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Research Article

# A RETROSPECTIVE STUDY: ANALYSIS OF ADVERSE DRUG REACTION IN PEDIATRIC PATIENTS IN A TERTIARY CARE HOSPITAL

**SUNIL KUMAR MATHUR[1], SAURABH KUMAR JAIN[2]*, AMUL MISHRA[2]**

[1]Department of Pharmacology, Jawaharlal Nehru Medical College, Ajmer, Rajasthan, India. [2]Faculty of Pharmacy, BN Institute of Pharmaceutical Sciences, Bhupal Nobel's University, Udaipur, Rajasthan, India. Email: saurabhpharma1983@gmail.com

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**ABSTRACT**

**Objective:** The objective of this study was to analyze various parameters such as admission type, demographics, type of reaction, organ system classification, drugs involved, action is taken, reaction outcome, causality assessment, severity assessment, and the preventability of Adverse drug reactions (ADRs) in pediatric patients.

**Methods:** This retrospective observational study was conducted during the period of September 2017 to June 2020 (34 months) at the ADR monitoring center, Department of Pharmacology, Jawaharlal Nehru Medical College, Ajmer, Rajasthan. All spontaneously reported ADRs were evaluated using various parameters such as type of reaction, causality assessment, preventability, and severity.

**Results:** In the present study, 72 (7.27%) ADRs were reported in relation to 65 pediatric patients. In this study, more ADRs were reported in male (53.85%) as compared to female (46.15%) pediatric patients. The majority of ADRs were considered type B (63.89%), probable (87.5%), moderate (51.39%), and definitely preventable (88.89%) in nature. The majority of ADRs were reported due to antimicrobial classes of drugs, including anthelmintic drug (Albendazole), followed by glycopeptide antibiotic (Vancomycin) and third-generation cephalosporin antibiotics (Ceftriaxone, Cefotaxime, and Cefixime). The organ systems most commonly affected were skin and subcutaneous tissue disorders (47.22%), followed by general disorders and administration site conditions (20.83%) and gastrointestinal disorders (16.67%).

**Conclusion:** The present study 30 different types of suspected ADRs that were reported with multiple frequencies, with included 34 different categories of drugs and combinations of drugs. The majority of patients recovered, with associated ADR, after necessary medical intervention and management. Our purpose is to minimize the incidence rate of ADRs in the pediatric population.

**Keywords:** World Health Organization, Program for international drug monitoring, Uppsala monitoring center, Adverse drug reaction.

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## INTRODUCTION

The word pharmacovigilance was reflected after a drug safety issue published in 1877 in the British Medical Journal, the chloroform issue. In 1898, the second issue was diacetylmorphine (heroin) that occurred. In the USA, 0.5 million heroin-dependent patients were reported [1].

In 1957, Thalidomide was launched onto the market and used as a hypnotic and sedative drug. This drug is used in pregnant women to control nausea. In the 1960s, a thalidomide tragedy came out. Newborn babies were born with agenesis of the limbs and phocomelia as an adverse effect of thalidomide. The WHO established its Program for International Drug Monitoring (PIDM) in response to the thalidomide disaster. Together with the WHO Collaborating Center for International Drug Monitoring, the Uppsala Monitoring Center was recognized to promote PV at the country level. At the end of 2021, 170 countries were part of the WHO PIDM. The aims of PV are to enhance patient care and patient safety in relation to the use of medicines and to support public health programs by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines [2].

The Indian government adopted this international program, named "Pharmacovigilance Program of India (PvPI)." PvPI was introduced in July 2010 by the Central Drugs Standard Control Organization with the support of the Ministry of Health and Family Welfare (MoHFW), the Government of India (GoI) the All India Institute of Medical Science, d New Delhi as a National Coordination Center (NCC). To ensure the execution of this program in a more active way, the NCC was recast at the Indian Pharmacopoeia Commission (IPC) on the 15th of April 2011. IPC is an autonomous institution of the MoHFW, GoI, and functions as the NCC for PvPI. At present, 567 Adverse drug reactions (ADR) monitoring centers are recognized under PvPI to detect, assess, understand, and prevent ADRs through the effective communication of health-care professionals. The World Health Organization (WHO) on July 18, 2017, recognized IPC-PvPI as a WHO-Collaborating Center for Pharmacovigilance in Public Health Programs and Regulatory Services [3].

