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Off Label Use of Drugs in Paediatrics - A Prospective Observational Study

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ANILASREE BP[1], SHAMNA NOUSHAD[2], SAHNOON JAVEED[3], JAPHIA SAJU*[4], UNNI KRISHNAN[5]

[1] Assistant professor Department of pharmacy practice, Devaki Amma Memorial College of Pharmacy, Chelembra, Malappuram. Kerala, India

[2,3,4] Pharm D intern, Devaki Amma Memorial College of Pharmacy, Chelembra, Malappuram, Kerala- India.

[5] Senior Pediatrician, PVS Hospital (P) Ltd, Calicut Kerala. India.

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ABSTRACT

Aim: The study aimed to determine the extent, safety, and categories of off-label drug use in children admitted to tertiary health care hospitals. **Method:** A prospective observational design was used for this study. The off-label drugs were identified and documented during ward rounds and case sheet analysis. **Result:**200 patients were taken for study purposes out of which 116 were male (58%) and 84 were female (42%). Of the 200 patients included in the study, a total of 155 patients received off-label drug prescriptions. The pediatric age group of 3-12years i.e children was seen to have received maximum off-label drugs;38% of total drugs, followed by infants with 32.07%, neonates with 21.38%, and adolescents with 7.54%.205(41.16%)drugs were classified as off-label of age, 21(4.21%)drugs as off label of dose, 4(0.80%)drugs as off label of weight, 192(38.55%)drugs as off label of lack of evidence, 5(1.00%)drugs as off label contra-indication, 67(13.45%)drugs as off label of indication and 4(0.80%)drugs as off label of the route of administration. Four cases out of 200 showed the occurrence of ADR. **Conclusion:** Large percentages of drugs do not have clinical data available for the pediatric population. The decisions are taken weighing the benefits over the risk of administering the drug. Initiating quality studies to support these treatment plans is essential to provide safe and effective use of the drugs. Clinicians should also be vigilant for the occurrence of ADR with particular off-label use.

INTRODUCTION:

The term off-label is usually misunderstood as illegal or unwanted use of medicine. While this can be debatable, the off-label use of medicines has grown largely over the last few years especially in the pediatric population. Currently, there is a lack of pediatric dosing, safety, and efficacy information for more than 75% of drugs approved in adults. Off-label use of medications is the use of drugs outside of its approved labeled indication. Such use is not considered improper or illegal; however, the decision for use should be based on clinical judgment and in the best interest of the patient. About 80% of hospitalized pediatric patients receive at least one off-label medication. This includes the use of medication in the treatment of illnesses not listed on the manufacturer's package insert, use outside the licensed age range, dosing outside those recommended, or use of a different route of administration. Pediatricians sometimes prescribe off-label drugs because there is no available approved drug or drug strength or formulation suitable for children. Although most marketed drugs are used in pediatric patients, only one-fourth of the drugs approved by the Food and Drug Administration (FDA) have indications specific for use in the pediatric population. Data on the pharmacokinetics, pharmacodynamics, efficacy, and safety of drugs in infants and children are scarce. Lack of this type of information led to disasters such as gray baby syndrome from chloramphenicol, phocomelia from thalidomide, and kernicterus from sulfonamide therapy. Such off-label use in infants and children is frequently based on limited data. The limitation to conducting clinical trials in children becomes the major reason for the increased use of off-label drugs in pediatrics. There are various off-label categories such as age, weight, dose, indication, lack of clinical evidence, contraindication, and route of administration. Paracetamol given to a premature infant is one example of off label drug use (age/weight); diclofenac used for abdominal pain (indication), adrenaline given through inhalation rather than intravenously (route of administration), and the administration of morphine or codeine as an analgesic (lack of clinical evidence), ethamsylate as a hemostatic agent for post-surgery(contraindication).

MATERIALS AND METHODS:

A prospective observational study design was used for identifying the extent, safety, and categories of off-label drugs used in the pediatric population of a 350 bedded hospital in Calicut, Kerala. The study was commenced after getting approval from the Institutional review board and Institutional ethics committee. A random selection of cases was carried out

during ward rounds and case sheet analysis. By comparing with the national formulary of India 2011 edition and Micromedex the off-label drugs were identified and the same was reported. The off-label drug used were categorized into the following variables as- Age, dose, weight, lack of pediatric clinical data, contra-indication, indication. On comparing the prescriptions with NFI India and Micromedex the various commonly used off-label drugs, their off-label categories and safety were determined.

RESULTS:

A total of 200 patients were taken for this study.

Demographic characteristics: A greater number of male patients were admitted during the period of study. The most common age group was 3-12years representing 39% of the total sample size, followed by infants (29%) and neonates (24%). The adolescents' age group constituted the lowest number in the total sample size.

