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Research Article

PATTERN AND CAUSALITY ASSESSMENT OF ADVERSE DRUG REACTIONS IN PEDIATRIC POPULATION IN AND AROUND KANNAUJ

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Abstract:

Objectives: To report, assess and compare Adverse Drug Reactions (ADRs) in healthy, malnourished and low birth weight children and to perform causality assessment of reported ADRs.

Methods: This was a prospective observational study conducted in the ADR Monitoring Centre, GMC, Kannauj after approval from the Institutional Ethics Committee from November 2023 to October 2024. Grade of malnutrition was assessed using IAP Classification of Malnutrition. Low birth weight assessment was done using WHO Fetal Growth Chart. ADRs were reported using CDSCO Suspected ADR Reporting Form. Causality Assessment was done using WHO-UMC Causality

Assessment Scale and Naranjo ADR Probability Scale. The data was analyzed using appropriate statistical tests.

Results: The study included 106 pediatric patients with ADRs aged 0-18 years. Out of these 90(84.9%) were healthy, 3(2.8%) were malnourished and 13(12.3%) low birth weight. The most common ADRs observed were skin rashes and itching (59.4%), followed by general symptoms including fever, angioedema, sore throat, headache (22.7%). Most common suspected medications were antibiotics (58.5%) followed by vaccines (28.3%). Most common antibiotics found to cause ADRs were cefixime (25.8%) followed by amoxicillin (24.19%). Causality assessment showed 70.6 % as probable using WHO-UMC scale and 71.7% using Naranjo scale. Association between suspected medications and reported ADRs was found to be statistically significant (p value 0.000). Association between ADRs and Low Birth Weight was found to be statistically significant (p value 0.033).

Conclusion: There is an urgent need for ADR monitoring to reduce morbidity and increase patient safety among pediatric population.

Keywords: Adverse Drug Reactions, Pediatric, Low birth weight, Antibiotics, Vaccines

INTRODUCTION

The World Health Organization (WHO) defines adverse drug reactions (ADRs) as unwanted reactions in humans caused by a drug on a therapeutic dose for the diagnosis, prophylaxis, or management of diseases [1]Preventable ADR's result from errors such as incorrect dosage, timing and relation with food or medication selection as per diagnosis, known allergies and inadequate monitoring. ADRs frequently occur in the healthcare industry. The median incidence of ADRs that resulted in hospitalization (ADRAd) and those that occurred while a patient was in the hospital (ADRIn) was 2.85% (IQR: 1.25-3.93%) and 6.34% (IQR: 3.36-16.37%), respectively [2].

In Pediatric population many medications are marketed without adequate clinical trials, thus this population is easily susceptible to adverse drug reactions (ADRs). A unique range of adverse reactions results from the substantial differences in

Pharmacodynamics and Pharmacokinetics between children and adults. The risk of ADRs is higher in neonates owing to their immature hepatic and renal systems. Almost 50% of ADRs in children occur due to antimicrobial, making them the second most reported cause of ADRs, after vaccines [3–5]. The most common ADRs include skin rashes, diarrhea, vomiting, and nausea. Around 40% of these ADRs are brought on by beta-lactam antibiotics. [6]. Paracetamol, NSAIDs, and opioids; main groups of analgesics being used to treat pain in children, often given inadequately during treatment, lead to collectively cause around 10% of pediatric ADRs[7] . Rieder M. (2019) [8] highlights the significant yet under appreciated risk of ADRs in children, challenging the misconception that children are less prone to ADRs than adults. Pediatric therapy presents unique challenges that place certain groups of children at high risk for ADRs.

An active drug surveillance system is of utmost importance for capturing and addressing ADR risks in children including newborns as well. As the literature on pediatric ADRs from India is limited, in addition to gaps in existing Pharmacovigilance system for children; there is need for focused research and studies in this aspect. The Pharmacovigilance is a science or activity related to detection, evaluation, understanding, and prevention of adverse effects or other drug-related problems. It involves identifying ADRs, collecting and analyzing relevant data, and implementing regulatory measures, forming a critical component of public health initiatives" [9]. Sheth et al. (2024) [10] conducted a study on pharmacovigilance in hospitalized pediatric patients at a tertiary care hospital. The study highlights the significance of pharmacovigilance in detecting, assessing, and preventing ADRs and ultimately ensuring medication safety.