Past study outcomes as a result of the incidence of ADRs causing hospital admission in children range from 0.4 to 10.3%, and their occurrence in hospitalized children is 0.6–16.8%. The overall incidence of ADRs in children is 2.9% [4]. Globally, ADR can lead to significant morbidity among children and have relatively more severe effects compared to adults. Pediatric pharmacovigilance needs to be implemented strongly in each health-care facility to minimize the incidence of ADRs among children [5]. A population group differs from adults anatomically, physiologically, immunologically, and psychologically, and a wide range of pharmacokinetic and pharmacodynamic variations of drugs occur during developmental stages. In neonates and infants, there is delayed gastric emptying time as a result of increased absorption time and a higher risk of adverse events [6,7]. As per previous studies, the outcome of ADRs in children is not limited to the result of prolonged hospitalization but may also lead to life-threatening, disability, or even death [8].

At present, there are different types of therapeutic formulations or products, including drugs, vaccines, and medical devices; available in the global market for the treatment of children, and new formulations come to the market every year. Pharmacovigilance of each product

needs to be required to control the morbidity rate and rational use of medicines [9,10].

## METHODS

### Study design

A retrospective analysis was carried out at the Department of Pharmacology, pharmacovigilance unit of the Adverse Drug Monitoring Centre at Jawaharlal Nehru Medical College and Associated Hospital, Ajmer, Rajasthan (India). We utilized the spontaneously reported voluntary ADRs reports of pediatric patients including outpatients and inpatients from September 2017 to June 2020. This study was approved by the Institutional Ethical Committee, letter No.1533Acad-III/MCA/2020 dated 30.07.2020.

The suspected ADR reporting form was recorded for adverse reactions related to drugs with all the relevant data such as patient details including initials, age at the time of event or date of birth, sex, weight, date of reaction started and recovery date, described reaction details, suspected medications including dose, route, frequency, date of therapy started and stopped, and indication, outcomes of event and reporter information [3].

### Evaluation of ADR data

The collected suspected ADR forms were verified by the expert committee members on a clinical basis, analyzed, and evaluated to understand the pattern of the ADRs with respect to patient demographics, characteristics of the reaction, type of reaction, characteristics or classification of the drugs involved, management and outcome of reactions, causality assessment, severity assessment, and preventability which were analyzed for inpatient and outpatient in the pediatric department in a tertiary care hospital.

Patient characteristics ADRs by age and sex were included for evaluation. Patients were divided into different age groups: 0–1 years, 1–3 years, 3–5 years, 5–8 years, 8–12 years, and 12–18 years. We utilized the classification of drug reactions given by Rawlins and Thompson [11]. System organ class, classified as per medical Dictionary for Regulatory Activities (MedDRA) [12]. The seriousness of ADRs was classified according to ICH E2A guideline criteria [13]. Drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system as per the WHO-ATC Index [14]. Management in respect to action taken due to ADRs that were categorized as drug withdrawn, dose reduced, dose not changed, and additional treatment for ADR. The outcome was finalized after confirmation dechallenge and rechallenge information. Causality assessment was analyzed using the WHO-UMC assessment scale [15]. The severity of ADRs was classified according to the modified Hartwig Siegel Scale [16]. The preventability of ADRs was classified using the criteria of preventability assessment modified Schumock and Thornton Scale [17].

## RESULTS

A total of 990 ADRs occurred in 749 patients between September 2017 and June 2020 (34 months), in which 72 (7.27%) adverse events were reported by pediatric patients, with respect to 65 (8.68%) pediatric patients including Outpatient Department (OPD) and IPD. The majority of the adverse events were reported by IPD 51 (78.46%) pediatric patients, and 14 (21.54%) were reported by OPD pediatric patients, as per Table 1.

**Table 1: Hospital admission type**

| Admission type | Number of pediatric patients associated with ADRs | % of pediatric patients associated with ADRs |
|---|---|---|
| IPD | 51 | 78.46 |
| OPD | 14 | 21.54 |
| Grand total | 65 | 100 |

ADR: Adverse drug reactions

In the evaluation of the demographic male to female ratio, there were 35 (53.85%) males and 30 (46.15%) female ADR forms reported. Details are given in Table 2.

