Original Article

Unlicensed and Off-label Utilization of Oral Drugs in Pediatrics in a Vietnamese Tertiary Teaching Hospital

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Abstract

Context: Off-label or unlicensed medicine utilization is very prevalent in pediatric practice. **Aims:** This investigation aimed to determine the frequency and nature of unlicensed and off-label oral medicine prescriptions in children. **Method:** A prospective cross-sectional research was carried out in a pediatric department in a tertiary university hospital for one month. **Results:** A total of 320 oral prescription medicines were assessed for 104 patients, with an average age of 2.9 years. The frequency of unlicensed and off-label administration of drugs was 17.8% and 28.1%, respectively. In all, 54 (51.9%) children received at least one unlicensed or off-label drug. All unlicensed drug utilizations were for marketed drugs with pharmacy compounding. The types for off-label utilization were unapproved age (15.9%) and unapproved dosage (12.2%). Paracetamol was the most frequently prescribed unlicensed and off-label drug. Oral solid preparation was more prone to unlicensed prescriptions ($p < 0.001$). Age (< 2 years), number of oral drugs per patient (> 3 drugs), and oral dosage forms (liquid) were highly correlated with off-label regimen ($p = 0.003$, 0.028, < 0.001, respectively). Off-label utilization was highly correlated with having difficulty in dosing ($p < 0.001$) while unlicensed utilization was highly related to having difficulty in taking the drug orally ($p < 0.001$). **Conclusion**: A high rate of unlicensed/off-label drug utilization was revealed and was also correlated with an enhanced risk of having difficulty in dose preparations and administrations. More efforts should be required to enhance rational drug utilization in children.

Keywords: unlicensed, off-label, pediatric, hospital, Vietnam

Introduction

The safety of the medications [1-3] and the quality of patient care have been global issues [4]. Pediatric medication has been a major concern for clinicians for a long time. Several reasons include changes in pharmacokinetics and pharmacodynamics profiles of many drugs [5], and lack of clinical trials in children due to ethical and economical questions reported in the literature [6]. This absence of research data in children makes drug license for pediatric patients difficult. To deal with this problem, governmental health agencies have tightened their regulations in the drug development process [6]. In spite of this work, off-label or unlicensed drug prescribing is greater in children than in adults [7, 8].

Unlicensed drug administration is described as the employment of a drug in the lack of a product license [9]. Off-label drug administration is known as the utilization of a marketed drug that is not in conformity with the marketing authorization issued by the country's regulatory agency [10]. Many investigations stated high rates of unlicensed (0.3% to 35%) and off-label (9% to 78.7%) drug utilization in various pediatric patient settings [8]. The proportion of unlicensed and/or off-label prescriptions associated with an adverse drug reaction ranged between 23 and 60% [7].

Oral drug use in children is common and has a risk problem. Delmas *et al*. found that the oral route of administration accounted for 46.9% in children, and 66.3% of formulary medicines and 15.1% prescriptions of medicines intended for oral utilizations were unsuitable [11]. Many accessible oral formulations are not proper for children, which often results in off-label and unlicensed utilization of adult drugs. The use of medications unsuitable for children may pose problems not encountered in adults, such as difficulty in accurately dosing, the ability to swallow large-sized pills, and problems associated with the unpleasant taste of the drug [12, 13]. These

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difficulties can cause several problems while taking oral drugs in children such as vomiting, choking, or smuggling [14].

Numerous investigations have determined the profile of unlicensed and off-label administration in children, particularly in the developed world [7, 15]. However, no article has investigated this issue regarding oral drugs in pediatric patients from Vietnam, which reveals special clinical and epidemiological features. Consequently, this article aimed to define the off-label and unlicensed utilization of oral drugs in children in a Vietnamese tertiary hospital to determine factors correlated with this phenomenon and to compare the obtained findings with other investigations.

Materials and Methods

Study design and settings

The prospective cross-sectional research was carried out in a pediatric department of a 600-bed tertiary care university hospital located in Hue, a central region of Vietnam. This pediatric department has thirty beds. Data collection was carried out by a clinical pharmacist on randomly selected days in October 2018 and involved examination of medical records received at the department.