Due to paucity of literature pertaining to Adverse Drug Reactions in pediatric population and laxity of reporting in children, we analyzed adverse drug reactions in healthy, low birth weight and malnourished children in healthcare system catering to the need of Rural population.

MATERIALS AND METHODS

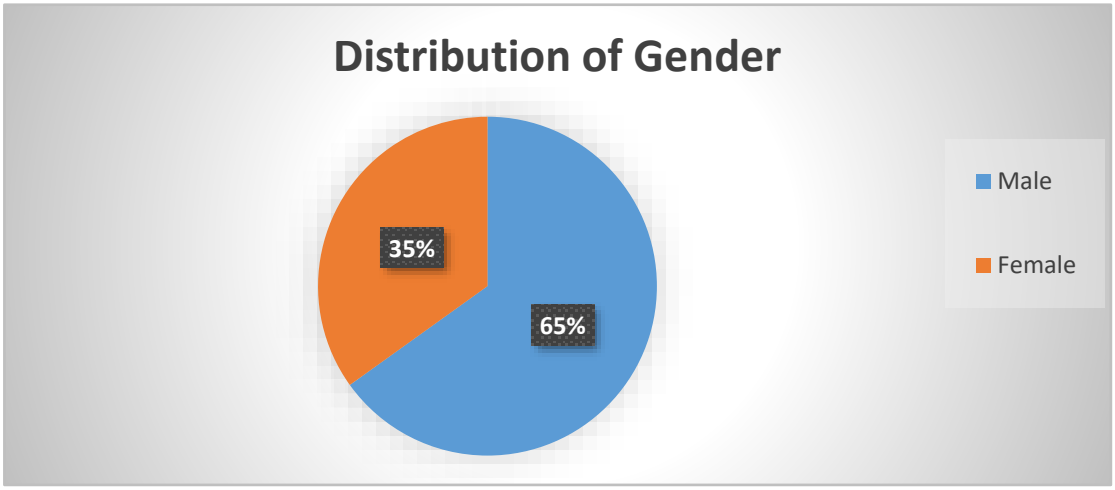
This was a prospective observational study conducted in the Adverse Drug Reaction Monitoring Centre (AMC) of a tertiary care hospital, Government Medical College, Kannauj. The study was conducted over a period of 12 months from November 2023 to October 2024. The study approved from the Institutional Ethics Committee (IEC)

of Government Medical College, Kannauj (review letter no. IEC/GMC, Kannauj /19, Dated -08 Nov 2023). Pediatric patients aged 0-18 years who experienced ADRs following the administration of any therapeutic agents during hospitalization or outpatient visits with written informed consent obtained from parents or guardians were included in the study. Sample Size**:** 106 pediatric cases were reported in the study. Data Collection: Data was collected from Pediatric patients in and around GMC, Kannauj presenting with suspected ADRs at outpatient departments, inpatient wards and the intensive care unit. ADR Documentation: ADRs were documented using the CDSCO form[11] provided by the Pharmacovigilance Programme of India (PvPI). Sub-group Analysis: ADRs were categorized into three groups for comparison: a. Healthy children. b. Malnourished children. c. Low birth weight children. Causality Assessment:The causality of reported ADRs were assessed using the WHO-UMC causality assessment scale[12] and Naranjo adverse drug reaction probability scale[13]

RESULTS

The study included 106 pediatric patients. The mean age of pediatric patients was 5.92 ± 5.02 years. The mean birth weight was 2.60 ± 0.22 kg with minimum birth weight of 2 kg and maximum of 3.5 kg

Fig 1: Distribution of Gender Among Patients



The male to female ratio in the pediatric patients was 1.86: 1 with 65% males and 35% females.

Table 1: Distribution of Nutritional Status Among Patients

Well nourished	Freq.	Percent
Yes	103	97.17
No	3	2.83
Total	106	100.00

Out of 106 pediatric cases, majority 103 (97.17%) were well nourished.