A total of 72 ADRs occurred in 65 pediatric patients, in which 2 (3.08%) belonged to the age group of 0–1 years, followed by 9 (13.85%) belonged to the age group 1–3 years, 5 (7.69%) belonged to the age group 3–5 years, 12 (18.46%) belonged to the age group 5–8 years, 17 (26.15%) belonged to age group 8–12 years, and 20 (30.77%) belonged to the age group 12–18 years. Details are given in Table 3.

The majority of ADR in this study were Type B 46 (63.89%) and Type A 26 (36.11%) reactions. According to the WHO causality assessment criteria, most of the ADRs were probable 63 (87.5%), followed by 5 (6.94%) possible, 3 (4.18%) certain, and 1 (1.38%) unlikely in nature. The reaction severity scale accounted for 31 (43.05%) ADRs being mild, followed by 37 (51.39%) moderate and 4 (5.56%) severe. On the evaluation of the preventability of ADR, 64 (88.89%) were definitely preventable, followed by 8 (11.11%) probably preventable, as per the modified Schumock and Thornton scale. The results are tabulated in Table 4.

**Table 2: Gender-wise distribution of ADRs reports**

| Gender | Number of pediatric patients associated with ADRs | % of Pediatric patients associated with ADRs |
|---|---|---|
| Male | 35 | 53.85 |
| Female | 30 | 46.15 |
| Grand Total | 65 | 100 |

ADR: Adverse drug reactions

**Table 3: Age-wise distribution of pediatric patients with ADRs (i.e., ADRs 65)**

| Age group (Year) | Number of ADR reports | % of ADR reports |
|---|---|---|
| (0–1) | 2 | 3.08 |
| (1–3) | 9 | 13.85 |
| (3–5) | 5 | 7.69 |
| (5–8) | 12 | 18.46 |
| (8–12) | 17 | 26.15 |
| (12–18) | 20 | 30.77 |
| Grand Total | 65 | 100 |

ADR: Adverse drug reactions

**Table 4: Analysis of ADRs (Reaction type, causality assessment, severity, and preventability)**

| Reaction type | Number of ADRs | (%) of ADRs |
|---|---|---|
| Type-A (Augmented) | 26 | 36.11 |
| Type-B (Bizarre) | 46 | 63.89 |
| Grand Total | 72 | 100 |
| Causality Assessment | | |
| Probable | 63 | 87.5 |
| Possible | 05 | 6.94 |
| Certain | 03 | 4.18 |
| Unlikely | 01 | 1.38 |
| Grand Total | 72 | 100 |
| Severity | | |
| Mild | 31 | 43.05 |
| Moderate | 37 | 51.39 |
| Severe | 04 | 5.56 |
| Grand Total | 72 | 100 |
| Preventability | | |
| Definitely preventable | 64 | 88.89 |
| Probably preventable | 08 | 11.11 |
| Non preventable | 00 | |
| Grand Total | 72 | 100 |

ADR: Adverse drug reactions

The organ systems most commonly affected were skin and subcutaneous tissue disorders 34 (47.22%), followed by general disorders and administration site conditions15 (20.83%), followed by gastrointestinal disorders12 (16.67%), followed by nervous system disorders 4 (5.55%) and Cardiac disorders 2 (2.78%). All types of ADR were managed with systematic medically treatment. The results are tabulated in Table 5.

In the present study, 30 different types of the suspected ADRs were reported with multiple frequencies due to 34 categories of drugs and a combination of drugs including vaccines also. The majority of ADRs were reported due to Albendazole 12 (16.67%), followed by Vancomycin 9 (12.5%), followed by Cyanocobalamin+Ferrous fumarate+Folic acid 6 (8.33%), Ceftriaxone sodium 5 (6.94%), Tramadol 4 (5.56), Dicycloverine hydrochloride 3 (4.17%), Ampicillin 2 (2.78%), Diphtheria vaccine toxoid+Pertussis vaccine+Tetanus vaccine toxoid 2 (2.78%), Glucose+Potassium chloride+Sodium chloride+ Sodium lactate 2 (2.78%), Immunoglobulin anti-corynebacterium diphtheria toxin 2(2.78%), and Prochlorperazine maleate 2 (2.78%).