The eligible patients had following criteria: (1) Active prescriptions of at least one oral drugs for children <18 years of age; (2) only one prescription was selected for each patient; (3) duration of hospitalized stay was three days or more; and (4) other routes of administration such as parenteral, rectal, dermal, nasal, pulmonary, and ocular drugs, electrolytes, hemoderivatives, oxygen therapy, and parenteral nutrition were excluded, and (5) whose parents had an oral consent.

Data collection

The demographic data collected were age, sex, weight, and admission diagnosis. The following information concerning drug administration was collected: drug name, dose, frequency, indication for utilization, form, and route of administration. The sign for the administration of the medicines was gained from detailed patient charts and when in doubt, the attending physician was checked. Cases of difficulty in the accurate dosage for children and cases having the problem of not capable of taking medicine (vomiting, choking, and smuggling) were also collected from parents and nurses.

Descriptions and research variables

Age was stratified in newborns (0-27 days), infants (28 days-23 months), children (2-11 years), and adolescents (12 - 18 years) [12], whereas admission diagnosis was characterized on the basis of the International Classification of Diseases (ICD-10). All drugs were classified on the basis of the Anatomical Therapeutic Chemical (ATC) classification system and differentiated to the second level of the ATC code. Types of oral drug formulations were classified as Ivanovska *et al.*'s study [16].

The following conditions were considered unlicensed if: (1) drugs were imported and not approved by the regulatory agency in Vietnam, (2) drugs were contraindicated to children, and (3) licensed dosage forms of drugs were modified for use in children (extemporaneous drug preparation obtained from a licensed medicine, such as when an adult preparation is not appropriate for utilization in children and a smaller dose must be formulated) [15, 17] The off-label category included all medicines whose prescription was not in line with the license issued by the Drug Administration of Vietnam (DAV), such as indication, age, dosage (dose and frequency) and route of administration [10, 17].

Sorting of drug utilization in unlicensed, off-label, or in-label was performed after accessing the Vietnamese National Formulary (VNF) and drug monographs by drug producers and issued by the DAV reachable in the https://drugbank.vn/, and British National Formulary For Children 2016-2017, which was considered the reference. For generic drugs, a drug monograph of the present drug producer was considered; if not obtainable, a drug monograph from another generic drug producer was considered. If no reference to "pediatrics" or "children" was comprised in the drug monograph, the prescription was thought to be off-label. For the unapproved age group, other standards were thought to be unsuitable. The unapproved indication was verified through a review of medical progress notes stated in the medical chart. These records addressed the definite medical issue the patient was facing and the situation in which the drug was prescribed. An unapproved dosage was expressed as a dose of 15% greater than the suggested maximal dose to account for dose rounding [18]. Unlicensed and off-label drug definitions were considered to be mutually exclusive [15].

Ethics

Before the start, the Research Ethics Committee from the Hue University of Medicine and Pharmacy (H2018/064) verified the research protocol. All the patients attending the pediatric department during this period were enrolled in the investigation after gaining oral informed consent of the patient's guardian.

Statistics

By dividing the number of unlicensed/off-label drug prescriptions by the total number of drug prescriptions, the unlicensed/off-label drug administration rate was measured. The proportions of off-label drug administration per unapproved criteria (e.g., administration route, indication, dosage, frequency, and age group) were also measured. For these findings, within any given prescription, each unapproved criterion was included individually for analysis (ie, one off-label prescription with both an unapproved indication and an unapproved dosage was considered in each of these off-label classes).

A descriptive analysis was performed to determine continuous variables. A Chi-square test was applied to confirm the probability of receiving at least one unlicensed or off-label drug with possible predictors. All data were assessed utilizing SPSS version 21.0®.

RESULTS

Characteristics of pediatric patients

A total of 104 patients were comprised in the investigation; the mean age was 2.9 years (range zero to 14 years); 62.5% were male. The weight varied from 3.1 kg to 57 kg and the mean weight was 13.2kg. The common diseases of children were respiratory diseases (50.8%). Among them, pneumonia was the major diagnosis observed in this study.

