

Original Research Article

Use of off-label and unlicensed drugs in pediatric patients: A longitudinal prevalence survey from Lahore, Pakistan

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Abstract

Purpose: To assess the extent of use of unlicensed/off-label drug in the children hospitalized in The Children's Hospital and Institute of Child Health, Lahore, Pakistan.

Methods: A prospective prevalence study was carried out in the selected hospital. A total of 1946 pediatric patients were hospitalized during study period. The patients' demographic data and unlicensed/off-label drug use were noted by the researcher using a structured questionnaire and then analyzed.

Results: During the survey period, 102 (5.24 %) pediatric patients received at least one off-label drug/unlicensed drug. The unlicensed drug was administered to 65 patients (63.7 %) while off-label drug was administered to 37 patients (36.3%). Milrinone (23.5%) was the most frequently prescribed unlicensed drug.

Conclusion: The administration of unlicensed/off-label drug to treat different diseases in pediatric population is widespread in the health facility studied. These findings will provide guidance to new researchers in clinical trials, especially on cardiovascular drugs, opioid analgesic, antiemetic and anticancer drugs.

Keywords: Pediatric, Off-label drugs, Unlicensed drugs

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INTRODUCTION

Many licensed drugs that are commercially available are used only for adults and are not utilized in pediatric practice in accordance with product licensing [1]. Moreover, available dosage forms of many drugs are not suitable for pediatrics [2]. Both prescription and over the counter drugs are used as off-label. Use of off-label drugs are mostly considered as legal as

long as it does not deviate the ethical guidelines or specifically safety measures, but it may have risk for health and have of legal liabilities [3]. In India, high prevalence of off-label drugs (50.6 %) has been reported in patients admitted in general pediatric units [4]. The off-label drug may be prescribed for pediatrics when there is no proper alternative drug available.

The duty of Drug Regulatory Authority (DRA) is to set a policy concerning pre-marketing evaluation (overall benefit/risk evaluation) and marketing authorization or registration of the drugs [5]. Most of the medications used for pediatrics reportedly are off-label which does not fulfill the standard of safety and efficacy. Product licensing procedure was initiated in response to adverse drug reactions (ADRs) that not only appeared in adults but also in infants (Grey Baby Syndrome induced by Chloramphenicol) and developing fetus (Phocomelia induced by Thalidomide) [6]. Due to the scarcity of pediatric clinical data, off-label or unlicensed drugs are used widely around the globe. Insufficient pediatric clinical data may be due to lack of resources provided by administration, hesitancy of parents or guardians to permit their children to participate in clinical trials and other ethical problems of research in pediatrics.

Multisite studies reported the unlicensed/off-label drug utilization and prospective drug surveillance for side effects or adverse drug reactions (ADRs) in pediatric population [6-8]. It has also been reported that neonates and infants are frequently received drug as unlicensed/off-label in healthcare settings [9]. In Germany, off-label/unlicensed drug was administered to 61% pediatrics hospitalized in general medicine pediatric wards [10]. In Brazil, a study of 272 pediatric patients of general medical wards, aged up to 16 years, recorded that about 22% of them received one unlicensed drug and 60% of them received a minimum of one off label drug during their stay in the university hospital [11]. The purpose of this study was to assess the use of unlicensed/off-label drug in hospitalized pediatric patients.

METHODS

A prospective prevalence study of unlicensed/off-label drug use in pediatric patients was executed in The Children's Hospital and Institute of Child Health, Lahore. This hospital was selected because this is the largest pediatric hospital of Pakistan. This research was approved by Human Ethical Committee of University College of Pharmacy, Punjab University, Lahore (approval no. HEC/PUCP/1954) and Ethical Review Board of The Children's Hospital, Lahore (approval no. 8227). Off-label or unlicensed drugs used by pediatric population was identified using British National Formulary (BNF) [12]. All the patients admitted in the four selected wards such as, Cardiology, Diarrhea, General Surgery & Gastroenterology of The Children's Hospital Lahore and at least one off-label or un-licensed drug prescribed were included in this study. The

patients with unconfirmed diagnosis were excluded from this study.

