Farmacia HOSPITALARIA
ÓRGANO OFICIAL DE EXPRESIÓN CIENTÍFICA DE LA SOCIEDAD ESPAÑOLA DE FARMACIA HOSPITALARIA

COMUNICACIONES BREVES

Off-label and unlicensed utilization of drugs in a Brazilian pediatric hospital

Vanessa Pereira Gomes[1], Kédma Melo da Silva[1], Suely Oliveira Chagas[2] and Igor Rafael dos Santos Magalhães[1]

[1]Faculdade de Ciências Farmacêuticas, Universidade Federal do Amazonas, Manaus, Amazonas. [2]Instituto de Saúde da Criança do Amazonas, Manaus, Amazonas. Brazil.

Abstract
Aim: To describe the off-label and unlicensed utilization patterns of drugs in a Brazilian pediatric hospital.
Methods: The research consisted of a descriptive, prospective and cross-sectional study.
Results: A total of 1,158 medicines were prescribed for 320 patients, accounting for 65 different drugs. Regarding the classification of drug utilization, the majority of the drugs were prescribed as in-label (57.2%), followed by off-label (36.4%) and by unlicensed (6.3%). The prevalences of unlicensed and off-label utilization of drugs in the studied population were 20.9 and 77.8%, respectively. Polypharmacy was highly associated to both off-label and unlicensed regimen (OR 12.9; 95% CI 3.07-54.2 and OR 3.68; 95% CI 2.02-6.69, respectively) whereas preschool children were less prone to unlicensed prescription (OR 0.39; 95% CI 0.19-0.79). Sex and length of hospitalization were not related to these outcomes.
Conclusions: Further studies are necessary to verify the impact of this pattern on the occurrence of adverse drug events.

KEYWORDS
Off-label use; Drug prescription; Pharmacoepidemiology

Farm Hosp. 2015;**39(3)**:176-180

Utilización de medicamentos off-label y sin licencia en un hospital pediátrico de Brasil

Resumen
Objetivo: Describir los patrones de utilización de medicamentos off-label y sin licencia en un hospital pediátrico de Brasil.
Métodos: La investigación consistió en un estudio descriptivo, prospectivo y de corte transversal.
Resultados: Un total de 1.158 medicamentos fueron prescritos para 320 pacientes, que representan 65 fármacos diferentes. En cuanto a la clasificación de la utilización de medicamentos, la mayoría de los medicamentos fueron prescritos como en la ficha técnica (57,2%), seguido off-label (36,4%) y por sin licencia (6,3%). Las prevalencias de uso sin licencia y off-label de drogas en la población estudiada fueron 20,9 y 77,8%, respectivamente. La polifarmacia fue muy asociada a ambos off-label y el régimen sin licencia (OR 12,9; IC del 95%: 3,07 a 54,2 y OR 3,68; IC del 95%: 2,02 a 6,69, respectivamente), mientras que los niños en edad preescolar fueron menos propensos a prescripción sin licencia (OR 0,39; 95% CI 0,19-,79). El sexo y la duración de la hospitalización no estaban relacionadas con estos resultados.
Conclusiones: Son necesarios más estudios para verificar el impacto de este patrón en la ocurrencia de eventos adversos en los medicamentos.

PALABRAS CLAVE
Off-label; Prescripción de medicamentos; Farmacoepidemiología

Farm Hosp. 2015;**39(3)**:176-180

* Autor para correspondencia.
Correo electrónico: imagalhaes@ufam.edu.br (Igor Rafael dos Santos Magalhães).

Recibido el 5 de febrero de 2015; aceptado el 11 de marzo de 2015.
DOI: 10.7399/fh.2015.39.3.8472

Introduction

The utilization of drugs in children and teenagers has raised concerns for a long time. Due to several reasons, including ethical and economical questions reported in the literature, this group has been considered as "orphan therapeutic" owing to the lack of sufficient information to use several agents safely in this population. Although some changes have been seen some years ago, mainly related to the modifications in US and European legislation, this issue remains to catch the attention from the scientific community[1].

In this context, the terms off-label and unlicensed drug use have been reported to describe the patterns of drug utilization in the clinical practice. Unlicensed drug use may be considered as "the employment of a drug in lack of a product license". Off-label drug use is known as "the use of a marketed drug outside the term of the product license" and it is generally associated to differences in age, dose, route and indication[2]. On the other hand, the in-label or licensed drug use is supposed to be the utilization of a drug according to the terms of license granted by the regulatory agency.

