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ORIGINAL ARTICLE

A STUDY ON ADVERSE DRUG REACTIONS INVOLVING CENTRAL NERVOUS SYSTEM, ITS SEVERITY AND CAUSALITY ASSESSMENT IN PEDIATRIC PATIENTS ADMITTED TO A TERTIARY CARE HOSPITAL

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ABSTRACT: A retrospective study was conducted in Department of pediatrics SCB Medical College and SVPPGIP for a period of 2 years i.e. September 2012 to August 2014. All the patients from birth to 14 years admitted to the pediatric ward in this study were under ADR surveillance. Patients admitted to our hospital with adverse drug reaction or patients developing adverse drug reaction in our hospital were studied; only those cases where the central nervous system was involved were taken in our study. The cases were compiled and the causality of offending drugs was found using WHO-UMC causality assessment score. The severity of drug reaction in every case was determined by using HARTWIG's severity scoring scale. Total 350 Adverse reactions were reported in this period with prevalence rate of 2.04% i.e. 20 out of 1000 children faced ADR due to drugs, with annual incidence rate of 0.9% and 1.14% over two years. Out of total 350 cases dermatological system was most commonly involved i.e. 207 cases (59.14%). This is followed by involvement of central nervous system 46 number of cases (13.14%). The GI system was involved in 34 cases i.e. (9.71%). Life threatening reactions like anaphylaxis, angioedema and shock like immediate life threatening ADRs were reported in 16 cases. Our study group was the patient in whom the ADR involved the CNS. Out of 46 such cases, there were 25 female and 21 male. Various reaction due to drug were encephalopathy, eps, febrile seizure, tremor, head reeling, ototoxicity, persistant cry, pseudotumor cerebri, psychosis, seizure, status epilepticus, toxic amblyopia, tremor, ataxia etc. The most common CNS manifestation was Extra pyramidal side effects (EPS) involving 21% of cases. The most common Drug causing CNS manifestation was ATT (HRZE) causing blindness, Eps, psychosis, toxic amblyopia blindness etc.
KEYWORDS: Adverse drug reaction, Central nervous system, extra pyramidal side effects.

INTRODUCTION: An ADR is defined by the World Health Organization (WHO) as 'a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man.[1] The safety of drugs used in patients of an adult age group cannot be extrapolated to a pediatric age group. The pharmacokinetics and pharmacodynamics of many commonly used drugs vary significantly between these two age groups of patients.[2] Adverse drug reactions (ADRs) in children can have a relatively more severe effect when compared to adults. Thus, the ADRs can lead to significant morbidity among children.[3] ADRs rank as one of the top ten leading causes of death and illness in the developed world (Lazarou et al JAMA 1998).[4] Recent data of US FDA shows that ADRs now ranks the 4th to 6th most common cause of death (Lazarou et al).[4]

