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**A Study of Adverse Reactions on Pediatric Patients**

P. K. Valsalakumari\*, G. R. Rajalakshmi and Helen William

College of Pharmaceutical Sciences, Medical College, Gandhinagar, Kottayam, (Kerala) - India

**Abstract**

The study of Adverse Drug Reactions was carried in 300 pediatric inpatients at Institute of Maternal and Child Health, Govt. Medical College, Kottayam, belonging to the age group of 1-10 years between the periods from January 2009 to December 2011. ADR was accessed for patients treated with various antibiotics, anti-viral, anti-fungal drugs etc. Data's were collected by directly visiting the home of individual patients. The concluded result showed a 10% incident rate of ADRs out of which the male showed a higher incident rate with 66.66% when compared to female with 33.33%. The antibiotic class mostly affected with ADRs was cephalosporin (23.33% followed by penicillin (20%). GIT was the organ system to be most affected (53.30%) followed by skin (26.70%) by ADRs. Also the Type A reaction (86.70%) was most common when compared to Type B (13.30%) reactions. The conclusive data suggests measures to improve detection and reporting of adverse drug reactions by all health care professionals, especially pharmacists and to develop and follow proper antibiotic guidelines for the prescription of the antibiotics. This would not only reduce the cost for treatment but also provide a better healthcare.

Key-Words: Pediatric patients, Adverse drug reactions, Antibiotics

**Introduction**

A wide range of drugs has been reported as being involved in ADR's in children. This include antibiotics NSAIDS, opiates, tuberculostatics, immunosuppressive agents, anticonvulsants etc. Incompletely developed intrinsic defense mechanisms predispose infants and neonates to infections and risks such as kernicterus or haemolytic anemia with sulphonamides and hearing loss with amino glycosides<sup>1</sup>. Developmental bone growth can be retarded with the use of tetracyclines and corticosteroids in children younger than 8 years of age. Percutaneous absorption of drugs is significantly enhanced in infants and children. Topical use amino glycoside- polymyxin sprays in young children has lead to permanent hearing loss and hexachlorophene sprays in neonates has caused neurotoxic related to increased absorption<sup>2</sup>. ADR's has been reported to occur frequently in children but not as frequently as in adults. Infants and very young children are at high risk of developing adverse drug reactions than adults because their capacity to metabolize drugs is not fully developed. For example new born cannot metabolize and eliminate the antibiotic chloramphenicol, new born who are given the drug may develop grey baby syndrome, a serious and often fatal reaction<sup>3</sup>.

If tetracycline another antibiotic is given to infants and young children during the period when their teeth are being formed [up to about age 8 years] it may permanently discolor tooth enamel<sup>4</sup>.

There are few publications among pediatric patients, though ADR incidence is usually stated to be higher in pediatric population. ADR's may adversely effects patients quality of life. It increases costs of patient care and may mimic disease resulting unnecessary investigation and delay treatment.

**Material and Methods**

**Study design**

This retrospective and follow up study was decided to conduct at, a community-based, tertiary care, teaching hospital ADRs are identified through several methods, including direct observation, participation in medical rounds, and notification by physicians and nurses. In our study, ADR report forms that were completed for pediatric patients (including neonates, infants & children) during their hospital stays between January 2009 to December 2011 were reviewed.

**Study Setting**

Data's collected from the tertiary care teaching hospital was identified and sorted according to the following criteria:

1. Age group (1-10 year)
2. Belonging to January 2009 to December 2011

\* Corresponding Author

E.mail: lekshmisiju@gmail.com

**Duration of Study**

November 2011 to November 2013 (Two years)

**Inclusion criteria**

- 1) Pediatric patients, aged between 1-10 years, treated with anti infective agents
- 2) Both male and female pediatric inpatients treated with antibiotics, anti viral, antifungal drugs etc are included in the study.

**Exclusion criteria**

- 1) Drug reactions that results due to medication errors, use of alternative systems of medicines, departments like Dentistry, Oncology, surgery etc are excluded from the study.

**Study variable**

ADR caused by anti infective agents in pediatric inpatients between age group 1-10 years. The suspected ADRs produced by commonly used antibiotics like ampicillin, amoxicillin, cephalosporins, azithromycin, erythromycin, linezolid etc. Then antiviral drug acyclovir, oseltamivir, anti-TB drug ethambutol etc was monitored by this study.