A total of 320 drug prescriptions were prescribed for 104 patients, accounting for 39 different drugs. These patients utilized a mean of 3.1 oral drugs with a range of 1 to 9 drugs. The most prescribed ATC group was the A03 drugs for functional gastrointestinal disorders (29.4%), followed by the M05 drugs for the cure of bone illnesses (25.6%) and by the R01-05 drugs for the respiratory system (8.4%). Paracetamol was the most prescribed for 76/23.8% of the patients studied, followed by probiotics (51/15.9%) and oral rehydration solutions (23/7.2%). Additionally, the powder and granule for reconstitution were the most common formulations employed (45.3%) and oral lipid preparations accounted for 64.7%.

Table 1: Characteristics of pediatric patients (n=104).

Variables			No of Patients (%)
Sex	Male		65 (62,5%)
	Female		39 (37,5%)
Age	Newborn (< 28 days of age)		7 (6,8%)
	Infant (28 days to 23 months of age)		40 (38,8%)
	Children (2 to 11 years of age)		55 (52,9%)
	Adolescent (12 to 18 years of age)		2 (1,9%)
	Mean ± SD		2,9 ± 0,30
Weight	≤10kg		51 (49.0%)
	10.1kg-20kg		36 (34.6%)
	>20kg		17 (16.4%)
	Mean ± SD		13,2 ± 0,90
Disease with ICD 10 code	J00-J99: Diseases of the respiratory system		64 (61.5%)
	A00-B99: Certain infectious and parasitic illnesses		29 (27.9%)
	D50-D89: Illnesses of the blood and blood-forming organs and certain disorders involving the immune mechanism		6 (5.8%)
	L00-L08: Infections of the skin and subcutaneous tissue		8 (7.7%)
	Others		25 (24.0%)
Number of oral drugs per patient	1-3		64 (61,5%)
	4-6		36 (34,6%)
	>7		4 (3,8%)
	Total number of medicine		320
	Average number of drug per patient (Mean ± SD)		3,1 ± 1,6
ATC drug groups*	A03 – drugs for functional gastrointestinal disorders		94 (29,4%)
	M05 – drugs for the treatment of bone diseases		80 (25%)
	A11-12 - Vitamins và minerals		45 (14,1%)
	J01 – Antibacterials for systemic use		37 (11,6%)
	R01-05 – drugs for the respiratory system		27 (8,4%)
	L02 - Hormones		17 (5,3)
	Others		20 (6,2%)
Oral dosage forms*	Liquid preparations	Solution, syrup, drop, suspension	62 (19,4%)

	Powder and granule for reconstitution	145 (45,3%)
Oral solid formulations	Tablet	85 (26,6%)
	Capsule	26 (8,1%)
	Effervescent tablet	2 (0,6%)

[*]rate was calculated in the sample of 320 prescribed oral drugs

Unlicensed and off-label use

The overall unlicensed drug utilization rate was 17.8% of all prescriptions. All unlicensed drug utilizations were for marketed drugs with pharmacy compounding which were associated with 57 drug products. The overall off-label drug utilization rate was 28.1%. The reasons for off-label utilization were unapproved age (15.9%) and unapproved dosage (12.2%), which were associated with 31 drug products. Paracetamol, prednisolone, and erythromycin were the most frequently prescribed unlicensed drugs whereas paracetamol, probiotics, esomeprazole were the most utilized in an off-label manner (**Table 2**). 54 (51.9%) children got at least one off-label or unlicensed drug.

