Indian Journal of Pharmacy Practice | Association of Pharmaceutical Teachers of India

Evaluation of Adverse Drug Reactions in Pediatric Patients

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ABSTRACT

Submitted: 17/05/2013 **Accepted: 12/08/2013**

To evaluate the occurrence of Adverse Drug Reactions (ADRs) in the children who are hospitalized, the follow-up processes resulting from it and to evaluate the reporting of ADRs by health care professionals. The occurrence of ADRs among hospitalized children has not been well established. As the clinical trials involving neonates, infants and children are absent or limited, the safety and tolerability of drugs are not well established among them hence the pharmacological actions of drugs are not similar to those identified for adults. A prospective observational study was conducted between June 2012 and March 2013 at Rajiv Gandhi Institute of Medical sciences (RIMS) an 800 bedded tertiary care teaching hospital, Kadapa. A total of 109 ADRs were identified. The most of the ADRs were mild(54.12%), severe were least (12.85%) and the moderate were between them (20.2%). Maximum of ADRs (89.91%, n-98) identified were predictable and least (10.09%, n-11) were non-predictable. Highest incidence is of GI effects (22.02%) and the lowest is of tinnitus (0.91%).ADRs rated high in severity resulted from anti convulsants (phenobarbitone), lowest resulted from Anti-malarials (Artemether). Mortality rate was restricted to 1.83% (n-2). Maximum ADRs were reported by pharmacists (89%), and least by patient representatives (2%). Measurements to be undertaken for the improvement of the detection and reporting of adverse drug reactions by all health care professionals, to enhance the impact of understanding these reactions in children and to promote the safe use of drugs in the pediatric patients.

Keywords: Adverse drug reactions, Pediatrics, Pediatric safety

INTRODUCTION

Adverse drug Reaction (ADR) is defined as "Any response to a drug which is noxious, unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function".[1]Monitoring and documentation of ADRs are considered as crucial processes to encourage and to ensure the safe use of drugs. A serious ADR leading to a new black box warning or withdrawal of drug from the market was detected for 1 of 5 medicines during post-marketing surveillance in the past 35 years.[2]As per the guidelines of Food and Drug Administrations (FDA), ADRs to be reported to by the drug manufacturers and all other health care professionals. Rising costs of patient care, increasing awareness of patients towards the untoward effects of drugs and the rise in the frequency of cases of litigation against doctors and hospitals have made clinicians, hospital administrators and health care planners aware of the necessity of closely monitoring ADRs. The Govt. of India in due recognition of this fact has established 6 - ADR monitoring centres to collect and classify ADR data in the Indian population. Though ADR monitoring has not received the importance relegated to it in the west, Indian physicians are becoming increasingly aware of the necessity of observing the profile of adverse events of a drug in our population. This may be just the beginning, but with time and experience ADR monitoring will become a part and parcel of the comprehensive health care provided to patients.[3]

Hospitals should monitor routinely for ADRs, for both preventable and non-preventable, and to report all the ADRs which results in a drastic event, these are based on regulations established by the Centers for Medicare and Medicaid Services and the Joint Commission on Accreditation of Healthcare Organizations.[4,5]ADRs can result in significant morbidity and mortality among pediatrics.[6-13] The incidence of ADRs among hospitalized children has not been well established, as the clinical trials involving neonates, infants and children are limited, the safety and tolerability of many pharmacologic agents are not well established. Often the pharmacologic actions of drugs in neonates, infants, and children are not similar to those identified for adults; therefore, information obtained from research with adults cannot be applied directly.[14] The Pediatric Rule for Labeling, which was came in to action in1994 by the FDA and its 1998 enactment requiring manufacturers of certain new and marketed drugs to conduct studies for pediatric labeling has increased the information available regarding drug safety for children.[15] In India the Central Drugs Standard Control Organization (CDSCO), Directorate General of Health

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Services under the aegis of Ministry of Health & Family Welfare, in collaboration with Indian Pharmacopeia commission, Ghaziabad initiated a nation-wide Pharmacovigilance programme of India (PvPI) in June 2010 to monitor ADRs in Indian population and to create awareness amongst health care professionals about the importance of ADR reporting in India. To achieve the long term objective **'Centre of Excellence'** for Pharmacovigilance in India, the PvPI National Coordinating Centre collaborating with the WHO Collaborating Centre - Uppsala Monitoring Centre (UMC) based in Sweden.[16] The present study is aimed to find the occurrence of ADRs in pediatric patients in a tertiary care teaching hospital (Kadapa), as it is a government organization the medicines are supplied at free of cost and only limited medicines are available for physicians to choose as their treatment strategies, hence there is ample scope for occurrence of ADRs.

MATERIALS AND METHODS

The study was approved by the Human Research Ethical committee, RIMS, Kadapa.

Study design: Prospective Observational Study

Study period: June 2012 to March 2013 (10 months)

Study population: 543 (Fig. 1)

Study place: RIMS, an 800 bedded tertiary care teaching hospital, Kadapa.