Table 2: Distribution of Moderate Acute Malnutrition (MAM) Status Among Patients

Moderate Acute Malnutrition	Freq.	Percent
Yes	3	2.83
No	103	97.17
Total	106	100.00

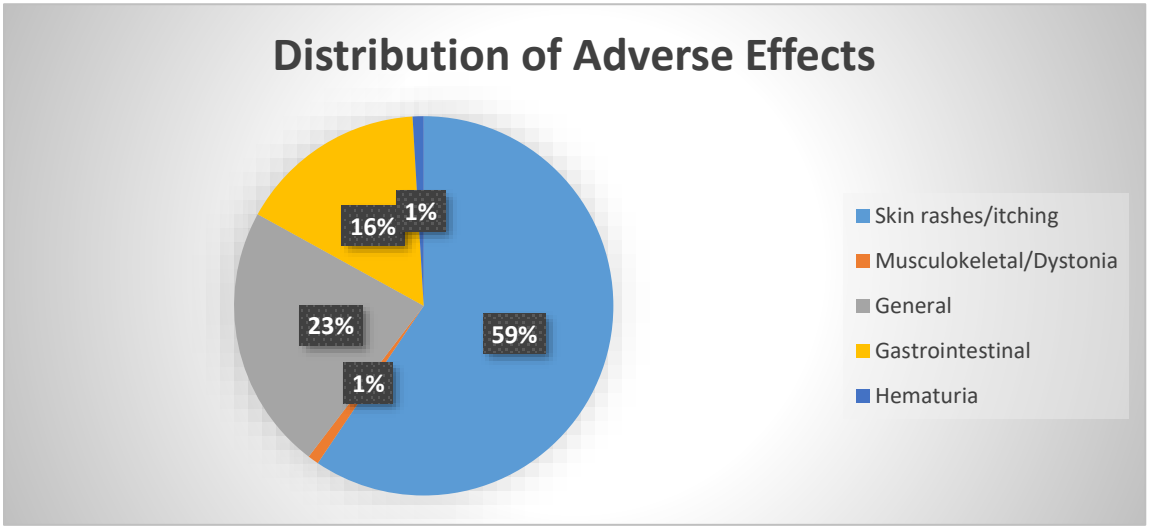
Out of 106 pediatric cases, majority 103 (97.17%) were well nourished but 3 (2.83%) were suffering from moderate acute malnutrition.

Table 3: Distribution of Low Birth Weight Among Patients

Low Birth Weight	Freq.	Percent
No	93	87.74
Yes	13	12.26
Total	106	100.00

Out of 106 cases, only 13 (12.26%) had low birth weight.

Fig 2: Distribution of Adverse Effects among Patients



The most common adverse effects noted were skin rashes and itching in 63 pediatric patients (59.43%), followed by general symptoms including fever, angioedema, sore, headache etc. (24; 22.64%), gastrointestinal infection (loose motion, abdominal pain, vomiting) contributed to 16.04%. While dystonia and hematuria were each reported in one pediatric patient.

Table 4: Association Between Suspected Medications and Reported Adverse Effects

Suspected Medication	Adverse Effects					Total N (%)	Fischer's Exact
	Skin Rashes/Itching N (%)	Musculoskeletal-Dystonia N (%)	General N (%)	Gastrointestinal N (%)	Urinary – Hematuria N (%)		
Antibiotics	41 (65.08)	0 (0.00)	7 (29.17)	13 (76.47)	1 (100.00)	62 (58.49)	p*= 0.000
Antipyretics	2 (3.17)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (1.89)	
Anti-emetics	0 (0.00)	1 (100.00)	0 (0.00)	1 (5.88)	0 (0.00)	2 (1.89)	
Vaccines	16 (25.40)	0 (0.00)	14 (58.33)	0 (0.00)	0 (0.00)	30 (28.30)	
Antifungals	2 (3.17)	0 (0.00)	0 (0.00)	2 (11.76)	0 (0.00)	4 (3.77)	

Analgesics	1 (1.59)	0 (0.00)	2 (8.33)	0 (0.00)	0 (0.00)	3 (2.83)	
Antispasmodic	1 (1.59)	0 (0.00)	1 (4.17)	1 (5.88)	0 (0.00)	3 (2.83)	
Total	63 (100.00)	1 (100.00)	24 (100.00)	17 (100.00)	1 (100.00)	106 (100.00)	

The adverse effects such as skin rashes and itching were commonly associated with antibiotic medications (41; 65.08%) followed by vaccines (16; 25.40%). General symptoms were reported due to vaccines (14; 58.33) and antibiotics (7; 29.17%). The gastrointestinal symptoms were observed more with antibiotics (13; 76.47%). The association between suspected medications and adverse effects was statistically significant (p = 0.000).

