modified Hartwig and Siegel^[9] while preventability was assessed using modified Schumock and Thornton scale.^[10]

RESULTS

Out of 3690 ADRs reported during the period, 160 were geriatric ADRs (4.33%) while 231 were pediatric ADRs (6.26%).

There were 115 men and 45 women with male:female ratio of 3.44:1 in geriatric patients. The mean age of geriatric patients with ADRs was 71.69 ± 0.45 years. While in pediatric group, there were 143 boys and 88 girls with boys: girls ratio of 1.63:1. The mean age of pediatric patients with ADRs was 2.98 ± 0.20 years.

Time for appearance of adverse drug reactions

Majority of the ADRs in geriatric (148, 92.5%) and pediatric (207, 86.61%) patients occurred within 4 weeks of drug therapy.

Clinical presentation of adverse drug reactions

The most commonly affected body system (as per SOC) was gastrointestinal disorders (53, 33.13%) followed by neurological disorders (26, 16.25%), and skin and appendages (20, 12.5%) in geriatric patients [Table 1 and Figure 1a].

While in pediatric patients, the most commonly affected body system was skin and appendages (73, 31.60%) followed by gastrointestinal disorders (58, 25.11%) and body as a whole (35, 15.15%) [Table 1 and Figure 1b].

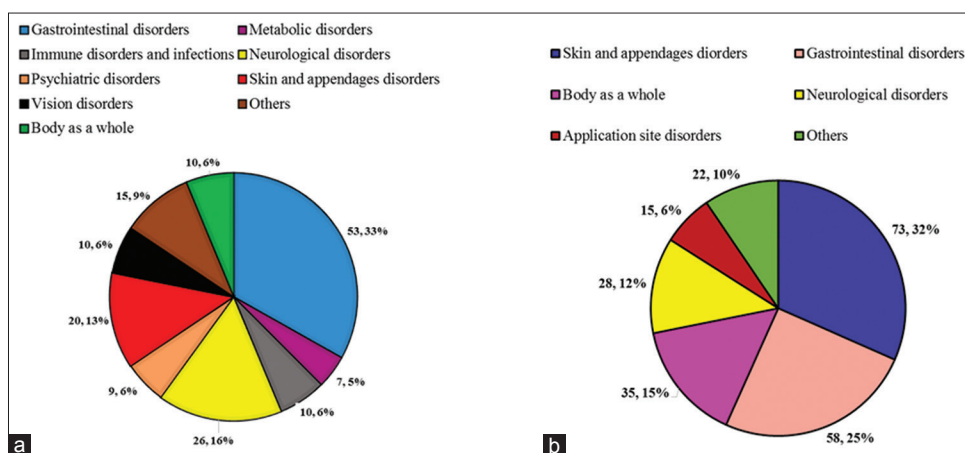


Figure 1: (a) Body systems affected by adverse drug reactions in geriatrics patients (n = 160). (b) Body systems affected by adverse drug reactions in pediatric patients (n = 231)

Table 1: Detail analysis of adverse drug reactions in geriatrics and pediatric patients

	Geriatric group (n=160)	Pediatric group (n=231)
Body systems affected (%)	Gastrointestinal (33.13) Neurology (16.25) Skin and appendages (12.5)	Skin and appendages (31.60) Gastrointestinal (25.11) Body as a whole (15.15)
Causal drug groups (%)	Cardiovascular drugs (23.75) CNS drugs (18.13) Antimicrobials (17.5)	Antimicrobials (33.46) Blood products (14.12) CNS drugs (9.84)
Routes of administration (%)		
Oral	125 (78.12)	149 (58.66)
Intravenous	15 (9.3)	66 (25.98)
Intramuscular	4 (2.5)	21 (7.87)
Topical	16 (9.3)	19 (7.48)
Seriousness (%)		
Nonserious	144 (90)	201 (87)
Hospitalization prolonged	8 (5)	9 (3.89)
Required intervention to prevent damage	4 (2.5)	16 (6.93)
Life threatening	4 (2.5)	2 (0.87)
Outcome (%)		
Continued	111 (69.37)	116 (50.22)
Recovered	31 (19.37)	86 (37.23)
Recovering	17 (10.62)	23 (9.96)
Causality (%)		
WHO-UMC		
Probable	49 (30)	113 (44.49)
Possible	111 (69.37)	141 (55.51)
Naranjo		
Probable	84 (52.5)	171 (67.32)
Possible	76 (47.5)	83 (32.84)
Severity (%)		
Mild level 1	99 (61.87)	39 (15.35)
Mild level 2	29 (18.13)	136 (53.54)
Moderate level 3	28 (17.5)	60 (23.62)
Moderate level 4	4 (2.5)	11 (5.11)
Severe level 5	-	6 (2.36)