This questionnaire was also approved by two pediatricians. The data collection included the following information: parent's profession and socioeconomic status, dietary status of patients, prescribed off-label and unlicensed drug associated with frequency, dose, and route of administration, condition of prescribing off label drug, co-morbidities, co-medications, use of any herbal drug, possible adverse drug reactions (ADRs) or side effects by the administration of these unlicensed and off label drugs and lab values of serological tests. The information of utilization of following drugs was not included: blood products, topical anesthetic creams, standard intravenous crystalloid solutions, oxygen therapy and total parenteral nutrition.

Data collection and processing

Prescription data of all admitted patients in selected pediatric wards during last 4 month period was evaluated. All prescriptions of unlicensed and off label drugs were collected and most commonly prescribed drugs were checked with the reference of British National Formulary. Patient's data regarding demographics and the unlicensed/off-label drug utilization were noted by the researcher himself from patient's treatment files. The data were categorized as infants, toddlers, preschoolers, early age schoolers, children and school age children. All the drugs were unlicensed and off-label if they were prescribed beyond the recommendation meant for the age group. Event effects were monitored with the aid of package insert, BNF and standard books to determine the side effects/adverse drug reaction (ADR).

RESULTS

Demographic characteristics

A total of 1946 admitted patients in selected wards of the hospital met the inclusion criteria for this study during the study period. As indicated in Table 1, most of the patients belonged to early age school children (29.4%) and infants (28.3%) category. Out of total 102 patients, 66 were males and 36 were females.

Unlicensed drug use with respect to different age groups and gender

Unlicensed drugs were prescribed in 63.7% of total prescriptions (Table 2). Unlicensed prescribed drugs were more common in males (36.3%) compared to females (27.4%). Drugs

Table 1: Division of patient numbers and prescriptions with different age groups

Age category	Age (years)	Total N (%)	Male N (%)	Female N (%)
Infant	≤ 1	29 (28.43)	21(20.6)	8(7.8)
Toddler	1-3	15(14.7)	9(8.8)	6(5.9)
Pre-schoolers	3-6	17(16.6)	10(9.8)	7(6.8)
Early-age school children	6-11	30(29.4)	17(16.7)	13(12.7)
School age children	11-15	11(10.8)	9(8.8)	2(1.9)

Table 2: Categorization of prescriptions of off-label and unlicensed drugs with respect to age group and gender

Variable	Off Label (N %)	Unlicensed (N %)
Age group		
Infant	20(19.6)	9 (88)
Toddler	2(1.96)	13(12.7)
Pre-schoolers	4(3.9)	13(12.7)
Early-age school children	10(9.8)	20(19.6)
School age children	1(0.98)	10(9.8)
Gender		
Male	29(28.4)	37(36.3)
Female	8(7.8)	28(27.4)

used in unlicensed manner were more common in early school age children as compared to any other age categories. Prescribed unlicensed drugs were in 9.8 % of school age children (11 – 15 y), in 19.6 % of early school age children (7 – 11 y), in 8.8 % of infants (1 m - 1 y), in 12.7 % of toddler (1 - 3 y) and 12.7 % of Preschoolers (3-6 y). Among unlicensed drugs, Milrinone was the most frequently prescribed unlicensed drug. The prescriptions of Milrinone are 24 (23.52%) out of total prescriptions. Of this total, Milirone was prescribed more in males (N = 14) than females (N=10, 9.80%).