Several studies have described the profile of unlicensed and off-label utilization in children, especially in the developed world[3-5]. However, some Brazilian reports also have been published lately[6-8]. On the other hand, none article investigating this issue regarding pediatric patients from the northern region of Brazil, which present single clinical and epidemiological features, has been found in the literature. Therefore, this article aimed to describe the off-label and unlicensed utilization patterns of drugs in a Brazilian pediatric hospital in order to identify factors associated with this phenomenon, and to compare the obtained results with other studies.

Methods

Setting and study design

The research consisted of a descriptive, prospective and cross-sectional study conducted in a reference pediatric hospital located in Manaus, northern Brazil. This health unit has 127 beds and an occupancy rate of 75-95% depending on the ward. Data collection was carried out between September 2012 – February 2013 and involved examination of prescriptions and medical records received at the hospital pharmacy.

Sample size calculation was done to achieve a number of patients sufficient to represent the studied population. Therefore, the prevalence of unlicensed and off-label utilization of drugs in a pediatric ward observed in another Brazilian report was taken as reference with an estimate error and confidence interval of 5 and 95%, respectively[6]. After calculations, the required number of samples in this study was 319.

Simple random sampling was chosen to select eligible patients and the following criteria were adopted in order to permit the comparison with other reports published in the literature: solely patients with prescribed drugs were eligible; only one prescription was selected for each patient; electrolytes, hemoderivatives, oxygen therapy and parenteral nutrition were not considered[3,9]. In addition, prescriptions from the first hospitalization day and from patients below the age of two years and from the intensive care unit were not included in the study[7,8].

The demographic data collected included age and sex whereas the clinical data comprised weight, the number of bed days, and the diagnosis or reason for the hospitalization. The following information regarding drug use was gathered: drug name, dosage, frequency, form and route of administration. Prior to the beginning, the study protocol was approved by the Research Ethics Committee from the Universidade Federal do Amazonas (CAAE number 02382912.5.0000.5020).

Classification

Age was stratified in pre-scholars (2 - 7 years), scholars (8 - 10 years), pre-adolescent (11 - 12 years) and adolescent (13 - 18 years) whereas diagnosis or reason for the hospitalization were categorized according to the International Classification of Diseases (ICD-9).

All drugs were categorized according to the Anatomical Therapeutic Chemical (ATC) classification system and differentiated to the second level of the ATC code and classification of drug utilization in unlicensed, off-label or in-label was achieved after consulting the Brazilian National Formulary (BNF), which was considered the reference document and contains the approved pediatric uses issued by the Brazilian regulatory agency.

Summarizing, the following conditions were considered unlicensed utilization: drug imported or not approved by the regulatory agency; drug contraindicated to children or teenagers; drug not evaluated in children regarding safety and efficacy; drug preparation obtained from a modified licensed medicine. On the other hand, off-label usage comprised the prescription of drugs outside the terms of the product license concerning age, dose, frequency, form and route of administration[6]. The classification was carried out independently by two examiners and by a third one for arbitration when discrepancies arose.

Finally, the prevalence was defined as the number of individuals who received at least one off-label or unlicensed prescribed drug in one hundred hospitalized patients[6,7].

Statistical analysis

Descriptive analysis was carried out to demonstrate continuous variables. Binary logistic regression was applied to verify the probability of receiving at least one

unlicensed or off-label drug with possible predictors. All analyses were performed using the statistical software STATA (version 11.2).

Results

A total of 320 patients were included in the study. Of them, 171 were male (53.4%). In relation to the age, the range was 28 months to 14 years with mean and median ages of 5.3 and 5.0 years, respectively. The pre-scholar category had more counts than the others (268/83.7%). The weight varied from 4.4 to 86.3 Kg with mean and median weight of 20.0 and 17.6 Kg, respectively.

The respiratory diseases group was the most common reason for hospitalization (508/43.8%). Among them, pneumonia was the major diagnosis observed in this study. In relation, to the number of bed days, the range was 2-24 days with mean and median of 3.7 and 3.0 days, respectively.

A total of 1,158 medicines were prescribed for 320 patients, accounting for 65 different drugs. These patients utilized mean and median of 3.6 and 3.0 drugs, respectively, with the range varying from 1 to 8 drugs. The most prescribed ATC group was the N02 – analgesics (25.9%), followed by the J01 – systemic antibacterials (24.7%) and by the A03 – drugs for functional gastrointestinal disorders (14.9%).