CNS=Central nervous system

Interestingly, total 17 (7.36%) adverse effect following vaccination were reported. The most common presentation was abscess at the site of injection (7, 41.17%) and pentavalent vaccine was the common causal agent (11, 64.70%).

Causal drug groups

The most common drug group causing ADRs in geriatric patients was cardiovascular drugs (38, 23.75%) followed by central nervous system (CNS) drugs (29, 18.13%), and antimicrobial agents (28, 17.5%). Among cardiovascular drug group, calcium channel blocker (9, 5.63%), diuretics (9, 5.63) beta blockers (6, 3.75%), and nitrates (5, 3.13%) were the most common causal drug groups. While in antimicrobials, fluoroquinolones (8, 5%), beta lactam antibiotics (7, 4.38%), antiameobic agents (3, 1.88%), and macrolides (2, 1.25%) were the most common causal drug groups. Opioid analgesics were the most common agents among CNS drugs [Tables 1 and 2].

Among pediatric patients, most common drug group was antimicrobial agents (85, 33.46%) followed by blood products (36, 14.12%). Among antimicrobials,

beta-lactum antibiotics (31, 36.47%) were the most common followed by macrolides (12, 14.12%), fluoroquinolones (6, 7.6%), antimalarial (6, 7.6%), and vancomycin (6, 7.6%) [Tables 1 and 2].

Routes of administration

Out of 160 geriatric patients, majority of the patients (125, 78.12%) received the causal drug orally followed by 15 (9.3%) intravenous and 4 (2.5%) intramuscular route.

Similarly, in pediatric patients, out of 254 suspected drugs, 149 (58.66%) were administered orally followed by 66 (25.98%) intravenous and 21 (7.87%) intramuscular route [Table 1].

Polypharmacy

Out of 160 ADRs in geriatric patients, polypharmacy (≥ 5 drugs per prescription) was observed in 31 (19.37%) patients. Among them, 8 (25.8%) were suffering from cardiovascular diseases, and 5 (16.12%) were on postoperative medications.

In pediatric group, only 14 patients (6%) were prescribed more than 5 drugs.

Table 2: Common adverse drug reactions and mapping to the common causal drug groups in geriatric and pediatric patients

	Common ADRs	Common drug groups
Geriatric group	Vomiting (10, 16.25%)	Antimicrobials (5, 50%) CNS drugs (2, 20%) NSAIDs (1, 10%) Multi-vitamin (1, 10%) Anti-retroviral (1, 10%)
	Dizziness (9, 5.63%)	α-blockers (4%) β-blockers (3, 1.9%) Diuretics (1, 0.62%) Opioids (1, 0.62%)
	Metallic taste (9, 5.63%)	Antidiabetic (5, 55.56%) Benzodiazepines (2, 22.22%) Anti-arrhythmic (2, 22.22%)
	Rash (8, 5%)	Antimicrobials (5, 62.5%) Laxatives (1, 12.5%) NSAIDs (1, 12.5%) Antiretroviral (1, 12.5%)
	Diarrhea (5, 3.13%)	Antimicrobials (4, 80%) Antipsychotic (1, 20%)
Pediatric group	Rash (64, 27.71%)	Antimicrobials (33, 51.56%) NSAIDs (10, 15.62%) Anticholinergic (7, 10.93%) Iron chelating agent (6, 9.37%)
	Diarrhea (20, 8.65%)	Antimicrobials (16, 80%) Iron chelating agent (3, 15%)
	Chills (14, 6.06%)	Blood products (12, 85.71%)
	Fever (10, 4.33%)	Blood products (6, 60%)
	Headache (9, 3.89%)	Blood products (8, 88.88%)

ADRs=Adverse drug reactions, CNS=Central nervous system, NSAIDs=Nonsteroidal anti-inflammatory drugs

Seriousness of adverse drug reactions

Majority of ADRs were nonserious (144, 90%) in geriatric groups while the criteria for serious ADRs were initial or prolongation of hospitalization (8, 5%) followed by required interventions to prevent damage (4, 2.5%). Moreover, there were 4 (2.5%) life-threatening ADRs manifested as Steven–Johnson syndrome, hyperkalemia, severe anemia, and gastric erosions. Two cases of Steven–Johnson syndrome was reported in geriatric patients. The causal drugs for both the cases were fixed dose combination of zidovudine + lamivudine + nevirapine and diclofenac, respectively.