Table 3: Unlicensed and off-label prescribed drugs

Generic name	Trade Name	Patients	Rationale /Approved for Patients older than (Years)
Unlicensed drugs			
Inj. Milrinone	Milron	24	Not licensed for use in children under 18 years
Inj. Octreotide	Sandostatin	7	Not licensed for use in children
Inj. Dopamine	Dopamine	1	Not licensed for use in children under 12 years
Inj. Cyclophosphamide	Cyclomide	2	Not licensed for use in children
Inj. Mesna	Mesnal	1	Not licensed for use in children
Off-label drugs			
Inj. Tramadol	Tradol	13	Above 12 years
Inj. Dimenhydrinate	Diemtil	21	Less than 01 year

Off-label drug use with respect to different age groups

Off-label drugs were prescribed in 36.3 % of total prescriptions to pediatric patients. Off-label prescribed drugs were more common in males (28.4%) compared to females (7.8%). A prominent difference has been observed in the frequency of off label drug administered in different age groups. Infants (19.6 %) and early School children (9.8 %) received at least one-off label drug. The different drugs which were most commonly prescribed as unlicensed and off label are presented in Table 3. Among off label drugs, Dimenhydrinate (N=21, 20.0%) was the most frequently prescribed drug used in pediatrics.

DISCUSSION

Over the past few years, multisite studies performed in different settings have reported that off-label/unlicensed drug use is commonly used in the pediatric population [6,13]. It is because as there is no alternative to such drugs in the market or no standard treatment plan is available due to the scarcity of pediatric clinical data. As per our knowledge, it is a first study associated with the unlicensed/off-label drug utilization in pediatric patients in Lahore, Pakistan.

The overall prevalence of off label/unlicensed drug use was 5.24 % which was comparable to the study performed in three European countries (5.8 %) [14]. However, the rate was much lower when compared with other studies performed in Netherland (44 %) and Germany (30 %) [15]. Another previous study reported the extent of unlicensed/off-label drug utilization in pediatrics in community practice was around 10 % [16]. The prevalence rate of off-label/unlicensed drug use was higher in early-age school children (6 - 11 years) which were comparable to studies performed in Ethiopia and Germany [15,17]. A study conducted in France documented that off-label drug is prescribed to neonates where the highest level of caution is required for safety [18].

Dimenhydrinate (20.5 %) was commonly used as off-label drug in pediatrics. Dimenhydrinate is commonly used for the treatment of vomiting and motion sickness [19]. Dimenhydrinate is often used as an off-label drug in pediatrics. A study reported that children received 85 % of prescription of Dimenhydrinate in the pediatric intensive care unit (ICU) [20]. The most common unlicensed drug used was Milrinone (23.5 %). Over the last 13 years, there is an increase in the use of Milrinone in pediatric patients. A study reported that 40 % of the infants experienced hypotension and thrombocytopenia [21]. Analgesics, anti-emetics and bronchodilators were the most prescribed off-label or unlicensed drugs in this study. Most of the drug categories used as off-label were ophthalmological/otologicals, blood and blood-forming organs, cardiovascular drugs and dermatological preparations [22]. In the past 30 years, the Food and Drug Administration approved 80 % of drugs with labeling disclaimer for pediatric use in United States [23]. Legislation regarding off-label or unlicensed drugs has been implemented to improve better prescribing knowledge on adequate dose, safety and efficacy of drugs [24]. WHO highlighted the issue regarding unlicensed/off-label drug use and adopted the Resolution "Better Medicines for Children" to improve the safety and efficacy of drug in pediatrics [15].

Limitations of the study

Since the present study was performed only in one hospital, the findings may not be representative of patients outside the hospital. This study only focused on evaluating the extent of off-label and unlicensed use of drugs in pediatrics and did not determine the benefits and adverse drug reactions (ADRs) or side effects associated with off-label/unlicensed drug utilization.

CONCLUSION

The utilization of unlicensed/off-label drugs is frequent in pediatric patients in the setting of the study. However, the quality of drug therapy is not necessarily related to its license status. Prescribers should avoid exposing their patients to unnecessary and inappropriate risk of unlicensed and off-label drugs. This study will also help to provide guidance to new researchers in clinical trials, especially on cardiovascular drugs, opioid analgesic, antiemetic and anticancer drugs. Due to the possible complications associated with off-label prescribing, such drugs should only be prescribed when the benefit is certain and when

patients have exhausted all other approved options, as may be the case with rare diseases.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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