The non-steroidal anti-inflammatory drug metamizole was the most used and prescribed for 90.0% of the patients studied, followed by metoclopramide (37.5%) and fenoterol (33.7%). Additionally, the intravenous route of administration was the most employed (74.0%).

Regarding the classification of drug utilization, the majority of the drugs were prescribed as in-label (57.2%), followed by off-label usage (36.4%) and by unlicensed employment (6.3%). Fenoterol, ceftriaxone and metamizole were the most commonly prescribed off-label drugs whereas ranitidine, omeprazole and captopril were the most used in unlicensed manner (Table 1).

Dosage and frequency of administration were mainly related to the off-label prescription (41.5 and 37.4, respectively). In relation to unlicensed usage, the conditions "drug contraindicated to children or teenagers" and "drug not evaluated in children regarding safety and efficacy" were more reported (56.2 and 34.2%, respectively) (Table 2).

Polypharmacy was highly associated to both off-label and unlicensed regimen (OR 12.9; 95% CI 3.07-54.2 and OR 3.68; 95% CI 2.02-6.69, respectively) whereas preschool children were less prone to unlicensed prescription (OR 0.39; 95% CI 0.19-0.79). Sex and length of hospitalization were not related to these outcomes (Table 3). The prevalence of unlicensed and off-label utilization of drugs in the studied population was 20.9 and 77.8%, respectively.

Discussion

This observational study attempted to describe the profile the utilization of drugs in unlicensed and off-label way in a pediatric hospital from the northern Brazil. The high utilization of metamizole both in licensed and off-label manner in this unit demands special attention due to the severe adverse events attributed to this drug, which is no longer admitted in USA, UK, Denmark and

Table 1. *Profile of drug utilization (n = 1158)*

Drug classification	Number of prescriptions (%)	Most frequent drugs
Licensed	57.2	Metamizole > metoclopramide > benzylpenicilline
Unlicensed	6.3	Ranitidine > omeprazole > captopril
Off-label	36.4	Fenoterol > ceftriaxone > metamizole

Table 2. *Drug prescriptions in each unlicensed and off-label cathegories*

Drug classification	Number of prescriptions (%)	Most frequent drugs
Unlicensed (n = 73)		
Drug contraindicated to children or teenagers	56.2	Ranitidine
Drug not evaluated in children regarding safety and efficacy	34.2	Omeprazole
Others	9.6	-
Off-label (n = 421)		
Dosage	41.5	Methamizole
Frequency	37.4	Ceftriaxone
Others	21.1	-

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

Predictors for receiving an unlicensed drug	OR (95% CI)	p value
Sex		
Male (reference)	-	-
Female	0.80 (0.45-1.43)	0.46
Age		
2 – 7 years	0.39 (0.19-0.79)	0.00*
8 ≥ 18 years (reference)	-	-
Days of hospitalization		
1 – 6 days (reference)	-	-
≥ 7 days	1.43 (0.56-3.60)	0.44
Occurrence of polypharmacy		
Yes	3.68 (2.02-6.69)	0.00*
No (reference)	-	-
Predictors for receiving an off-label drug		
Sex		
Male (reference)	-	-
Female	0.95 (0.54-1.67)	0.87
Age		
2 – 7 years	1.46 (0.70-3.00)	0.30
8 ≥ 18 years	-	
Days of hospitalization		
1 – 6 days (reference)	-	-
≥ 7 days	1.48 (0.47-4.64)	0.49
Occurrence of polypharmacy		
Yes	12.9 (3.07-54.2)	0.00*
No (reference)	-	-

*Statistically significant result ($p < 0.05$). OR: odds ratio; CI: confidence interval.

Sweden, but is approved and used in many European countries, such as Germany and Spain[10]. This observation was already performed in another Brazilian study some years ago although lower rates were seen[6].

The rates of unlicensed and off-label prescriptions observed in this study were high and are in good agreement with those reported in other recent papers[11,12]. Furthermore, the reasons for off-label and unlicensed utilization were similar to the observed in other studies, in which dosage and frequency of administration are more associated to the off-label prescription whereas drug contraindication and lack of appropriate knowledge for use in children are more implicated to the unlicensed[5,6,13].