Similarly, in pediatric group, out of 231 ADRs, 201 (87%) were nonserious in nature. Among the serious ADRs, 16 (6.93%) required intervention to prevent damage followed by prolonged hospitalization (9, 3.89%). Moreover, two ADRs, laryngospasm and toxic epidermal necrolysis were life-threatening [Table 1]. One case of laryngospasm was reported in pediatric patients treated with intravenous contrast medium.

Outcome at the time of reporting

Majority of geriatric ADRs were continuing at the time of reporting (111, 69.37%). However, 31 (19.37%) recovered, and 17 (10.62%) were recovering. While the

majority of ADRs in pediatric patients were continuing (116, 50.22%), 86 (37.23%) were recovered, and 23 (9.96%) were recovering at the time reporting [Table 1].

Causality assessment

According to the WHO-UMC scale, majority of the geriatric and pediatric ADRs were categorized as possible (111, 69.37%; 141, 55.51%) followed by probable (49, 30%; 113, 44.49%) in nature. Whereas according to the Naranjo Algorithm, 84 (52.5%) and 171 (67.32%) were probable while 76 (47.5%) and 83 (32.68%) were possible in pediatric and geriatric patients, respectively [Table 1].

Severity and preventability

In geriatric group, severity of the ADRs were mild level 1 (99, 61.87%), mild level 2 (29, 18.13%), moderate level 3 (28, 17.5%), and moderate level 4 (4, 2.5%) while severity of pediatric ADRs were mild level 2 (136, 53.54%), mild level 3 (60, 23.62%), moderate level 4 (11, 5.11%), and severe level 5 (6, 2.36%) according to the Hartwig and Siegel scale. Preventability according to Schaumock and Toronto scale were not preventable for both pediatric and geriatric patients [Table 1].

DISCUSSION

This retrospective study is an attempt to analyze ADRs occurred in geriatric and pediatric patients at tertiary care teaching hospital. In our study, the reporting rate of geriatric ADR was 4.33% which is lower than Mandavi *et al.*^[11] While in pediatric group, the reporting rate of ADR was high (6.26%) compared to Digra *et al.* (0.3%).^[12] Men were more commonly affected than women. Our study observed that most of the geriatric patients belonged to 65–70 years while study done by Pauldurai *et al.* showed that common age was 60–65 years.^[13] The common pediatric age affected in our study was 5–10 years while Priyadarshini *et al.* reported more number of ADRs in 1–6 years.^[3]

The most common body system affected was gastrointestinal followed by neurological and skin and appendageal disorders in geriatric patients. Our observation was similar to Pauldurai *et al.* [Table 3]. This may be because most of the suspected drugs were administered orally in present study. In addition, most common causal drug groups were cardiovascular and antimicrobial agents which are known to cause gastrointestinal and skin reactions. In pediatric group, skin and appendages were commonly affected body system followed by gastrointestinal and body as a whole, which is similar to Digra *et al.* and Priyadharsini *et al.* [Table 3]. A study by Ghataliya *et al.* also reported that cutaneous ADRs are common with blood transfusion in pediatric patients.^[14] Probably dermatological reactions are easy and

Table 3: Comparison of geriatric and pediatric adverse drug reactions with available literature

