

RESEARCH ARTICLE

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The Unlicensed and Off-Label Prescription of Medications in General Paediatric Ward: An Observational Study



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Abstract: Background: Unlicensed (UL) and Off-label (OL) prescription of medications is common in paediatrics and does not constitute negligent practice since there is often no approved alternative according to FDA bulary.

Aim: The study aimed to determine the current frequency of UL and OL prescriptions in children from one month to 12 years of age in a Paediatric Inpatient Unit (PIU).

Methods: This is an observational, prospective study, reviewing the prescriptions of all patients admitted to the PIU in a university hospital in a single week in August 2014 and a single week in January 2015.

Results: We included 157 patients of median age 18 months and median length of stay 24 days. There were 1,328 prescription items (average of 8.4 items/patient) and only two patients without UL/OL use. During the winter season (August), 27% of prescriptions were classified as UL and 44.6% as OL, and during summer (January), 29.6% as UL and 45.1% as OL. We identified 188 medications, of which the most prescribed were paracetamol (11%) and dipyron (9.5%). The most frequent OL classification was regarding drug formulation (15.8%). In the winter week, the most frequent reasons for admission were respiratory (44%), followed by other clinical causes (CC) (17.3%), while in the summer week, they were CC (26.3%), followed by surgical and gastro-hepatic (23.7%).

Conclusion: The OL prescription of medicines for children in Brazil is in accordance with the international literature. The higher prevalence of OL due to formulation found in this study is related to the use of formulations other than those used by the FDA.

Keywords: Off-label, prescribing, paediatric medication, unlicensed, prescription, paediatric pharmacology, hospital pharmacology, formulation.

1. INTRODUCTION

The lack of specific drugs and licensing for the paediatric population is a chronic global problem - first detected as a concern in the late 1960s in the US by Shirkey (1968), who classified children as therapeutical orphans [1]. According to the American Academy of Pediatrics (AAP), 80% of drugs prescribed for children are not administered according to a recommended standard [2], while Meadows WA *et al.* (2008) estimated that 80-90% of paediatric patients are

prescribed drugs that are insufficiently studied or completely untested in paediatric populations [3]. The concept of non-standard or Off-label use (OL) and unapproved or unlicensed (UL) medication in children may vary according to the authors. In general, the term unapproved drugs is used to refer to drugs manufactured or modified in a hospital [4], chemicals used as medicines such as chloral hydrate, zinc and copper and some agents used exclusively in the treatment of children, such as nitric oxide in pulmonary hypertension [5]. Some studies include the use of drugs that are not indicated in children, or used without a specific dosage in this category [6-11]. Off-label drug use is defined as prescribing the drug in a way other than that directed in the manufacturer's instructions - regarding age group, presentation, dose, frequency and route of administration, or the indication for use in children. Therefore, it is the unauthorized

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use of a drug for a purpose other than the one approved by the US Food and Drug Administration (FDA) [9-11].

The recognition of OL and UL use as a problem by health authorities, even in developed countries, is recent. FDA has been seeking regulatory measures to economically motivate the pharmaceutical industry to meet the needs of medicines suitable to be used for children since 1960 [12]. To this end, the US government provides incentives to pharmaceutical companies to test paediatric medications by ensuring to them six months of exclusive market rights to existing patents for all formulations of any product that is appropriately studied in children [13]. In Europe, in early 2007, the European Medicines Agency (EMA) introduced a set of specific measures to regulate drugs for the paediatric population as well as some incentives for clinical research and drug development for children [14]. As for Brazil, there is no specific regulation for the registration and use of medicines in children and no policy of encouraging clinical research in paediatrics.

The AAP reports that the off-label use of drugs is not a negligent practice, as it may be necessary to ensure the patient's treatment when there is no other approved alternative [2]. This demonstrates that science and medicine are moving faster than the bureaucratic procedures of the drug registration. However, such use may result in incorrect treatment, as the extrapolated dose may be insufficient, or lead to toxicity, when the dose is higher than the required dose.

Regarding the use of drugs in patients in paediatric wards, off-label and unlicensed uses are frequent [15], reaching up to 60 % of medications [16]. Of all active substances approved by the EMA from October 1995 to September 2005, only 33 % were approved for use in children, 23% in infants and only 9% in neonates [17], demonstrating that the lower the child's age, the harder the standardization of medications.