Logistic regression analysis was conducted to identify possible predictors related to the occurrence of unlicensed and off-label prescription. The analyses indicated that the prevalence of unlicensed and off-label use were associated with a polytherapy regimen (utilization of five or more drugs), corroborating other studies[12]. Interestingly, children from the preschool category were less likely to receive unlicensed drugs. However, the increase of use of at least unlicensed drug with age was already observed in another Brazilian report[6].

The conclusions of this study are limited owing to some reasons. First, there are some discrepancies regarding the definitions of unlicensed and off-label drugs between different studies, which may impair comparisons[14]. Second, the association of the prescription of unlicensed and off-label drugs and the occurrence of adverse drug reactions (ADRs) was not verified due to practical difficulties in the field. This result would be an important contribution to the current discussion debating whether this phenomenon is a significant risk factor to the emergence of ADRs[15].

Acknowledgements

Vanessa Pereira Gomes and Kédma Melo da Silva were recipient of Fundação de Amparo à Pesquisa do Estado do Amazonas (FAPEAM) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) scholarships, respectively.

Bibliography

1. Laughon MM, Benjamin DK, Capparelli EV, Kearns GL, Berezny K, Paul IM. Innovative clinical trial design for pediatric therapeutics. Expert Rev Clin Pharmacol. 2011; 4: 643-52.
2. Neubert A, Felisi M, Bonifazi A, Manfredi C, Wong ICK, Ceci A. Off-label and unlicensed use of medicines for children. Pharmaceut Policy Law. 2009; 11: 41-9.
3. Jong GW, van der Linden PD, Bakker EM, N. van der Lely N, Eland IA, Stricker BHC. Unlicensed and off-label drug use in a paediatric ward of a general hospital in the Netherlands. Eur J Clin Pharmacol. 2002; 58: 293-7.
4. Sturkenboom M, Felisi M, Manfredi C, Neubert A, Cantarutti L, Padula R. Paediatric status and off-label use of drugs in children in Italy, United Kingdom and the Netherlands. Pharmaceut Policy Law. 2009; 11: 51-9.
5. Ballard CDJ, Peterson GM, Thompson AJ, Beggs SA. Off-label use of medicines in paediatric inpatients at an Australian teaching hospital. J Paediatr Child Health. 2012; 49: 38-42.
6. Santos DB, Clavenna A, Bonati M, Coelho HLL. Off-label and unlicensed drug utilization in hospitalized children in Fortaleza, Brazil. Eur J Clin Pharmacol. 2008; 64: 1111-8.
7. Dos Santos L, Heineck I. Drug utilization study in pediatric prescriptions of a university hospital in southern Brazil: off-label, unlicensed and high-alert medications. Farm Hosp. 2012; 36: 180-6.
8. Ferreira LA, Ibiapina CC, Machado MGP, Fagundes EDT. Alta prevalência de prescrições de medicamentos off-label e não licenciados em unidade de terapia intensiva pediátrica brasileira. Rev Assoc Med Bras. 2012; 58: 82-7.
9. Hsien L, Breddemann A, Frobel A-K, Heusch A, Schmidt KG, Läer S. Off-label drug use among hospitalised children: identifying areas with the highest need for research. Pharm World Sci. 2008; 30: 497-502.
10. Huber M, Andersohn F, Sarganas G, Bronder E, Klimpel A, Thomae M. Metamizole-induced agranulocytosis revisited: results from the prospective Berlin Case–Control Surveillance Study. Eur J Clin Pharmacol. 2015; 71: 219-27.
11. Khdour MR, Hallak HO, Alayasa KSA, AlShahed QN, Hawwa AF, McElnay JC. Extent and nature of unlicensed and off-label medicine use in hospitalised children in Palestine. Int J Clin Pharm. 2011; 33: 650-5.
12. Lee JL, Redzuan AM, Shah NM. Unlicensed and off-label use of medicines in children admitted to the intensive care units of a hospital in Malaysia. Int J Clin Pharm. 2013; 35: 1025-9.
13. Pandolfini C, Bonati M. A literature review on off-label drug use in children. Eur J Pediatr. 2005; 164: 552-8.
14. Bellis JR, Kirkham JJ, Nunn AJ, Pirmohamed M. Adverse drug reactions and off-label and unlicensed medicines in children: a prospective cohort study of unplanned admissions to paediatric hospital. Br J Clin Pharmacol. 2013; 77: 545-53.
15. Mason J, Pirmohamed M, Nunn T. Off-label and unlicensed medicine use and adverse drug reactions in children: a narrative review of the literature. Eur J Clin Pharmacol. 2012; 68: 21-8.