	Geriatric group		Pediatric group	
	Our study (n=160)	Pauldurai et al. (n=97/520)	Our study (n=231)	Priyadharsini et al. (n=30)
Affected body system	Gastrointestinal Neurology Skin and appendages	Gastrointestinal Neurology Musculoskeletal	Skin and appendages Gastrointestinal Body as a whole	Skin and appendages
Causal drug group	Cardiovascular drugs Antimicrobials CNS drugs	Antimicrobial agents Cardiovascular drugs Endocrine drugs	Antimicrobial agents Blood products CNS drugs	Antimicrobial CNS drugs Cardiovascular drugs
Causality (%)				
WHO-UMC				
Probable	30	70.10	44.49	Not done
Possible	69.37	27.83	55.51	
Naranjo				
Definite	-	-	-	3
Probable	52.5	70.10	67.32	80
Possible	47.5	29.89	32.84	17
Severity (%)				
Mild	80	20	68.89	-
Moderate	20	74	28.73	77
Severe	-	3	2.36	23
Preventibility (%)				
Definitely preventable	-	Not done	-	3
Probably preventable	2.5		0.87	87
Not preventable	97.5		99.13	10

CNS=Central nervous system

immediately identified, and antimicrobials agents as well as blood products are common causal drug groups known to cause skin reactions. The most common causal drug group for geriatric patients was cardiovascular groups followed by antimicrobial agents which are supported by other Indian studies too [Table 3].^[15,16] This may be attributed to common cardiovascular morbidities and prevalence of infectious diseases in geriatric age group. Thus, cardiovascular and antimicrobials were figured as two of the most common drug groups causing ADRs in elderly. While in pediatric patients, most common causal drug group was antimicrobial agents followed by blood products which are similar to Indian study by Mandha *et al.*^[16] Another study by Smyth *et al.* performed at United Kingdom (UK) has shown that nonsteroidal anti-inflammatory drugs (NSAIDs) were the most common causal drug group. This indicates that the prevalence of infectious diseases is less in the UK^[17] whereas infections and malnutrition are the common problems in India. Antimicrobial agents and blood products are most commonly associated with hypersensitivity reactions. Thus, it further supports our previous finding that dermatological ADRs are common in pediatric patients. While injection site abscess following, vaccination denotes medication administration error. A study by Patel *et al.* has reported medication administration error is common in pediatric patients.^[18] This calls for need of training of health-care workers and monitoring following vaccination.

Our study shows that 19% of geriatric patients were prescribed more than 5 drugs while it was 86% as reported

by Pauldurai *et al.* It also substantiates that polypharmacy is very common in India. The chance of drug–drug interactions and risk of ADRs are more with polypharmacy. Thus, polypharmacy is one of the risk factors for developing the ADRs in geriatrics. Although majority of the ADRs were nonserious in nature, the common criteria for serious ADRs were initiation or prolongation of hospitalization and required intervention to prevent damage in geriatric and pediatric group, respectively. Similar observation has been reported by Prajapati *et al.*^[19]

The common causality association with suspected drug was ‘possible’ or ‘probable’ in majority of cases. Similar observations have been reported by Pauldurai *et al.* and Priyadharsini *et al.* [Table 3]. The absence of other alternative causes and positive dechallenge justifies the probable criteria. Frequently causality assessment has been a challenge due to lack of information on dechallenge and rechallenge, simultaneous starting of multiple drugs and existence of comorbidities with similar symptoms. Thus, causality association comes down to lower ‘possible’ grade. However, this does not undermine the importance of causal association with suspected drug and causality assessment *per se*.

Majority of ADRs were mild in nature in geriatric patients contrary to Pauldurai *et al.* study. This is because the most common affected body system was gastrointestinal system that includes mild reactions such as nausea, vomiting, metallic taste, and diarrhea for which stoppage of drugs and hospitalization are generally not required. Interestingly, the majority of ADRs were nonpreventable because skin was

the common target in both the age groups and most of the cutaneous reactions are idiosyncratic in nature^[20] [Table 3].

This was a retrospective study, wherein all ADRs were reported spontaneously. Underreporting, inability to find incidence rate, 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 data provides an opportunity for devising strategies to closely monitor geriatric and pediatric age group patients for ADRs.

CONCLUSION

ADRs are common in geriatric and pediatric patients usually within first 4 weeks of oral therapy. Reactions, mostly mild, nonserious, are common with cardiovascular and CNS drugs, antimicrobials and blood products and frequently target gastrointestinal, skin, and CNSs. Polypharmacy and extremes of age increase the risk of ADRs. This calls for the need for active surveillance of drug safety monitoring in these vulnerable populations.

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Conflicts of interest

There are no conflicts of interest.

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