**Procedure in detail**

Retrospective Study of ADR events may have occurred at ICH, Medical College, Kottayam during the period of 2009-2011 and follow up study of such cases either by direct contact or telephonic information. Direct contact by visiting the home of individual patients by train, bus and auto .Then interview the patient and collected information from the patient related to the anti infective therapy and recorded. After a detailed analysis and study, we will submit the report.

A retrospective reporting study of ADRs was carried out in a general pediatric inpatient department of Institute of Maternal and Child Health, Govt. Medical College, Kottayam during 2009 to 2011. A total number of 300 pediatric patients will be included in

the study. All the suspected ADR's due to anti-infective medication in pediatric inpatient aged between 1 to 10 years were noted and reported by various departments of this hospital are included in this study. Drug reactions that results due to medication errors, use of alternative systems of medicines, and departments like dentistry, surgery, oncology etc are excluded. The study was reviewed and approved by Institutional Ethics Committee of Medical College Kottayam.

The causality assessment of the reported ADR's was carried out using "Naranjo causality assessment scale. The Naranjo Algorithm, the drug reaction can be classified as definite, probable, as possible. The modified Schumock and Thornton Scale classify ADR's as definitely preventable, probably preventable and not preventable based on a set of questions for each level. The modified Hartwig and Siegel Scale classifies severity of ADR as mild, moderate or severe with various levels according to factors like requirements for change in treatment, duration of hospital stay, and the disability produced by adverse drug reaction. The data for the study was taken from case sheets, treatment charts, investigation reports of patients who had experienced an ADR.

**Analysis of Results**

The data collected during the period are to be statistically analyzed for the following parameters.

- The total number of ADRs reported.
- Age groups and gender of the patients
- Assessment of causality based on 'Naranjo Scale'
- Assessment of level of severity of ADRs using 'Hart wig Scale'
- Assessment of Preventability using 'modified Shumock and Thornton method'

**Table 1: List of ADRs reported during the study period**

ANTI INFECTIVE AGENT	DOSAGE FORM	REPORTED ADR
PENICILLIN	TAB	NAUSEA,GASTRIC IRRITATION
AMPICILLIN	INJ	LOOSE STOOLS, RASHES
METRONIDAZOLE	TAB	EPIGASTRIC DISTRESS, VOMITTING
AMOXYCILLIN	SYP	FATIGUE, ABDOMINAL PAIN, VOMITTING
VANCOMYCIN	INJ	MACULOPAPULAR RASH ON FACE, NECK
CEFTRIAZONE	INJ	THROMBOPHLEBITIS, CANNULA SITE INFLAMMATION,SHIVERING
AMIKACIN& CEFTRIAZONE	INJ	LOOSE STOOL
AMPICILLIN & CLOXACILLIN	TAB	NAUSEA, GASTRITIS

CIPROFLOXACIN	TAB	ITCHING, SKIN RASHES, TENDONITIS
CEFIXIME	TAB	DYSPEPSIA, SEVERE HEAD ACHE
CLOXACILLIN	CAP	DIARRHOEA, EPIGASTRIC DISTRESS
ACYCLOVIR & CEFTRIAXONE	INJ	GREEN COLOURED LOOSE STOOL, HAIR FALL
ERYTHROMYCIN	TAB	GASTRITIS, GINGIVITIS, STOMATITIS
CEFTACIDINE	TAB	NAUSEA, DIARRHOEA
GENTAMICIN	INJ	DIARRHOEA, NAUSEA
CEFUROXIME	INJ	DIARRHOEA
CEFOTAXIME	INJ	DIARRHOEA, HEAD ACH
AMOXICILLIN & CLOXACILLIN	CAP	DIARRHOEA, MILD SKIN RASHES
CEPHALEXIN	DS TAB	LOOSE STOOL, GASTRITIS,
SEPTRAN	TAB	NAUSEA, VOMITING
CEFPODOXIME	SYR	GASTRIC IRRITATION
OSELTAMIVIR	TAB	DISCOMFORT, INSOMNIA, COUGH
ACYCLOVIR	TAB	LOOSE STOOL, NAUSEA,
LINEZOLID	TAB	NAUSEA, VOMITING, DIARRHOEA
ETHAMBUTOL	TAB	LOSS OF APETITE, ABDOMINAL PAIN
AZITHROMYCIN	SYR	EPIGASTRIC DISTRESS, DIARRHOEA
CIPROFLOXACIN	TAB	MUSCLE PAIN, GASTRITIS
ALBENDAZOLE	TAB	ANOREXIA
OSELTAMIVIR	TAB	NAUSEA, ABDOMINAL PAIN
AMPICILLIN	CAP	ITCHING, RASHES