Department: Department of Pediatrics (NICU, PICU and Pediatric Wards)

Study Materials: Patient data collection proforma, ADR Reporting Form (modified CDSCO form)

Inclusion criteria: Pediatric in-patients, Patients with poly pharmacy, Drug regimens susceptible for ADRs occurrence, Patients with lethal or life threatening diseases

Exclusion criteria: Pediatric out-patients, Patients with photo therapy

Methods of ADRs Assessment: Naranjo's causality assessment scale, Hartwig and Siege severity scale

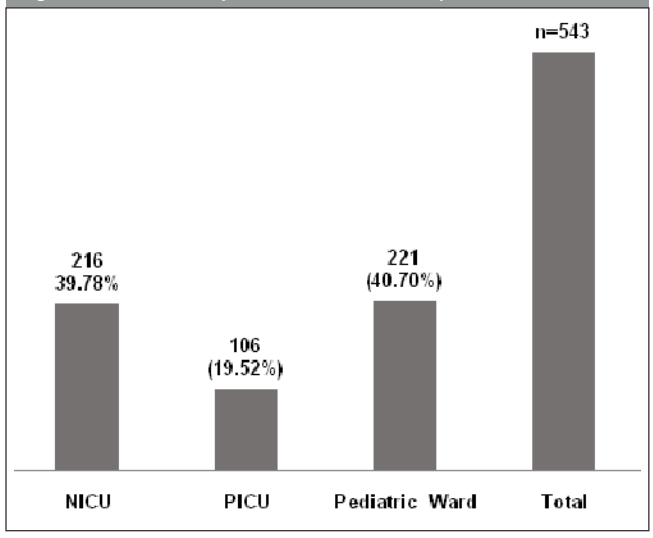
RESULTS AND DISCUSSION

216 39.78% 106(19.52%) 221(40.70%) n=543 NICU PICU PediatricWardTotal

A total of 543 patients were followed during the study, of which, 39.78% from neonatal intensive care unit (NICU), 19.52% from Pediatric intensive care unit (PICU), 40.70% from General Pediatric ward {Fig No. 1}.

A total of 109 ADRs (n=109) were found in the study, among

Fig. 1: Distribution of patients in Pediatric Department



that 56 ADRs were in General Pediatric ward followed by PICU (36) and NICU (17).

Out of total 109 ADRs identified 89.91% were predictable (Type-A) and 10.09% were non-predictable (Type-B) {Table No.1}, suggests that ADRs can be controlled if we follow the strict strategies to control it. Suspected reactions were 42 (38.53%) and Reported reactions were 67 (61.47%).

ADRs Assessment:

Table 1:Analysis of ADRs

Category	No. (%) (n=109)
Type - A	98 (89.91)
Type - B	11 (10.09)
Total	**109 (100)**

ADRs assessment was made by using the Hartwig and Siege severity scaleand Naranjo's causality assessment scale. Considering the severity levels most of the ADRs (54.12%) were mild, least (12.85%) were severe and moderate (20.2%) were between them {Table No. 2}. The highest (58.21%) ADRs were reported as Definite and least (16.42%) were reported as possible {Table No. 3}. Most of the drugs were assessed by Dechallenging and followed by the scoring according to the scale. Rechallenging of the drugs was not made as it is not entertained in the pediatric patients as the situation may become worsen, hence it became a major limitation for the assessment of the ADRs, however the results were reliable.

Mortality rate was restricted to 1.83% (n-2), resulted from the

Table 2: Analysis of ADRs based on Severity

ADRs Severity	No. (%)(n=109)
Mild	59 (54.12)
Moderate	22 (20.2)
Severe	14 (12.85)
Those Requiring Intensive care	12 (11)
Death due to ADRs	2 (1.83)

Table 3: ADRs Assessment Using Naranjo's Sale

Category	No. (%)
Possible	11 (16.42)
Probable	17 (25.37)
Definite	39 (58.21)

Apnoea by the use of Phenobarbitone2mg/kgIV BD in a 7 years old male patient and from the liver damage, increased liver function test, jaundice by the use of paracetamol 15mg/kg in 6 years old female patient, it was a suspected case of over dose because the patient was only on paracetamol therapy for 5 day prior to death here the study deviates from the exclusion criteria where monotherapy was excluded.

The frequency and the number of ADRs resulted from class of drugs are listed in Table 4, most commonly prescribed drugs were Antibiotics (35.3%) followed by Antipyretics (21.5%)next to antipyretics Anticonvulsants were widely used (19.1%) as seizures in Pediatrics became high over here, provides the site of interest for further studies in this area, and least prescribed drugs were steroids (1.3%). (Table 5-7).

Out of 109 only 13 ADRs were developed after ceasing the drug use, they might occured because of the previously used drug (Suspected drug), it may be due to the increase in the dose (dose dependent).

Reporting and follow up process:

Maximum of the ADRs were reported by the Pharmacists (89%), followed by the Nurses (5%), Physicians (4%) and the Patient representatives (2%) {Fig No. 2}.