In the study most commom antibiotics was cefixime (25.81%) which caused ADRs, 2nd most common antibiotics was amoxicillin(24.19%), 3rd was ceftriaxone (19.35%) and others azithromycin , ofloxacin, vancomycin etc.

Table 5: Association Between WHO Causality Assessment and Reported Adverse Effects

Causality Assessment	**Adverse Effects**					**Total**	**Fisher's Exact**
	Skin Rashes/Itching N (%)	Musculoskeletal-Dystonia N (%)	General N (%)	Gastrointestinal N (%)	Urinary – Hematuria N (%)	N (%)	
Certain	0 (0.00)	1 (100.00)	2 (8.33)	0 (0.00)	0 (0.00)	3 (2.83)	p*= 0.020
Probable	43 (68.25)	0 (0.00)	20 (83.33)	11 (64.71)	1 (100.00)	75 (70.75)	
Possible	17 (26.98)	0 (0.00)	2 (8.33)	6 (35.29)	0 (0.00)	25 (23.58)	

Unlikely	3 (4.76)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (2.83)	
Total	63 (100.00)	1 (100.00)	24 (100.00)	17 (100.00)	1 (100.00)	106 (100.00)	

The assessment by WHO causality assessment scale showed that out of 106 ADRs, 3 (2.83%) were certain, 75(70.75 %) were probable and 25(23.58%) were possible, 3(2.83%)were unlikely.[Table 10]

Table 6: Association Between Naranjo's Scale and Reported Adverse Effects

Naranjo Scale	**Adverse Effects**					**Total**	**Fischer's Exact**
	Skin Rashes/Itching N (%)	Musculoskeletal-Dystonia N (%)	General N (%)	Gastrointestinal N (%)	Urinary – Hematuria N (%)	N (%)	
Definite (≥9)	0 (0.00)	1 (100.00)	2 (8.33)	0 (0.00)	0 (0.00)	3 (2.83)	p*=0.001
Probable (5-8)	43 (68.25)	0 (0.00)	21 (87.50)	11 (64.71)	1 (100.00)	76 (71.70)	
Possible (1-4)	20 (31.75)	0 (0.00)	1 (4.17)	6 (35.29)	0 (0.00)	27 (25.47)	
Doubtful (0)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	
Total	63 (100.00)	1 (100.00)	24 (100.00)	17 (100.00)	1 (100.00)	106 (100.00)	

Table 7: Association Between Adverse Effects and Nutritional Status (Well Nourished)

Adverse Effects	**Well Nourished**		**Total**	**Fischer's Exact**
	Yes N (%)	No N (%)	N (%)	
Skin Rashes/Itching	62 (60.19)	1 (33.33)	63 (59.43)	

Musculoskeletal- Dystonia	1 (0.97)	0 (0.00)	1 (0.94)	p*= 0.379
General (fever, angioedema, sore, headache etc.)	23 (22.33)	1 (33.33)	24 (22.64)	
Gastrointestinal	16 (15.53)	1 (33.33)	17 (16.04)	
Urinary - Hematuria	1 (0.97)	0 (0.00)	1 (0.94)	
Total	103 (100.00)	3 (100.00)	106 (100.00)	

There were only three pediatric patients who were not well nourished while remaining 103 out of 106 pediatric patients were well nourished. Adverse effects such as skin rashes and itching were reported in 63 (59.43%) pediatric patients (62; 60.19% well nourished and 1; 33.33% in those who were not well nourished). Fischer's exact value of 0.379 showed that there was no statistically significant association between nutritional status and adverse effect.

Table 8: Association Between Adverse Effects and Moderate Acute Malnutrition (MAM) Status

Adverse Effects	**Moderate Acute Malnutrition (MAM)**		**Total**	**Fischer's Exact**
	Yes N (%)	No N (%)	N (%)	
Skin Rashes/Itching	1 (33.33)	62 (60.19)	63 (59.43)	p*= 0.379
Musculoskeletal- Dystonia	0 (0.00)	1 (0.97)	1 (0.94)	
General (fever, angioedema, sore, headache etc.)	1 (33.33)	23 (22.33)	24 (22.64)	
Gastrointestinal	1 (33.33)	16 (15.53)	17 (16.04)	
Urinary - Hematuria	0 (0.00)	1 (0.97)	1 (0.94)	
Total	3 (100.00)	103 (100.00)	106 (100.00)	

There were only three pediatric patients who were suffering from moderate acute malnutrition (MAM). Fischer's exact value of 0.379 indicates no statistically significant association between nutritional status and adverse effect.