The objective of this study was to determine the current frequency of UL and OL prescriptions in children from one month to 12 years of age in a Paediatric Inpatient Unit (PIU), as well as why they are classified as such and if there is any association with the reason for hospitalization.

2. METHODS

This is a cross-sectional observational study, reviewing data from the medical records of patients admitted during the study period in the PIU of a university hospital. The exclusion criteria were: hospital readmission in the same study week; age less than 30 days and more than 12 years; and medications such as blood products, total parenteral nutrition, oxygen, saline, dextrose, vaccines and barrier ointments. Data were collected retrospectively from all patients admitted to the PIU of this hospital during one week in August 2014 and in one week in January 2015. For each patient admitted during the study periods, data form was generated, identifying demographic data and the main reason for hospitalization. Patients were followed up for a period of 30 days - or less, if they were discharged to home, died, or transferred to the Paediatric Intensive Care Unit (PICU). Patients were included only once during the study week. In

order not to influence the prescribing patterns or medical records, neither the patients, nor their medical staff was made aware of the study, and the research team was not identified.

The research group recorded all prescription items and each medication was evaluated to determine if its prescription was approved, Unlicensed (UL), or Off-label (OL). The drugs prescribed to inpatients in the PIU were classified according to the FDA drug library. Medications contraindicated for use in children, manufactured or modified in the hospital, those with no specific dosage for children or those imported were classified as UL. Drugs prescribed for use in a way other than that contained in the manufacturer's instructions (regarding age group, formulation, dose, frequency and route of administration, or the indication for use in children) were classified as OL. Patients included in the study were divided into 5 groups according to the most frequent reasons for hospitalization: Surgical (S), Gastroenterological-Hepatological (GH), Neuro-psychiatric (N), Respiratory (R) and other Clinical Causes (CC). This classification was made in order to evaluate differences between summer and winter prescriptions.

Statistical data were analysed using the Statistical Package for Social Sciences (SPSS), version 18.0, and the chi-square, Kruskal-Wallis and Mann-Whitney U tests were used, with a p-value of <0.05. Chi-square was used due to the number of events in each group. The comparison tests were used due to the non-normal distribution of the sample

The sample size was calculated based on studies in the Neonatal Intensive Care Unit (NICU) and PICU in the same Hospital [9, 18]. To detect a difference of 21% between UL or OL and approved prescriptions, considering an $\alpha = 0.05$ and power of 80%, 76 patients were considered. For the period of 14 days, spread over two months, approximately 132 patients were estimated, since there were 66 beds available and the average length of stay was 10.7 days in August and 10.27 days in January (institutional data of 2013 and 2014 respectively).

The project was submitted to the Ethics in Research Committee of Hospital de Clínicas de Porto Alegre (GPPG No. 14-0507). For the present study, the data used was from the clinical file, copied from the patient folder, which was anonymized and identified by a code number. A Statement of Commitment for Use of Data was filled.

3. RESULTS

During a 2-week study period, covering one week in August 2014 and one week in January 2015, we included 157 patients - 84 male, median age of 18 months and median length of stay of 24 days.

During that period, 1328 items were prescribed (8.4 items/patient) - 641 in the winter period (7.9 items/patient) and 687 in summer (9 items/patient). There were 188 studied medications - the most prescribed drugs were acetaminophen (11%), dipyrone (9%) and metoclopramide (5%). The same frequency was maintained when each study period was analysed separately (Table 1).

Table 1. The most prescribed medications according to study period.

Medications	Total Frequency (%)	Winter Frequency (%)	Summer Frequency (%)
Acetaminophen	148 (11)	75 (12)	73 (10.5)
Dipyron	127 (9)	61 (9.5)	66 (9.5)
Metoclopramide	67 (5)	32 (5)	35 (5)
Omeprazole	46 (3)	21 (3)	25 (3.5)
Ondansetron	47 (3)	18 (3)	29 (4)
Phenobarbital	33 (2)	22 (3)	11 (1.5)
Ibuprofen	32 (2)	14 (2)	18 (2.5)
Prednisolone	29 (2)	18 (3)	11 (1.5)

Table 2. The most prescribed drugs according to classification.