The majority of ADRs were reported including 12 (16.67%) chronic abdominal pain, followed by 8 (11.11%) generalized urticarial rash, followed by 6 (8.33%) generalized rash, 5 (6.94%) erythematous skin rash, 3 (4.17%) rash on face, 3 (4.17%) shivering, 3 (4.17%) administration site erythema, 3 (4.17%) red man syndrome, and 3 (4.17%) Stevens–Johnson Syndrome. Details are given in Table 6.

In this study, a total of 61 (84.72%) ADR were found non-serious and 11 (15.28%) ADR were found serious. Details are given in Table 7.

In the present study, the drug was withdrawn in the majority of 45 (69.23%) ADR cases, followed by 4 (6.15%) that did not change and 16 (24.62%) were not applicable. Details are given in Table 8.

In the present study, 59 (81.95%) of ADR were recovered, followed by 12 (16.67%) under recovering and 1 (1.38%) of cases not recovered at the time of reporting of ADR and no fatal/death case was reported in this study. Results are given in Table 9.

## DISCUSSION

In the present study, 72 (7.27%) ADRs were reported by pediatric patients in the age group of 0–18 years. The majority of ADRs were reported from IDP patients (78.46%) as compared to OPD patients, because admitted pediatric patients were treated with more drug therapies, including injectable formulation, which increased the probability of ADR. OPD patients were prescribed limited drug therapy, including oral treatment mainly. Another reason that low ADRs were reported from OPD patients is that during the OPD timing, the majority

**Table 5: Organ system-related disorder due to ADRs**

| Organ system | Number of ADRs | (%) of ADRs |
|---|---|---|
| Skin and subcutaneous tissue disorders | 34 | 47.22 |
| General disorders and administration site conditions | 15 | 20.83 |
| Gastrointestinal disorders | 12 | 16.67 |
| Nervous system disorders | 4 | 5.55 |
| Cardiac disorders | 2 | 2.78 |
| Eye disorders | 1 | 1.39 |
| Hepatobiliary disorders | 1 | 1.39 |
| Immune system disorders | 1 | 1.39 |
| Reproductive system and breast disorders | 1 | 1.39 |
| Respiratory, thoracic, and mediastinal disorders | 1 | 1.39 |
| | 72 | 100 |

ADR: Adverse drug reactions

**Table 6: Description of suspected drugs, individual reaction with frequency and total number if ADRs associated with drugs**

| Suspected drug/Active ingredients | ADRs (Frequency of occurrence) | Number of ADRs |
|---|---|---|
| Dextrose and electrolyte | Erythematous Skin rash | 1 |
| Aceclofenac+Paracetamol | Stevens Johnson syndrome | 1 |
| Albendazole | Chronic abdominal pain | 12 |
| Amikacin sulfate | Erythematous Skin rash | 1 |
| Ampicillin | Administration site erythema<br>Administration site swelling | 2 |
| Azithromycin | Stevens Johnson syndrome | 1 |
| Cefalexin | Stevens Johnson syndrome | 1 |
| Cefixime | Maculopapular rash | 1 |
| Cefotaxime sodium | Generalized itching | 1 |
| Ceftriaxone sodium | Erythematous Skin rash<br>Generalized rash (2)<br>Generalized urticarial rash (2) | 5 |
| Ceftriaxone sodium+Sulbactam sodium | Generalized urticarial rash | 1 |
| Cyanocobalamin+Ferrous fumarate+Folic acid | Administration site erythema (2)<br>Administration site induration<br>Administration site swelling<br>Injection site hyperpigmentation<br>Injection site itching | 6 |
| Diclofenac sodium+Paracetamol | Generalized urticarial rash | 1 |
| Dicycloverine hydrochloride | Generalized urticarial rash (2)<br>Itching – generalized | 3 |
| Diphtheria vaccine toxoid+Pertussis vaccine+Tetanus vaccine toxoid | Convulsion<br>Seizure like phenomena | 2 |
| Factor viii (Antihemophilic factor) | Genital itching | 1 |
| Folic acid+Iron | Generalized urticarial rash | 1 |
| Glucose+Potassium chloride+Sodium chloride+Sodium lactate | Chills<br>Rigors | 2 |
| Ibuprofen | Generalized rash | 1 |
| Immunoglobulin anti-corynebacterium diphtheria toxin | Erythematous Skin rash | 2 |
| Immunoglobulin human anti-rabies | Facial swelling | 1 |
| Isoniazid | Drug-induced hepatitis | 1 |
| Ofloxacin | Facial swelling | 1 |
| Ofloxacin+Ornidazole | Laryngeal edema | 1 |
| Ondansetron | Generalized urticarial rash | 1 |
| Paracetamol | Maculopapular rash | 1 |
| Phenytoin | Generalized rash | 1 |