Table 2. Profile of unlicensed and off-label use (n = 320)

Drug classification	Number of prescriptions (%)	Most frequent drugs
Unlicensed	**57 (17.8%)**	
No license	0	
Contraindication in children	0	
Modified formulations	57 (17.8%)	Paracetamol > Prednisolone > Erythromycin
Off-label	**90 (28.1%)**	
Unapproved indication	0	
Unapproved age group	51 (15.9%)	Paracetamol > Erythromycin > Esomeprazol
Unapproved dosage	39 (12.2%)	Probiotics > Paracetamol > Prednisolone
Unapproved route of administration	0	

Predictors for receiving at least one unlicensed and off-label utilization

Oral solid preparation was more likely to unlicensed prescriptions ($p < 0.001$). Age (< 2 years), number of oral drugs per patient (> 3 drugs), and oral dosage forms (liquid) were highly correlated with off-label regimen ($p = 0.003$, 0.028, < 0.001, < 0.001, respectively) (**Table 3**). Off-label administration was highly correlated with having difficulty to dosing ($p < 0.001$). Unlicensed utilization was highly correlated with having difficulty to take drugs orally ($p < 0.001$).

Table 3. Predictors for receiving at least one unlicensed and off-label use

Predictors	Unlicensed drug		Off-label	
	N	p value	N	p value
Sex				
Male (n = 65)	39	0.170	55	0.458
Female (n = 39)	18		35	
Age				
<2 years (n = 47)	27	0.694	46	0.003*
≥ 2 years (n = 56)	30		44	
Weight				
≤ 10 kg (n = 51)	25	0.245	44	0.938
> 10 kg (n = 53)	32		46	
Number of oral drugs per patient				
1-3 (n = 63)	10	0.905	18	0.028*
>3 (n = 40	6		**20**	
Oral dosage forms[#]				
Liquid preparation (n = 207)	0	<0.001*	**78**	<0.001*

Solid formulation (n = 113)	57		12	
Having a difficult to dosing#				
Yes (n = 53)	12	0.314	26	<0.001*
No (n = 267)	45		64	
Having a difficult to take the drug orally #				
Yes (n = 109)	28	0.008*	36	0.161
No (n = 211)	29		54	

#rate was calculated in the sample of 320 prescribed oral drugs. *p< 0.05

Discussion

Unlicensed and off-label utilization

The accessibility of oral pediatric formulations is generally absent in low and middle-income countries, for instance, because of illness burden and financial limitations, as well as disconnected supply chains and uneven healthcare systems. The nonexistence of authorized pediatric medicines repeatedly leads to the administration and manipulation of products intended for adults, with an enhanced risk of mis-dosing and difficulty to administration [19]. Based on our knowledge, this is the first investigation which aimed to define characteristics of unlicensed and off-label utilization in children in Vietnam, its correlated factors, and its influences.

The prevalence of unlicensed and off-label utilization of drugs in the investigated population was 17.8% and 28.1%, respectively. A systematic review of Gore *et al.* in 2017 revealed that many investigations noted high rates of unlicensed (0.3% to 35%) and off-label (9% to 78.7%) drug utilization in different pediatric patient settings in fourteen research from different countries [8]. Nevertheless, the off-label and unlicensed classification techniques varied, making the findings difficult to compare but providing an overall picture of the problem [20].

Concerning unlicensed drug utilization, the only reason was the inaccessibility of pediatric oral formulations (17.8%). In our investigation, at least 57 drug products were considered unlicensed because nurses or parents had to compound a formulation suitable for children. This rate is comparable one in a study of the 17.668 prescriptions of medicines intended for oral utilization in children under six years old found that 15.1% were unsuitable pharmaceutical forms [11]. Prescribing practices also vary between countries. Many preparations in Netherlands hospitals are prepared from commercial presentations. This finding in a greater number of unlicensed medicine prescriptions, range from 28% to 42% [7, 21]. However, only a limited number of pharmacy preparations were issued in Vietnamese hospitals. Many capsules were opened and mixed with patients' food. Some were not capable to swallow tablets and needed conversion of pharmaceutical products into proper forms for children by crushing, dissolving, and dividing. These raised issues of bioavailability, the accuracy of the dose administered, and stability. Unpackaging and repackaging these medicines also enhances the risk of medication errors [22].

Unlike other studies in other countries, there was no case which required using an unmarketed drug in our study. Vietnamese hospitals don't have a clear policy to resolve a drug shortage or unlicensed drug use, which make physicians not to be confident to prescribe the unlicensed drug in the patient's medical records. In some situations, physicians prescribed in a separate prescription form and asked patients to buy by themselves and did not document in the patient records.