Classification	Total (%)	Drugs
Approved	355 (26.7%)	Valproic acid, prednisolone, paracetamol, ondansetron, diazepam
Unlicensed	377 (28.3%)	Dipyron, chloral hydrate, metoclopramide, metronidazole, morphine
OL for age	159 (11.9%)	Beclomethasone, omeprazole, ondansetron, salbutamol, topiramate
OL for dose	102 (7.6%)	Furosemide, gentamicin, hydroxyzine, omeprazole, ondansetron, paracetamol, vancomycin
OL for formulation	211 (15.8%)	Vitamins A+D, ferrous sulfate, nystatin cream, ibuprofen, phenobarbital
OL for frequency	38 (2.8%)	Cefepime, omeprazole, ceftazidime, gentamicin, vancomycin
OL for indication	75 (5.6%)	Ondansetron, sulfamethoxazole and trimethoprim, cefuroxime, l-carnitine, metronidazole, oxiconazole

*OL=Off-Label.

Regarding the total number of drugs classified as approved (26.7%), the most frequently prescribed were valproic acid, prednisolone and acetaminophen. Among the UL prescription drugs (28.3%), the most frequent were dipyron, chloral hydrate and metoclopramide. The drugs classified as OL (45%), included vitamins A & D, beclomethasone and furosemide (Table 2).

In the winter sample, only two patients without UL/OL use were identified. There were 27% UL and 44.6% OL prescriptions. The most frequent OL classification was regarding drug formulation (37%), and the most prescribed drug in this category was phenobarbital (18%). From a total of 136 medications, the most prescribed were acetaminophen (11.5%) and dipyron (9.5%).

In the summer sample, all patients received at least one UL/OL prescription. There were 29.6% UL and 45.1% OL prescriptions. The most prescribed UL drug was dipyron (32.5%). The most frequent OL use was also for formulation (34%), and the most prescribed drug in this category was ibuprofen (13.3%). From a total of 146 medications, the most prescribed were acetaminophen (10.6%) and dipyron (9.6%).

As for the reasons for admission, in winter, the most frequent were respiratory diseases (R) and during the summer week, there were other Clinical Causes (CC) (Table 3). A

comparison of the reasons for hospitalization in both groups showed a statistically significant difference ($p = 0.001$, chi-square test), regarding R in the winter and GH in the summer, after the posthoc test. When comparing the reason-for-hospitalization groups using the Kruskal-Wallis test, it was found that during the winter, the median for UL prescriptions was higher in the GH group compared to the R group (3 vs. 1, $p = 0.001$), while the other comparisons showed no statistical significance.

4. DISCUSSION

The unlicensed and off-label prescription of medications was similar among patients in the samples studied both in the winter and in the summer seasons. This is the first report in the literature to study the frequency of those prescription standards regarding seasonality.

We found frequencies of UL use of 28.3% and off-label use of 45%, which are superior to the results described elsewhere, probably due to different formularies in different countries. Doherty *et al.* (2010) compared three databases for different classifications in three different hospitals and found a frequency between 50 and 60% UL/OL in two databases and 10% in the third [19]. The most commonly prescribed medications in that study were like those described in our population. Other recent studies have shown that the most frequently UL or OL prescribed medications among

Table 3. Reason for admission frequency in Summer and Winter groups.

-	Winter 2014	Summer 2015
Other clinical causes	17.3%	26.3%
Surgical	16%	23.7%
GH	7.4%	23.7%*
Neuropsychiatry	14.8%	9.2%
Respiratory	44.4%*	17.1%

*chi-square test, p=0.001.

paediatric ward patients are paracetamol, fentanyl, salbutamol and midazolam [4, 6, 15, 19].

Turner *et al.* (1998) reported the UL/OL prescription of medications in 25% of patients in a surgical and clinical paediatric ward, with salbutamol, folic acid, diclofenac and morphine among the most prescribed drugs [4]. Moreover, as found in our sample, the same study found that OL prescriptions are more prevalent than UL in the paediatric population [4]. In that study, as in another publication [18], the main OL sub-classification was regarding dosage, in contrast to our sample, where OL due to formulation was the most frequent, probably due to the different formularies used.