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Detection and prevention of ADRs at the earliest is very important to reduce the morbidity and mortality & also the high health care cost involved in the management of the ADR. It is a matter of concern that drug which is studied in adult without having any information on safety pediatric patients has been used rampantly. Most of the organ system of the pediatric age group is immature, study shows that the adult level of GFR reaches by 1 year of age, the respiratory cartilages develops by 3 months of age and matures in preschool age. Nervous system of pediatric age group is especially vulnerable to the effect of drugs used in this age group as it is very immature and the blood brain barrier of pediatric age group is not well devolved specially below 1 year. 80% of brain growth occurs by the age of 3 years. The drug administered can easily penetrate in to Central nervous system and cause adverse drug reaction. Research with adults and drugs which are safe and effecting minimally to the Nervous tissue cannot simply be generalized or extrapolated to infants, children, and adolescents. If adult humans have been the "animal of necessity" in clinical research, then children have often been "therapeutic orphans," as characterized over 35 years ago by clinical pharmacologist. To a considerable degree, children retain this disadvantaged status, despite the recent creation of policy incentives for clinical research involving children.[5] A survey of the 1991 edition of the Physician's Desk Reference found that approximately 80 percent of the listed medications had labels that provided no prescribing information for children.[6] When drug labels lack pediatric prescribing information, physicians can still legally prescribe drugs for children on an "off-label" basis—and they do. According to Choonara and Conroy (2002), European studies suggest that at least one-third of hospitalized children and up to 90 percent of neonates in intensive care receive such prescriptions.[7] The American Academy of Pediatrics has argued that the shortage of pediatric research creates an ethical dilemma for physicians, who "must frequently either not treat children with potentially beneficial medications or treat them with medications based on adult studies or anecdotal empirical experience in children".[8] The widespread off-label prescription and use of drugs for children tend to further diminish the incentives to finance pediatric research on drugs that are already approved for use by adults. In addition, companies may be unfamiliar with the clinical, ethical, and regulatory requirements for pediatric studies, and they may be concerned about financial or public relations consequences of adverse experiences in research involving children, reactions against abusive or questionable research practices involving both adults and children have led to an evolving set of policies and practices to protect all human participants in research, with additional protections for children and other vulnerable populations. The adoption of special protections for child research participants and the growing awareness of researchers' ethical obligations have curbed what are now regarded as unethical and harmful research practices. Notwithstanding these benefits, some of these protections have also made some research involving children more administratively burdensome in certain respects than research involving adults. Debate continues about what constitutes an appropriate balance between scientific priorities and protection of child participants in research. Now it's became very important to study Adverse drug reaction on children with by drugs and its effect on various organ system of the children.

STUDY MATERIAL AND METHODS: The study was conducted in Department of pediatrics SCB Medical College and SVPPGIP for a period of 2 years i.e. September 2012 to August 2014. All the

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patients from birth to 14 years admitted to the pediatric word were under ADR surveillance. Patients admitted to our hospital with adverse drug reaction or patients developing adverse drug reaction in our hospital were studied; only those cases where the central nervous system was involved were taken in our study. The cases were compiled and the causality of offending drugs were found using WHO-UMC causality assessment score. The severity of drug reaction in every case was determined by using HARTWIG's severity scoring scale.

RESULTS: Total 350 Adverse reactions were reported in this period with prevalence rate of 2.04% i.e. 20 out of 1000 children faced ADR due to drugs, with annual incidence rate of 0.9% and 1.14% over two years. Out of total 350 cases dermatological system was most commonly involved i.e. 207 cases (59.14%). This is followed by involvement of central nervous system 46 number of cases (13.14%). The GI system was involved in 34 cases i.e. (9.71%). Life threatening reactions like anaphylaxis, angioedema and shock like immediate life threatening ADRs were reported in 16 cases. Our study group was the patient in whom the ADR involved the CNS. Out of 46 such cases, there were 25 female and 21 male. Various reaction due to drug were encephalopathy, eps, febrile seizure, tremor, head reeling, ototoxicity, persistent cry, pseudotumor cerebri, psychosis, seizure, status epilepticus, toxic amblyopia, tremor, ataxia etc.(Table-3) The most common CNS manifestation was Extrapyramidal side effects(EPS) involving 21% of cases. Dechallenge test was positive in 37 cases. With WHO-UMC causality assessment score, 18 cases were having certain, 11 cases having possible and 17 cases were having probable causality of ADR(Table 1).there were no death report due to ADR involving Central Nervous system. There were 3 cases having Hartwigs severity of 6 i.e. 3 having residual disability due to drug reaction. (Table 2)

Causality Assessment of ADR by WHO-UMC scale	Number of ADR	Percentage
CERTAIN	18	39.13
POSSIBLE	11	23.91
PROBABLE	17	36.96
Grand Total	46	100

Table 1

ADR Severity by Hartwig Scale (Levels)	Number of Cases	Percentage
3	4	08.70
4	35	76.08
5	4	08.70
6	3	06.52