CHARACTERISTICS	FINDINGS		NUMBER AND PERCENTAGE
1. Demographics of the study population	Gender	Male	116 (58%)
		Female	84 (42%)
	Age	0-1month	48 (24%)
		2months-2years	58 (29%)
		3-12years	78 (39%)
		13-16years	16 (8%)
2. Off-label drug use in different Paediatric age groups	Neonates (0-1month)		34 (21.38%)
	Infants (2months-2years)		51 (32.07%)
	Children (3-12years)		62 (38.99%)
	Adolescent (13-16years)		12 (7.54%)
3.Off-label Categories	Age		205 (41.16%)
	Dose		21 (4.21%)
	Weight		4 (0.80%)
	Lack of pediatric clinical data		192 (38.55%)
	Contra-indication		5 (1.00%)
	Indication		67 (13.45%)
	Route of administration		4 (0.80%)

Off-label drug use in pediatric age group: The age group that showed maximum usage of off-label drugs was 3-12years i.e 62 (38.99%) showed off-label drug use in the age group of 3-12years. These children had a mean age of 7.5. This was followed by infants which showed 51 (32.07%) cases of off-label drug use and neonates with 34(21.38%) cases of Off label drug use.

Off-label categories: A greater number of off-label prescribing was seen in the category of age(41.16%), followed by lack of evidence(38.55%) and indication(13.45%). Paediatric patients received off-label drugs that were indicated for a greater age group than that which of administered. For example, piperacillin + tazobactam was indicated for an age group above 12years, lorazepam as IV formulation was indicated for 18years and above.

Examples of off label drugs used:

Table 2: Examples of off Label Drugs used

Sl.No	Drugs	Off label use	Recommendation
1.	Phenobarbitone	Used to induce liver enzyme to incase of NNHB	For status epilepticus, seizures, sedation.
2.	Aspirin	Used in Kawasaki disease	For cardiac disorder
3.	Ondansetron	Used below 12years for indications like vomiting and gastroenteritis	Prevention and post-operative treatment of radiotherapy and chemotherapy-induced nausea and vomiting
4.	Piperacillin+ tazobactum	Used below 12years	Indicated above 12years
5.	Ethamsylate	Prescribed for prophylaxis or pyelonephritis	Unsafe as it's associated with an acute attack of porphyria
6.	Adrenalin	Given as Nebulization to increase the bioavailability	Usually given as IM/IV
7.	Lorazepam	Given for <18years for seizures	Safety and efficacy not established in the pediatric population

About 41% of drugs showed off-label category of age, i.e patients received drugs that were recommended for age greater than that administered. 38% of patients showed an off-label category of lack of pediatric clinical data thus making the administration of such drugs risky. These results are evidence that the clinical trials in pediatric drugs are limited and their safety and efficacy are not well established. For drugs whose safety and efficacy are not established, physicians were found to make use of evidence-based therapy to get the best results.

Safety of Off label drugs:

Table 3: ADR of off label drugs

Sl.No	**Off label drug**	**ADR**	**Wills and brown classification**	**Naranjo's causality**
1.	Salbutamol	Tachycardia and tachypnea	Type A	Possible ADR
2.	Cloxacillin	Gastric intolerance	Type A	Possible ADR
3.	Amoxicillin+clavalonate	Neutrophilic predominance	Type C	Probable ADR
4.	Amoxilicillin+clavalonate	2 episodes of vomiting	Type A	Possible ADR

Out of a total of 200 cases, only 4 cases showed Adverse drug reactions from off-label drugs used. Three cases of possible ADR and one case of probable ADR were seen. This data is not sufficient to conclude the safety of off-label drugs. According to the study conducted label use of drugs was found to be relatively safe. While as an occurrence of any major ADR by any off-label drug prescribed will bring about legal proceeding against the physician in charge. Thus its best recommended to avoid off-label use of drugs as much as possible to ensure legal and safe administration of drug substances to the pediatric population.

DISCUSSION:

The findings of our study revealed that the magnitude of Off label prescribing is relatively high in the case of the pediatric population. The use of the off-label drug was found to be greater between the age group 3-12years i.e children. Age and lack of pediatric clinical data

were identified as the main contributor to off-label prescribing. According to our study findings, the use of off-label drugs does show certain ADR's but the data received are not sufficient to conclude the safety of off-label drugs. But the use of off-label drugs increases the chances for the occurrence of adverse events in the pediatric population. Clinicians should be vigilant for the occurrence of ADR with particular off-label use. Strong follow-up and monitoring should be done for checking the safety of drugs prescribed. As there is a relatively larger percentage of drugs without clinical data available for the pediatric population, physicians must initiate the reporting of any ADR that occurred due to the administration of the off-label drug.

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