Table 9: Association Between Adverse Effects and Low Birth Weight

Adverse Effects	Low Birth Weight		Total	Fischer's Exact
	No N (%)	Yes N (%)	N (%)	
Skin Rashes/Itching	59 (63.44)	4 (30.77)	63 (59.43)	p*=0.033
Musculoskeletal- Dystonia	0 (0.00)	1 (7.69)	1 (0.94)	
General (fever, angioedema, sore, headache etc.)	20 (21.51)	4 (30.77)	24 (22.64)	
Gastrointestinal	13 (13.98)	4 (30.77)	17 (16.04)	
Urinary - Hematuria	1 (1.08)	0 (0.00)	1 (0.94)	
Total	93 (100.00)	13 (100.00)	106 (100.00)	

The table and graph depict that the adverse effects such as skin rashes and itching were observed more in those who had normal birth weight (59; 63.44%) compared to those with low birth weight (4; 30.77%). General and gastrointestinal symptoms were each reported in 30.77% of low birth weight pediatric patients. The (p = 0.033) showed that there was statistically significant association between low birth weight and adverse effect.

DISCUSSION

In present study, total 106 pediatric patients were enrolled with mean age of 5.92 ± 5.02 years, with males (65%) to females (35%) ratio of 1.86:1. Similar finding was reported in study by Das M et al. (2022)[14] with 68% males and 32% were females .

In the present study the most commonly suspected medications were antibiotics and the most common adverse effects noted were skin rashes and itching (59.43%), followed by general symptoms (22.64%) and gastrointestinal disorders (16.04%). Most common antibiotic found to cause ADR was cefixime. The adverse effects such as skin rash and itching were commonly associated with antibiotic medications followed by vaccines.

The study by Birhane H et al. (2021)[15] showed similar findings with predominance of skin ADR followed by general symptoms which were in concordance to present study. In the present study there was significant association noted between low birth weight and adverse drug reactions (p = 0.033). General and gastrointestinal symptoms were observed more in low birth weight pediatric patients, reason for ADR in LBW patient because of lesser immunity. Although malnourished also had lesser immunity, but no significant association was observed between nutritional status and adverse drug reactions (p = 0.379) this may be due to small number of malnourished children in the present study. This finding contrasts with Tola WO et al. (2023)[16] where malnourished was one of the key factors for adverse drug reactions. It was observed that around 27% of children had severe acute malnutrition, which was not observed in the present study. The underreporting of adverse medication reactions is the greatest obstacle in pharmacovigilance[17]. Improving patient safety, quality of life, and treatment cost-effectiveness requires early detection and management of adverse medication reactions.

The present study had several strengths and positive aspects that helped in understanding the adverse drug reactions in pediatric patients. The most of the findings were aligned and validated with existing literature in terms of presence of skin related ADR, antibiotics as the most susceptible medication and causality of ADR categorized as probable, thus confirming the trends and patterns observed in previous studies. [18]

However, the study provided valuable insights into pediatric adverse drug reactions comparing its findings with other studies will help in understanding the broader perspective of patient drug safety, management of ADR, pharmacovigilance and planning a future long term follow up study.

CONCLUSION

The findings of the present study helps in informing about the various aspects of adverse drug reactions which will expand the detection and monitoring of pediatric patients with ADR, drug safety, dosage requirement

The pediatric population is a major health asset for the growth of a country. Medications must be rational and ethical in a pediatric patient as this population is highly prone to develop ADRs due to polypharmacy, previous adverse reaction to another drug, impaired liver or renal function, off-label and unlicensed drug use and

genetic polymorphism . Healthcare Professionals have an important responsibility in monitoring the ongoing safety of medicines.

The incidence of adverse drug events is not directly proportional to the number of drugs being taken but increases remarkably as number of drugs rises.

The reporting of these ADRs is of utmost importance to be done by HCPs dealing with pediatric population viz. Pediatricians, Pediatric nurses & Vaccinators , NICU & PICU Staff. Additionally, further research may be planned to assess the severity, preventability, recovery after ADR etc. so as to generate more comprehensive evidence to inform policy changes in Pharmacovigilance programme.

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