Table 2

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Suspected Medications	Number of ADRS	Types of Reaction Observed
Amikacin	1	Seizure
Att(hrze)	8	Blindness, EPS, head reeling, psychosis, toxic amblyopia
Carbamazepine	2	Ototoxicity, Head reeling
Ceftriaxone	2	Ototoxicity, Psychosis
Chloramphenicol	1	Head reeling, Bluring of vision,
Ciprofloxacin+tinidazole	1	Tremor
Cyclophosphamide	1	Tremor, Ataxia
Doxycycline	1	Tingling sensation
Dpt booster	3	Convulsion, Persistant crying
Haloperidol	1	Tremor
Kanamycin	1	Eps
Levocetrizine	3	Head reeling, tingling sensation, eps
Measeles vaccine	2	Seizure, status epilepticus
Norfloxacin + metronidazole	1	Tremor
Ofloxacin + metronidazole	1	Eps
Norfloxacin	2	Dystonia, ototoxicity
Norfloxacin + tinidazole	2	Eps, hypotension, tingling
Ofloxacin	1	Head reeling
Ofloxacin + ornidazole	2	Eps, ototoxicity
Valproic acid	3	Eps, encephalopathy
Paracetamol	1	Delirium,
Phenytoin	4	Dystonia,eps, tremor
Risperidone	1	Tremor
Vitd3,multivitamins	1	Pseudotumor cerebri
Grand total	46	

Table 3

Age group	Adverse Drug Reactions	Percentage
Birth to 5 years	23	50.00%
5 years to 10 years	13	28.26%
>10years	10	21.74%

Table 4: Adverse Drug reaction in various age group

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DISCUSSION: ADRs involving various organ system of the children (table-5) shows that, Most of the ADRs involved Skin (59.14%) followed by nervous system (13.14%). The next common system to be involved was GI system which was involved in (9.71%) cases. There were many studies showing cutaneous manifestation of ADR but few studies separately depicting the adverse drug reaction involving CNS. When we analyzed the incidences of serious ADR involving various systems, we found that was more incidences of serious ADRs when it involved Nervous system than dermatological system. The Chi-square statistic value= 23.362 with P value is < 0.0001, considered extremely significant

Study	% of Dermatological Involvement	% of CNS Involvement	% of Gastrointestinal Involvement
Uppal et al[10]	38.8	7.3	28.4
Arulmani et al[11]	34.1	18.9	17.7
Jose et al[12]	23.5	-	-
Our study	59.14%	13.14%	9.71%

Table 5

Most studies like those of Montastruc JL et al,[13] Richard et al,[14] Zopf et al,[15] concluded that ADRs are more common in females compared to males.in our study Out of 46 there were 25 female and 21 male.

Study	Result on Gender difference in ADR reporting
Montastruc JL et al[13]	ADRs more common in females (53%)
Richard et al[14]	Incidence in males (12.9) is less than that in females (20.6) per 10000 patients
Zopf et al[15]	Significant influence of female gender on the risk of encountering ADRs (odds ratio=1.596
Jennifer Le at al	ADRs in males 48.30%.
Our study	Female: Male= 1.2:1

Table 6

CONCLUSION: The pediatric Central nervous system is different from that of adult; the drug safety proved in adult cannot be generalized in to children. It is also very difficult to prove drug safety by drug trial on experiment basis as it is done in adult before marketing release due to social and ethical issues. So it is very important to conduct studies to see various adverse drug reaction that pediatric age group suffers due to drug that to its impact on various organ system of the children. Much more this kind of studies should be promoted to see the real scenario of ADRs involving different organ system.

LIMITATION: Very few literatures were available on adverse drug reaction involving CNS; in fact this was 1st such study in India so our study could not be compared much with other results. A bigger sample size involving outdoor patients would have better results. A comparative study of ADRs in Hospitalized children and ADRs in children in Community would be more informative, as most of the hospitalized children are suffering from various diseases, are sick with poor organ functions so in many cases there was dilemma whether the reaction was due to ADR or disease process itself. The reporting of ADR was voluntary and a lot of ADRs expected to be missed due to under reporting.

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