All the reported ADRs were documented in the drug information center at RIMS for further assistance and discussed with the physicians for further prevention of the ADRs .

Fig. 2: ADRs Reporting Percentage

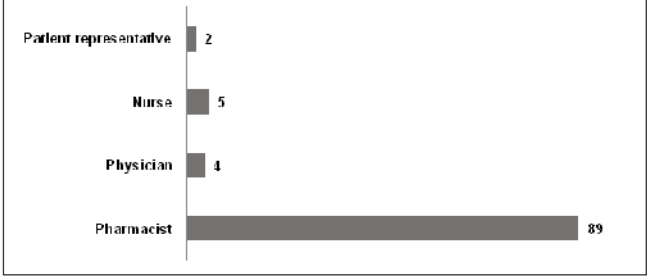


Table 4: Commonly prescribed class of drugs and percentage

Drug Class	Frequency (%)	No. of ADRs (%) (n=109)
Antibiotics	**192 (35.3)**	**43 (39.44)**
Amoxicillin+ Clavulanic acid	43	11
Ceftriaxone	35	9
Gentamicin	17	3
Metronidazole	11	2
Ciprofloxacin	21	3
Norfloxacin	9	2
Chloroquine	27	6
Artemether	29	7
Anticonvulsants	**104 (19.1)**	**39 (35.77)**
Carbamazepine	24	12
Diazepam	36	7
Phenobarbitone	32	11
Phenytoin	12	9
Antiemetic's	**37 (6.8)**	**6 (5.5)**
Domperidone		
Antihistamines	**61 (11.2)**	**10 (9.17)**
Pheniramine	32	4
Cetrizine	29	6
Antipyretics	**117 (21.5)**	**2 (1.83)**
Paracetamol		
NSAIDs	**25 (4.6)**	**5 (4.58)**
Ibuprofen		
Steroids	**7 (1.3)**	**4 (3.66)**
Hydrocortisone	4	3
Prednisolone	3	1

Note: Percentages are expressed in weighted percentages

CONCLUSION

Children should never be considered as the *Half Adult,* Measurements to be undertaken for the improvement of the detection and reporting of ADRs by all health care professionals, to enhance the impact of understanding these reactions in children, strategies to be implemented for early detection of adverse drug reactions by targeting the specific drugs as we have seen that most of the reactions were predictable in this study, follow up processes should be incorporated to provide the awareness of the ADRs among all health professionals and also for patient representatives topromote the safe use of drugs in the pediatric patients.

Table 6: Distribution of ADRs with the possible offending drugs

ADRs	Offending drugs
Abdominal pain	Carbamazepine, Phenytoin, Metronidazole, Artemether
Apnoea	Phenobarbitone
Anorexia	Metronidazole
Diarrhea	Ibuprofen, Amoxicillin+Clavulanic acid, Ceftriaxone, Artemether
Drowsiness	Domperidone, Phenytoin, Diazepam, Carbamazepine, Phenobarbitone
GI effects	Ibuprofen, Phenytoin, Domperidone, Metronidazole, Amoxicillin+Clavulanic acid, Chloroquine
Liver damage	Paracetamol
Hyperglycemia	Phenytoin
Hyperactivity	Phenobarbitone, Pheniramine
Metallic taste	Metronidazole
Nausea	Artemether, Ceftriaxone, Amoxicillin+Clavulanic acid, Metronidazole, Ibuprofen
Sedation	Phenobarbitone, Phenytoin, Pheniramine
Thrombophlebitis	Ceftriaxone, Diazepam
Tinnitus	ArtemetherUrticariaChloroquine, Amoxicillin+Clavulanic acid
Vomiting	Artemether, Gentamicin, Ceftriaxone, Metronidazole
Rash	Ibuprofen, Hydrocortisone, Domperidone, Gentamicin

Table 5: Common types of ADRs identified and there percentage

ADRs	No. (%)(n=109)	Low Severity(n)	High Severity(n)
Abdominal pain	11(10.09)	10	1
Apnoea	6(5.5)	0	6
Anorexia	5(4.59)	5	0
Diarrhea	9(8.25)	8	1
Drowsiness	3 (2.75)	3	0
GI effects	24(22.02)	19	5
Liver damage	4(3.67)	2	2
Hyperglycemia	4(3.67)	3	1
Hyperactivity	3(2.75)	2	1
Metallic taste	6(5.5)	6	0
Nausea	3(2.75)	3	0
Sedation	2(1.83)	2	0
Thrombophlebitis	18(16.51)	14	4
Tinnitus	1 (0.91)	1	0
Urticaria	5(4.59)	5	0
Vomiting	2(1.83)	2	0
Rash	3(2.75)	2	1
Total ADRs	**109(100)**	**89(81.65)**	**22(20.18)**

Table 7: Consequence of ADRs on the prescription in disease

Consequence	No. (%)(n=109)
Patient continued the drug	10(9.2)
Patients with increased dose	39(35.77)
Patients with decreased dose	47(43.11)
ADRs developed after ceasing the drug1	3(11.92)

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