The assessment of off-label drug administration rates is more complex than that of unlicensed drug administration rates. First, it necessitates a medical chart review to recognize indications for drug prescription. Second, the classification of a drug prescription as on- or off-label will be dependent on the gold standards designated for comparison (e.g., scientific databases, drug monographs, books) [15]. Our investigation indicated that 28.1% of all drug prescriptions inspected were off-label and were unapproved for the age group (15.9%) and dosage (12.2%). Unlike these earlier investigations, our findings demonstrate that there were no off-label prescriptions correlated with unproved indication and route of administration. Corny *et al.* in Canada reported that there were unapproved drugs for the age group (53.2%), dosage (27.6%), frequency (25.2%), administration route (5.6%), and indication (5.5%) [15]. The research of Santos *et al.* in Brazil reported that dose/frequency was the most frequent method of off-label drug administration [9].

Paracetamol was the most frequently prescribed unlicensed/off-label drug. In the research of Corny *et al*., the most frequent off-label drug prescriptions were paracetamol, dimenhydrinate, and morphine sulfate [15]. Delmas *et al.* revealed that the proportion of off-label prescriptions by ATC class was maximum in the cardiovascular system (77.2%).

Predictors for receiving at least one unlicensed and off-label utilization

Numerous investigations determined predictors for receiving off-label and unlicensed administration. Research in the Netherlands indicated that the percentage of patients utilized one or more unlicensed or off-label prescriptions was meaningfully greater in children below six months of age than in older children [21]. Another investigation in Malaysia noted that children aged 28 days to 23 months, preterm infants, patients with hospital stays of more than 2 weeks, and those prescribed increasing numbers of medicines were more probable to get medicines for unlicensed administration.

Term neonates and patients prescribed increasing numbers of medicines had improved the risk of receiving medicines for off-label utilization [23].

Our study determined that predictors were age (<2 years), number of oral drugs per patient (> 3 drugs), and oral dosage forms (liquid) for off-label regimen; and was oral dosage forms (solid) for the unlicensed prescription ($p < 0.05$).

The oral route of administration is the favored route for patients of all ages owing to ease and stability. Drugs given orally include liquid dosage methods (such as suspensions, syrups, solutions, and emulsions) as well as solid dosage methods (such as tablets and capsules). Oral liquid drops can deliver small and flexible volumes or low doses of a drug to children with the utilization of suitable measuring devices (such as oral syringes, graduated pipettes, or measuring spoons). Conventional tablets are restricted by their rigid dose content and the capability of the child to swallow a tablet [24]. Our study found that 53 (51.0%) drug prescriptions had difficulty in the accurate dose preparation and 109 (34.1%) drug prescriptions had difficulty in completely taking drugs orally. Boztepe *et al.* indicated that the most regularly reported issues in the preparation of drugs were the incomplete dissolution of tablets or non-homogeneous distribution in fluids (54.6%) and difficulty in breaking tablets in proper doses (45.3%), and the most regularly reported issue during the administration of drugs was the rejection of drugs which tasted bad by babies/children or spitting out the drug (75.9%) [13]. Results from our study found that off-label use was prone to having difficulty in dosing and unlicensed use was highly likely to have difficulty taking the drug orally. Other investigations also indicated that unlicensed/off-label drug utilization was significantly correlated with medication errors [22] and adverse drug reactions [9].

A study limitation that needs to be considered when interpreting findings is the study conducted in one pediatric department with a modest sample size (104 patients and 320 drug prescriptions).

Conclusions

A high rate of unlicensed/off-label drug utilization was revealed and was also correlated with an increased risk of having difficulty in dose preparations and administrations. More efforts should be required to enhance rational drug utilization in children.

Key Messages: A high rate of unlicensed/off-label drug utilization was revealed and was also correlated with an enhanced risk of having difficulty in dose preparations and administrations

Declarations

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Conflicts of Interest

All authors declared that there were no conflicts of interest concerning this work.

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Ethics approval and consent to participate:

The research protocol was approved by a university academic committee (H2018/064).

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