*(Contd...)*

**Table 6: *(Continued)***

| Suspected drug/Active ingredients | ADRs (Frequency of occurrence) | Number of ADRs |
|---|---|---|
| Prochlorperazine maleate | Dystonia<br>Extrapyramidal syndrome | 2 |
| Rabies antiserum | Generalized rash | 1 |
| Salbutamol | Palpitation | 1 |
| Snake venom antiserum | Palpitation<br>Shivering (3) | 4 |
| Tramadol | Abnormal eye movements | 1 |
| Vancomycin | Anaphylactic reaction<br>Itchy rash (2)<br>Rash on face (3)<br>Red man syndrome (3) | 9 |
| Vitamin b complex | Generalized rash | 1 |
| Grand Total | | 72 |

ADR: Adverse drug reactions

**Table 7: Distribution of ADRs according to seriousness**

| Seriousness of reaction | Number of ADRs | % of ADRs |
|---|---|---|
| Non Serious | 61 | 84.72 |
| Serious | 11 | 15.28 |
| Grand Total | 72 | 100 |

**Table 8: Management of ADRs reports**

| Action taken | Number of ADRs | (%) of ADRs |
|---|---|---|
| Drug Withdrawn | 45 | 69.23 |
| Dose not Changed | 4 | 6.15 |
| Not Applicable | 16 | 24.62 |
| Grand Total | 65 | 100 |

**Table 9: Final outcome of ADRs**

| Final outcome | Number of ADRs | (%) of ADRs |
|---|---|---|
| Recovered | 59 | 81.95 |
| Recovering | 12 | 16.67 |
| Not Recovered | 1 | 1.38 |
| Fatal/Death | 0 | 0 |
| Grand Total | 72 | 100 |

of doctors were busy treating patients due to high patient load. Therefore, reporting of ADRs was practically impossible.

In our study, a total of 65 pediatric patients suffered from ADRs, among whom there was a male (53.85%) preponderance as compared to female (46.15%) which is similarly supported by a study carried out by Aagaard *et al*., Kalyani *et al*., and Divyalasya *et al*. [4,18,19].

The majority of ADRs occurred in the age groups of 12–18 years (30.77%) and 8–12 years (26.15%), followed by age groups of 5–8 years (18.46%), 3–5 years (7.69%), 1–3 years (13.85%), and 0–1 year (3.08%). As per this result, fewer numbers of ADRs were reported from neonates and infants as compared to the children age group. A dissimilar study was conducted by Divyalasya *et al*. [4]. Most of the ADRs were reported in neonates and infants.

In this study, most ADRs were found to be Type B (63.89%) as compared to Type A (36.11%). This may be due to the majority of ADR being unpredictable in nature and not related to the pharmacological properties of drugs. Most of the ADRs were reported as skin and subcutaneous tissue disorders (47.22%) including different types of rashes and generalized itching. All these reactions were considered Type B reactions on the basis of immunological and genetics.

According to the WHO-UMC causality assessment, it was found that the majority of ADRs were probable (87.5%), followed by possible (6.94%), certain (4.18%), and unlikely (1.38%). Similarly, results were found in a study done by Divyalasya *et al*. [4].

The majority of ADRs were moderate (51.39%) in severity, followed by mild (43.05%) and severe (5.56%) which were similar to a study carried out by Priyadharsini *et al*. [20].