**Results and Discussion**

Total number of ADRs due to anti infective agents

Total number of subject (N)	300
Number of reported ADRs	30

Among 300 pediatric patients treated with anti infective agents, 30 ADRs were reported and the incidence rate was found to be 10%.

Division of ADRs based on gender of the patients

Sex	Number	Percentage
Male	20	66.66
Female	10	33.33

The incidence rate was found to be more in males 20 (66.66%) and less in female pediatric patient 10 (33.33%).

Therapeutic class of anti infective agent

Class of anti infective agents	Number	Percentage
Penicillin	6	20
Glycopeptide	1	3.33
Oxazolidinone	1	3.33
Cephalosporin	7	23.33
Aminoglycosides	2	6.66
Macrolides	2	6.66
Fluroquinolones	1	3.33
Co trimoxazole	1	3.33
Amoebicide	1	3.33
Anti TB	1	3.33
Anthelmintic	1	3.33
Anthelmintic	2	6.66
Combinations	4	13.33

The antibiotic class mostly affected with ADRs in pediatric inpatients was cephalosporin 7

(23.33%) followed by penicillins 6 (20%) and Combinations of two anti infective agents 4 (13.33%).

<b>preventable</b>		
<b>Not</b>	0	0
<b>preventable</b>		

Organ system affected due to ADRs

Organ system	Number	Percentage
<b>GIT</b>	16	53.30
<b>Skin</b>	8	26.70
<b>Nephro toxicity</b>	0	0
<b>Respiratory</b>	0	0
<b>Haematological</b>	0	0
<b>Local reaction</b>	6	20

Organ system most affected by ADRs due to antibiotics was found to be GIT 16 (53.30%) followed by skin 8 (26.70%) and local reactions 6 (20%).

Classification of ADRs

Type of ADRs	Number	Percentage
<b>Type A</b>	26	86.70
<b>Type B</b>	4	13.30

Type A reactions 26 (86.70%) was most common compared to type B 4 (13.30%).

Route of administration of anti infective agents that cause ADRs

ROA	Number	Percentage
<b>Oral</b>	22	73.33
<b>Parenteral</b>	8	26.66

Among 30 reported ADRs 22 (73.33%) was due to oral route of administration and 8 (26.66%) parental.

Predictability of reported ADRs

Predictability	Number	Percentage
<b>Predictable</b>	22	73.30
<b>Non predictable</b>	8	26.60

In 30 reported ADRs 22 (73.30%) reactions were predictable and 8(26.70%) were not predictable.

Level of severity of reported ARDs (using modified hart wig and siegel scale)

Severity	Number	Percentage
<b>Mild</b>	12	40
<b>Moderate</b>	18	60
<b>Sever</b>	0	0

Moderate reactions accounted for 18 (60%) followed by mild 12 (40%) and no reactions were found to be severe.

Preventability of reported ADRs (using modified Shumock and Thornton method)

Preventability	Number	Percentage
<b>Definitely preventable</b>	20	66.70
<b>Probably</b>	10	33.3

Preventability of reported ADRs was assessed using modified Shumock and Thornton method, 20 (66.70%) definitely preventable, while 10(33.33%) were probably preventable.

Causality assessment of ADRs (using Naranjo scale)

	Number	Percentage
<b>Definite</b>	0	0
<b>Probable</b>	15	50
<b>Possible</b>	12	40
<b>Unlikely</b>	3	10

Using Naranjo scale for causality assessment 15(50%) was probable, 12 (40%) were possible, 3(10%) were unlikely.