Other examples of different classifications due to the use of different national pharmaceutical formularies are dipyrone and phenobarbital. Although widely used in Brazil, due to its availability for intravenous administration, the FDA classifies dipyrone as UL and its use is not approved in any population, because of the risk of inducing aplastic anaemia and agranulocytosis. Similarly, phenobarbital is available in a different formulation in the US, bottled at a lower concentration for greater safety than in Brazil [20].

One medication classified as UL was chloral hydrate, which is manipulated in the hospital pharmacy, because there is no commercial presentation available for the age group in our country. A Dutch study also obtained a high frequency of UL prescriptions (40%) due to a large number of medications manufactured in hospital [18]. Chloral hydrate is widely used for sedation in procedures such as magnetic resonance imaging, during which the child has to remain still, as there are few pharmacological alternatives suitable for that purpose [10].

Lindell-Osuagwu *et al.* describe paracetamol, fentanyl, salbutamol and midazolam as the most frequently prescribed UL or OL medications in the paediatric ward [15]. Since fentanyl and midazolam are used only in the PICU in our hospital, they were not prescribed for the studied population. Paracetamol is classified as approved for most patients included in this study, as well as in the literature. In the winter sample, salbutamol is the most age-related OL prescribed drug, which is consistent with the literature [4, 6, 15].

Respiratory diseases were the leading cause of hospitalization of the population studied in the winter period, which is consistent with the literature [9, 11, 15, 21, 22]. Tramonina *et al.* found that the main reasons for children hospitalization were related to cancer, probably due to the presence of a specific cancer ward at the studied hospital, followed by

respiratory causes and prematurity [23]. The first and third causes were not included in our sample. It is important to note that hospitals have different profiles and different reason-for-hospitalization ratings were used in these studies. Three of them include PICU patients in their study populations, whereas the population in our study was from a general ward, which constitutes a quite different population [9, 21, 22].

The UL or OL use of medicines in children in our center does not seem to vary greatly according to the reason for hospitalization, according to the data provided above. The only study analysing reason for hospitalization was conducted by Turner *et al.* (1998), in which data was collected from various paediatric sectors of a tertiary hospital in the UK to analyse the off-label use, and found no difference in the percentage of UL or OL prescriptions in the general paediatric ward when compared to the surgical ward [4]. Moreover, in our study, the higher median number of UL prescriptions in the GH group compared to the R group is possible since patients with respiratory diseases currently receive little medication, as they were often bronchiolitis and the current treatment guidelines recommend only supportive therapy.

No other studies have examined UL/OL prescriptions regarding reasons for hospitalization, which is a positive strength of our study. Further studies with larger samples in more hospitals are needed to confirm the findings of the present study. Nevertheless, the UL/OL use of drugs in children in our centre does not seem to vary greatly according to reasons for hospitalization, but rather, it depends on season (and probably also on severity). Apparently, the larger number of patients seen in winter is due to the higher turnover of acute respiratory cases, which are less frequent in the summer.

Comparison among studies reflects the lack of evidence regarding the effectiveness and safety of medications for young patients and the lack of alternatives to meet the needs of this age range [9]. Since infants exhibit important pharmacodynamic differences in comparison to older children, more clinical studies with this population are necessary.

CONCLUSION

From the data obtained, it can be concluded that the UL/OL use of medicines in children in our hospital is in accordance with the world literature. Homogeneity between winter and summer groups in our sample decreases the likelihood that the significant differences found in our study

were due to chance. Probably, the high frequency of formulation-related off-label use of drugs in this study is related to the use of other formulations in Brazil. This implies the need to evaluate prescriptions within a national formulary in order to arrive at more precise conclusions.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Study was approved by the Ethics and Research Committee of Hospital de Clínicas de Porto Alegre Brazil (GPPG No. 14-0507).

HUMAN AND ANIMAL RIGHTS

No animals were used in this study, the reported experiments on humans were in accordance with the ethical standards of the committee responsible for human experimentation (institutional national), and with the Helsinki Declaration of 1975, as revised in 2008 (<http://www.wma.net/>).

CONSENT FOR PUBLICATION

Written informed consent was obtained from all the participants for this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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