The majority of ADRs (88.89%) in our study were definitely preventable, followed by probable preventable (11.11). Our finding is in contrast to the study done by Kalyani *et al*. and Divyalasya TVS *et al*. [4,19].

The most commonly seen skin and subcutaneous tissue reaction (47.22%), in our study, was similar to the study conducted by Sindhu *et al*. and Mrutunjay *et al*. [21,22]. Skin and subcutaneous tissue are the most common organ system class involved in drug hypersensitivity reactions [23,24].

A dissimilar study was conducted by Rajalakshmi *et al*. which affected the gastrointestinal system (43.7%) followed by the skin and subcutaneous tissue system (25%) [25].

In the present study, several antimicrobial classes of drugs were responsible for the majority of ADRs, including anthelmintic drugs (Albendazole, 16.67%), glycopeptide antibiotics (Vancomycin, 12.5%), third-generation cephalosporin antibiotics (Ceftriaxone 6.94%, Cefotaxime 1.38%, and Cefixime 1.38%), and hematinics agents (Cyanocobalamin+Ferrous fumarate+Folic acid). This consists of past study done by Smyth *et al*. [26]. Most ADRs were reported due to the cephalosporin class of antibiotics, because they are commonly used to treat infections in pediatric patients.

In this study, 12 children suffered from chronic abdominal pain due to an albendazole oral tablet taken during the National Deworming day at the school level. After that, 12 children were admitted to the pediatric emergency unit and medically treated. Finally, all the children were recovered and discharged from the hospital.

In this study, the majority of ADRs were non-serious (84.72%), and only (15.28%) of them were found serious with prolonged hospitalization. These included Stevens–Johnson Syndrome due to Aceclofenac+Paracetamol, Azithromycin, and Cefalexin, followed by generalized urticarial rash due to Ceftriaxone sodium and Ceftriaxone sodium+Sulbactam Sodium, Laryngeal edema due to Ofloxacin+Ornidazole, Facial swelling due to immunoglobulin human Antirabies, Drug induce hepatitis due to Isoniazid, Anaphylactic reaction due to Vancomycin, and abnormal eye movement due to Tramadol. A dissimilar study was done by Divyalasya *et al*. and Priyadharsini *et al*. [4,20].

In the present study, for the management of ADRs, in the majority of cases, the suspected drug was withdrawn (69.23%) to prevent adverse events. About 24.62% of cases of ADRs action taken were not applicable due to single-dose therapy including vaccines or Albendazole tablet and 6.15% of cases ADRs suspected drug treatment did not change due to the priority of the patient's life, for example, in the case of snake venom antiserum prescribed for snake bite.

In the case of final outcome results, (81.95%) of ADRs were recovered, followed by 16.67% recovering and 1.38% not recovered at the time of ADR reporting. These results were similar to a study carried out by Rajalakshmi *et al*. [25].

ADRs developed within a week of the initiation of drug treatment. If the patient informs the physician quickly, the physician can quickly understand and prevent the patient's ADR. Similar findings have been made before by Ramesh *et al*. [27]

## CONCLUSION

In this study, ADRs occurred more frequently in the children's age group compared to neonates and infants. More ADRs were reported in males as compared to females. The majority of ADRs were reported due to the antimicrobial class of drugs. The majority of the adverse effects are thought to be caused by the skin and subcutaneous tissue organ system class. As per data analysis of ADRs, most of the reactions were non-serious, type B, probable, moderate, and definitely preventable and recovered in nature. A pediatric pharmacovigilance system needs to be established in every health-care facility to closely monitor the ADRs among pediatric patients to reduce the ADRs in pediatric patients and minimize their morbidity rate. India has a lower number of ADRs reporting. There is a need to conduct more pharmacovigilance awareness and ADR monitoring and reporting training programs for health-care professionals and consumers to increase the ADR reporting culture in India and to calculate the actual rate of incidence and prevalence of ADRs in the Indian population.

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## AUTHORS' CONTRIBUTION

All the authors contributed to the study design, literature review, data collection, and data analysis.

## CONFLICTS OF INTEREST

None.

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