During the study period, a total of 30 adverse reactions of anti infective agents were reported among pediatric patients aged between 1 to 10 years among 300 pediatric inpatients; the incidence rate of antibiotic adverse reactions was found to be 10%. And about 20 (66.66%) male pediatric patients predominated over female 10 (33.33%) in ADR occurrence. This study was a retrospective follow up reporting study. Results revealed that GIT 16 (53.30%) was the most affected organ system by adverse reactions due to antibiotics followed by skin 8 (26.70%). The Antibiotic class mostly affected with ADR in pediatric inpatients was cephalosporin 7 (23.33%) followed by penicillin 6(20%)and combination of two anti infective agents (13.33%).Of the reported ADRs, Type A 26 (86.70%) was most common compared to type B 4 (13.30%) reactions.

As per Naranjo scale 15 (50%) were probable 12 (40%) were possible, 0 (0%) were definite and 3% were unlikely. Of the reported ADRs moderate reactions accounted for 18 (60%) followed by mild 12(40%).and no reactions were found to be severe. Preventability of the reported ADRs was assessed and the result were revealed that 20 (66.70%) of the ADRs were definitely preventable, while 10(33.33%) were probably preventable.

Antibiotics are used for treatment and prophylaxis of various infectious conditions and are considered as safer drugs when used rationally. But, like other drugs, they also show some adverse reactions in various patient conditions. In the studies carried out in Nigerian children and R. Priyadharsini *et al.*<sup>5</sup> antibiotics are the most accounted drug class in ADR occurrence. Infants and very young children are at high risk of developing ADRs than adults because their capacity



to metabolize drugs is not fully developed.

In this study, predominance of male sex for adverse drug reactions may be due to majority of the admitted pediatric patients were male with more antibiotic use during the study period. The study conducted by Jimmy Jose *et al.*<sup>6</sup> showed male predominance, where as two other studies by G.Starveva *et al.*<sup>7</sup> and M.M Hussain *et al.*<sup>8</sup> showed female predominance.

More number of antibiotic adverse drug reactions were detected in general pediatric medicine department, and may be due to increased use of antibiotics in these departments for treatment and prophylaxis of various diseases. The documented antibiotic adverse drug reactions were mainly affecting GIT and skin and this study also pointed out the same.

The results revealed that penicillin's were the most accounted antibiotic class that causes ADRs in pediatrics. This result is in line with the study of R.Priyadharsini *et al.*<sup>5</sup> ie, vancomycin and penicillins were most frequent in their study.

Predictability of the reactions was based on the incidence of the reactions and literature reports, found that majority of them were predictable. Majority of the paediatrics were recovered from the ADRs because none of the reported reactions was fatal. Preventability analysis revealed that majority of the reactions were definitely preventable followed by probably preventable with only less number of them were not preventable. This is in line with the study of K.A.Oshikoya *et al.*<sup>9</sup> and Jimmy Jose *et al.*<sup>6</sup> According to a study conducted by Bates<sup>10</sup>, antibiotics were responsible for 9% of preventable ADRs and 30% of non preventable ADRs.

### Conclusion

Adverse drug reactions are one of the drug related problems in the hospital setting and is a challenge for the ensuring drug safety. Antibiotics comprise the major volume of the drug family and inpatient prescriptions, and are the most irrationally prescribed drug class. So that implementation of antibiotic guidelines form the hospital scenario and strict adherence should be ensured to promote their rational use in children. The health system should promote the spontaneous reporting of adverse drug reactions, proper documentation and periodic reporting to regional pharmacovigilance centers to ensure drug safety.

The most commonly prescribed drugs are those most often implicated in ADRs in children. Penicillins, cephalosporins, aminoglycosides, macrolides, antiviral agents, anthelmintics, etc. are the commonly prescribed class of anti-infective agents in pediatric

department, during the study period. The antibiotic class mostly affected with ADRs was found to be penicillins followed by cephalosporins.

The study concluded that spontaneous reporting of Adverse Drug Reaction is fairly good in our hospital setting. ADRs may increase costs of patient care and may mimic disease, resulting in unnecessary investigations and delay in treatment. Active involvement of a well trained clinical pharmacist for detecting the Adverse Drug Reaction and delivering the awareness classes for the healthcare professionals regarding the need of reporting ADRs, particularly those that are serious or rare.

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